

Probing the ‘bipolar’ nature of the carbonic anhydrase active site: Aromatic sulfonamides containing 1,3-oxazol-5-yl moiety as picomolar inhibitors of cytosolic CA I and CA II isoforms

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ABSTRACT

A series of potent inhibitors of human carbonic anhydrase (CA) isoforms I and II has been prepared via a direct, chemoselective sulfochlorination of a range of 1,3-oxazolyl benzenes and thiophenes, followed by primary sulfonamide synthesis. The latter functionality is a known zinc-binding group (ZBG) responsible for anchoring the inhibitors to the CA's zinc metal ion. The compound's periphery as well as the overall scaffold geometry was designed to enable optimal interactions with the two distinct sides of the enzyme's active site, one of which is lined with hydrophobic residues and while the other is predominantly hydrophilic. As a result, several compounds inhibiting the therapeutically important cytosolic CA I and CA II in picomolar range have been identified. These compounds are one of the most potent CA inhibitors identified to-date. Not only the remarkable (>10 000-fold), cytosolic CA I and CA II selectivity vs. the membrane-bound CA IX and CA XII isoforms, but also the pronounced CA II/I selectivity observed in some cases, allow considering this series as a set of isoform-selective chemical biology tools and promising starting points for drug candidate development.

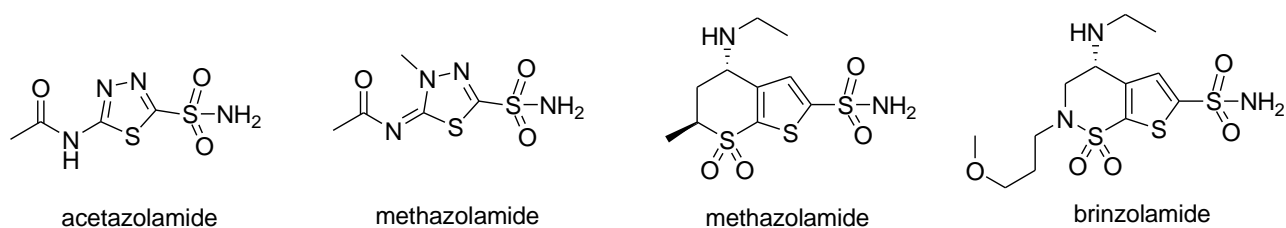
Keywords: drug discovery, carbonic anhydrase inhibitors, isoform selectivity, anti-glaucoma drugs, 1,3-oxadiazol-5-yl aromatics, chemoselective sulfochlorination.

1. Introduction

Carbonic anhydrases (CAs) catalyse the fundamental biochemical process of carbon dioxide hydration (a reversible reaction producing a bicarbonate anion and a proton) and are, therefore, one of the principal regulators of cellular pH homeostasis [1]. The potential of this enzyme family as an important class of biological targets for chemotherapeutic intervention was recognized several decades ago [2]. This has led to the development of several effective drugs in areas as diverse as ophthalmology (glaucoma), metabolic disease (diabetes) and gastroenterology (gastric and duodenal ulcers) [3].

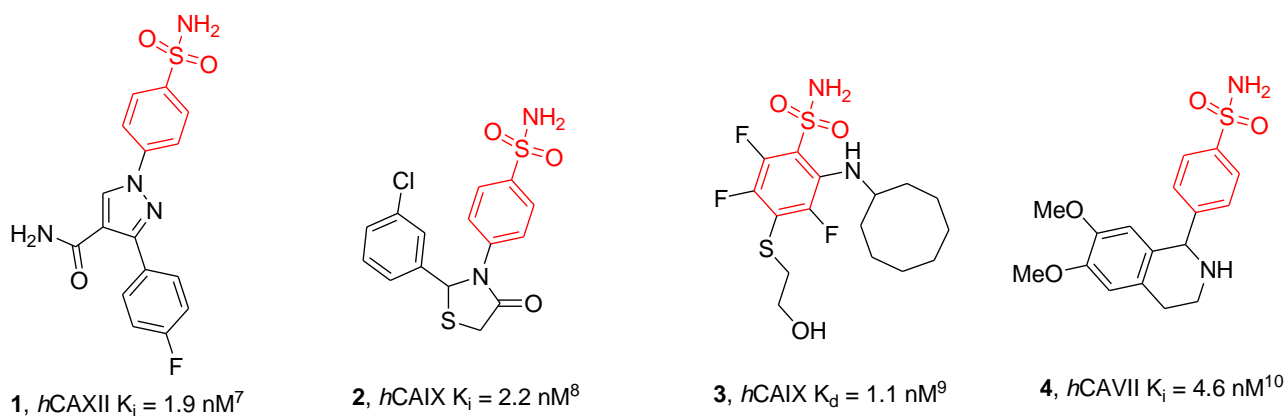
The earlier CA inhibitors (CAIs) (examples of which include acetazolamide, methazolamide, dorzolamide, brinzolamide – Fig. 1) are almost exclusively non-selective, pan-inhibitors of all human CAs (of which there are currently 16 isoforms known). More recent research efforts were directed toward the discovery of isoform-selective CAIs and understanding the guiding structural principles that can help achieve the desired selectivity [4].

Figure 1. Examples of the early pan-CA inhibitors – clinically used drugs.



Primary sulfonamides are the central and most prominent class of CAIs [5]. The sulfonamide functionality in these compounds is responsible for coordination to the enzyme's prosthetic metal ion (which is almost exclusively Zn²⁺ across the known CAs). It is, therefore, denoted as a zinc-binding group (ZBG). It is, however, the CAI molecule's periphery that determines the potency and selectivity. This is illustrated by the evolution of the weak and non-selective CA inhibitor benzenesulfonamide [6] into highly potent isoform-selective sulfonamides 1–4 (Fig. 2) [7], [8], [9], [10]. In the latter, the substituents in the benzene ring (besides the pharmacophoric sulfonamide group) are thought to be responsible for additional contacts in the CA active site, some of which are with the amino acid residues that are unique to specific isozymes.

Figure 2. Examples 1-4 of isoform-selective benzene sulphonamides.



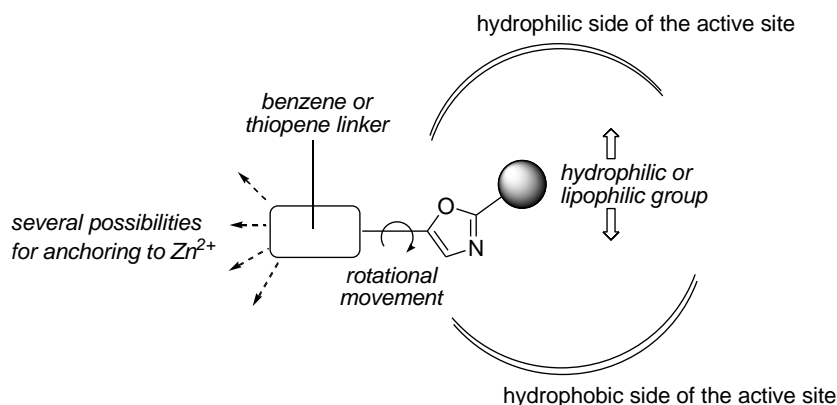
The vast structural information accumulated to-date via extensive X-ray studies of numerous CA-CAI complexes led to establishing a very notable feature that is characteristic of all the CA active sites [11], [11](b). Regardless of the species, all the known CAs possess generally rather big active sites that are divided into two distinct sides, one of which is lined with hydrophobic residues and the other – with polar, hydrophilic ones [12]. While the size of the CA active site may appear puzzling in light of the very small size of the substrates, it is the unique, ‘bipolar’ environment surrounding the catalytic ‘scene’ that allows for an efficient binding of the two closely related, yet vastly different substrate molecules - a hydrophobic gas (CO₂) and a polar, water-soluble anion (HCO₃⁻) [13](b), [13], [13](a).

The information on the specific setup of the CA active site has provided substantial grounds for designing potent and isoform-selective inhibitors. The notable examples include 4-ureidobenzene sulfonamides recently described by McKenna and Supuran [14]. According to the X-ray analysis, the ureido tails in these compounds selectively occupy pockets on the hydrophobic side of the active site, leading to potent and selective inhibitors of CA II. Even more striking example of exploration of the two halves of the CA II active site with polar as well as lipophilic moieties appended onto acetazolamide molecule was recently disclosed by Poulsen and Supuran [15]. In the latter work, a thorough comparison of single-vs. dual-tail inhibitors was made, which offered a unique insight into the importance of varying the nature of the periphery groups on the inhibitor potency toward a particular CA isoform.

We became interested in using the synthetically accessible variants of 1,3-oxazol-5-yl aromatics as the template for linking the pharmacophoric primary sulfonamide group and the distal periphery motifs (polar or lipophilic). Such a template, in our view could enable several possibilities for projecting the sulfonamide ZBG toward the ‘bottom’ of the active site while the substituents on the 1,3-oxazole ring could not only be easily varied in nature but can also be expected to adopt a range of conformations (due to the rotational freedom present in the diaryl linker) for optimal interactions

with both sides of the active site (Fig. 3). In this paper, we present the synthesis and biological evaluation of the new CAIs conforming to this general design idea.

Figure 3. Scaffold geometry and periphery projection for optimal inhibitor anchoring and probing of the two distinct sides of the CA active site.

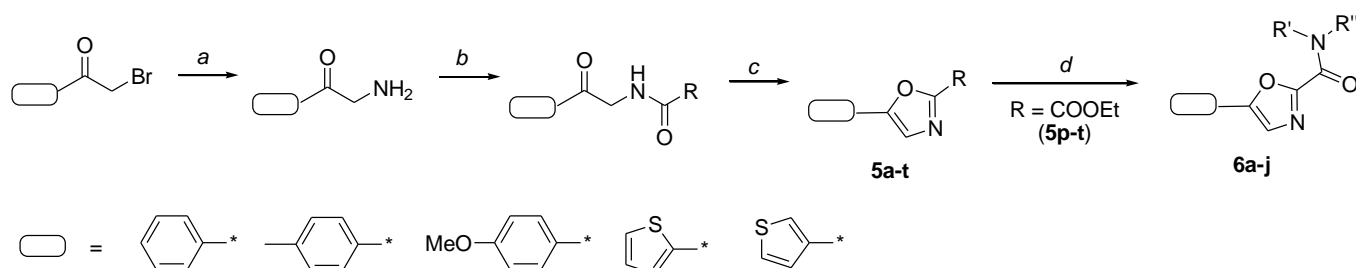


2. Results and discussion

2.1 Chemistry







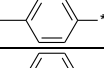
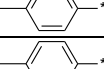

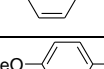

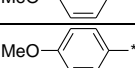
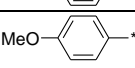

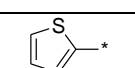












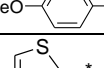
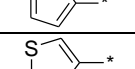


In order to confirm that the 1,3-oxadiazol-5-yl aromatic templates are suitable for the CAI design, twenty core **5a-t** were synthesized using the Robinson-Gabriel synthesis involving cyclodehydration of α -acylaminoketones (prepared, in turn, in nearly quantitative yields from readily available starting materials) under forcing conditions, in good yields (Table 1).¹⁶ The 1,3-oxazole precursors **5a-o** containing lipophilic R groups (Me, cyclopropyl, cyclobutyl) were set aside for the subsequent introduction of the sulphonamide warheads (*vide infra*). The five ester compounds **5p-t** were transformed into morpholine and pyrrolidine carboxamides **6a-j** as the ‘polar periphery’ precursors (Scheme 1). It should be noted that the direct amidation of these 1,3-oxazole-2-carboxylic esters was mandated by the marked instability of the respective carboxylic acids (obtained by alkaline hydrolysis) toward de-carboxylation (even at ambient temperature).

Scheme 1. Synthesis of 1,3-oxazol-5-yl aromatic substrates **5a-t** and **6a-j** for subsequent sulfochlorination.



Reagents and conditions: (a) i. urotropine, EtOH, 2h, ii. HCl, EtOH, 24 h; (b) RCOCl, py, 80 °C, 1h; (c) H₂SO₄, 80 °C, 1.5 h (2- and 3-thienyl, 4-tolyl) or POCl₃, 80 °C, 2h (4-MeOC₆H₄); (d) R'NHR'' (neat), 50 °C, 2h.

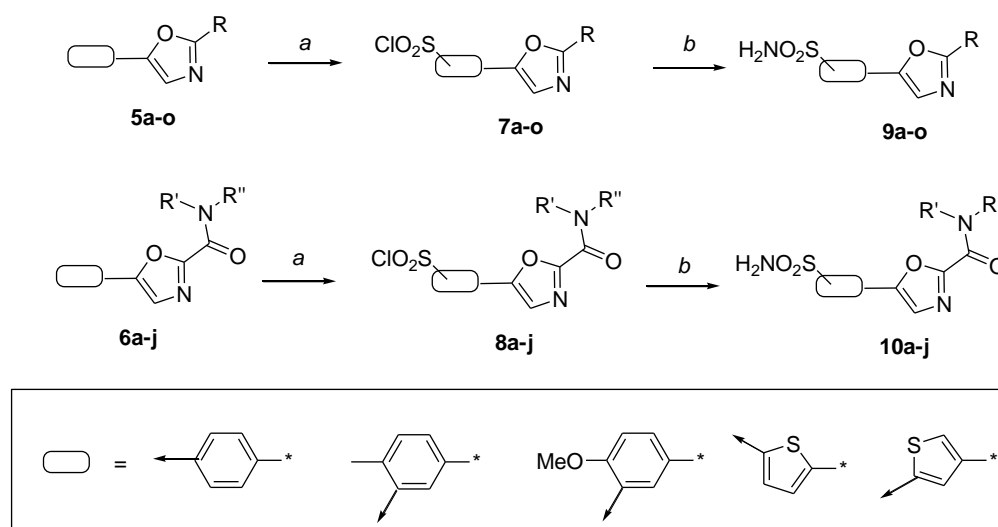
Table 1. 1,3-Oxazoles **5a-t** prepared in this work (the yield of the cyclodehydration step is provided).

Compound		R	Yield (%)
5a		Me	82
5b			79
5c			73
5d		Me	65
5e			48
5f			56
5g		Me	83
5h			75
5i			72
5j		Me	64
5k			73
5l			74
5m		Me	68
5n			67
5o			81
5p		COOEt	50
5q		COOEt	47
5r		COOEt	52
5s		COOEt	59
5t		COOEt	61

The 1,3-oxazole substrates **5a-o** and **6a-j** were then subsequently subjected to direct sulfochlorination and the respective sulfonyl chlorides **7a-o** and **8a-j** were produced in high yields and as a single regioisomer, as indicated by the arrow. The 1,3-oxazole ring remained intact in the reaction conditions, in accordance with the literature precedent.¹⁷ The target sulphonamides **9a-o**

(lipophilic periphery) and **10a-j** (polar periphery) were obtained on treatment of the respective sulfonyl chlorides with aqueous ammonia (Scheme 2; yields are provided in Section 4 of this article). The regiochemistry of the sulfochlorination step (initially determined based on ¹H NMR spectra of the sulfochlorides) was further confirmed by the through-space interactions observed in the NOESY spectra of representative sulfonamides **9i**, **9l** and **9o** (see Supplementary Data). Notably, the choice of the aromatic groups for direct sulfochlorination determined the wide range of possibilities for the ZBG sulphonamide to be orientated relative to the linear diaryl linker, in accordance with the general CAI design idea articulated depicted in Figure 3.

Scheme 2. Preparation of sulphonamides **9a-o** and **10a-j** studied in this work.



Reagents and conditions: (a) HSO_3Cl , SOCl_2 , 60 °C, 2 h; (b) NH_3 , 1,4-dioxan, 75 °C, 2 h.

2.2 Biological activity

The biological activity of the twenty-five compounds **9a-o** and **10a-j** as CA inhibitors was evaluated against the human CA I, II, IX and XII. The cytosolic isoforms I and II are the usual off-targets for the membrane-bound isoforms IX and XII. While CAI and II are both involved in edema¹⁸⁻¹⁹ (and CAII is a validated target for treating glaucoma²⁰), CAIX and XII are the highly pursued targets for the development of new cancer treatments.²¹ The inhibition data are presented in Table 2 and are grouped according to the geometry of the ZBG sulfonamide relative to the diaryl core, for easier analysis of the structure-activity relationships (SAR).

The *p*-phenylidene-linked subseries is an apparent source of some really potent and selective CAII inhibitors: the *picomolar* inhibition of the enzyme by **9a-c** appeared very promising, particularly when considering the 100-1000-fold selectivity vs. other three enzymes (including CAI) were

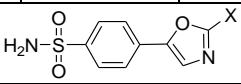


consistently observed. Interestingly, the CAII/I selectivity was completely lost in the ‘polar tail’, carboxamide compounds **10a-b** (the trend is rationalized by in silico docking – see Section 2.3).

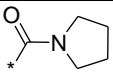
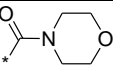
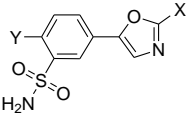




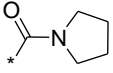
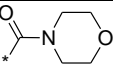
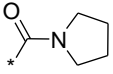
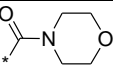
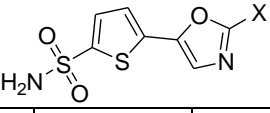


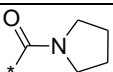
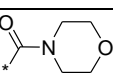
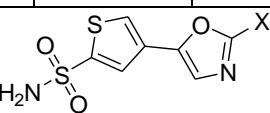


In the *m*-phenylidene-linked subseries, the inhibitory potency across all four isoforms appeared to be depleted for the ‘lipophilic tail’ compounds (**9d-i**). However, in the ‘polar tail’ counterparts (**10c-f**), the inhibitory effect toward CAII (and, to some extent, toward CAIX) is abruptly restored, leading to the best CAII/I and CAII/XII selectivities (> 100,000-fold) in the entire series investigated here.

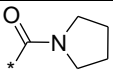
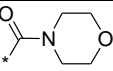
The 2,5-thiophene and 2,4-thiophene-linked subseries displayed a very interesting SAR pattern, illustrating, in our view, the intricacy of the hydrophobic/hydrophilic ‘tail’ contributions to the observed compounds’ potency and selectivity. The compounds in question (**9j-o** and **10g-j**) generally appear biased toward CAII. It also appears, in case of the 2,5-thiophene-linked compounds, that small-alkyl substitutions (except cyclobutyl) in the 1,3-oxazole ring produce weaker CAII inhibitors compared to the carboxamide substitutions in the same position. These compounds also display a 1000-fold CAII/I selectivity. This pattern becomes completely scrambled when it comes to the 2,4-thiophene-linked counterparts: the selectivity seems to be lost and the 2-methyl-1,3-oxazole compound (**9m**) is nearly equipotent toward CA I and CA II. Additionally, the CAI/CAII selectivity of latter subseries appears to be particularly sensitive to the variations in the carboxamide portion. Indeed, **10i** is >880-fold less potent than **10j** toward CA I.

Overall, the analysis of the biological activity data (with respect to potency and selectivity) allowed us to nominate several front-runners compounds for further investigation as CA II inhibitor drug leads (**9a**, **10a**, **10e**, **10h**, **10i**). The analysis of the SAR also resulted in several important observations that we further attempted to rationalize via in silico docking experiments using currently available crystal structures of several CA isoforms.

Table 2. Inhibition of four isoforms of human CA by 5-(sulfamoyl)aryl 1,3-oxazoles **9a-o** and **10a-j** prepared in this work.

Compound	X	K _i (nM)			
		CA I	CA II	CA IX	CA XII
					
9a	Me	96.3	0.05	23.1	8.5
9b	 *	4.8	0.01	3.2	6.2
9c	 *	55.3	0.02	6.5	8.7

10a		0.01	0.009	1.7	42.3
10b		0.01	0.008	1.6	6.9
					
9d (Y = Me)	Me	45.4	7.1	274	245
9e (Y = Me)		289	63.9	318	381
9f (Y = Me)		231	283	285	1395
9g (Y = MeO)	Me	>10 000	4420	276	3535
9h (Y = MeO)		>10 000	8860	438	7960
9i (Y = MeO)		6110	58.2	3.1	62.8
10c (Y = Me)		8.5	0.01	42.5	2790
10d (Y = Me)		58.6	0.28	3.7	557
10e (Y = MeO)		>10 000	0.01	4.1	8570
10f (Y = MeO)		>10 000	0.05	4.5	>10 000
					
9j	Me	141	6.3	10.5	9.4
9k		130	4.8	122	9.2
9l		36.8	0.01	156	5.1
10g		41.9	0.01	18.7	6.7
10h		22.5	0.02	36.4	30.3
					
9m	Me	0.05	0.01	26.3	3.6
9n		22.0	2.5	13.1	8.7
9o		9.0	0.01	25.9	6.6

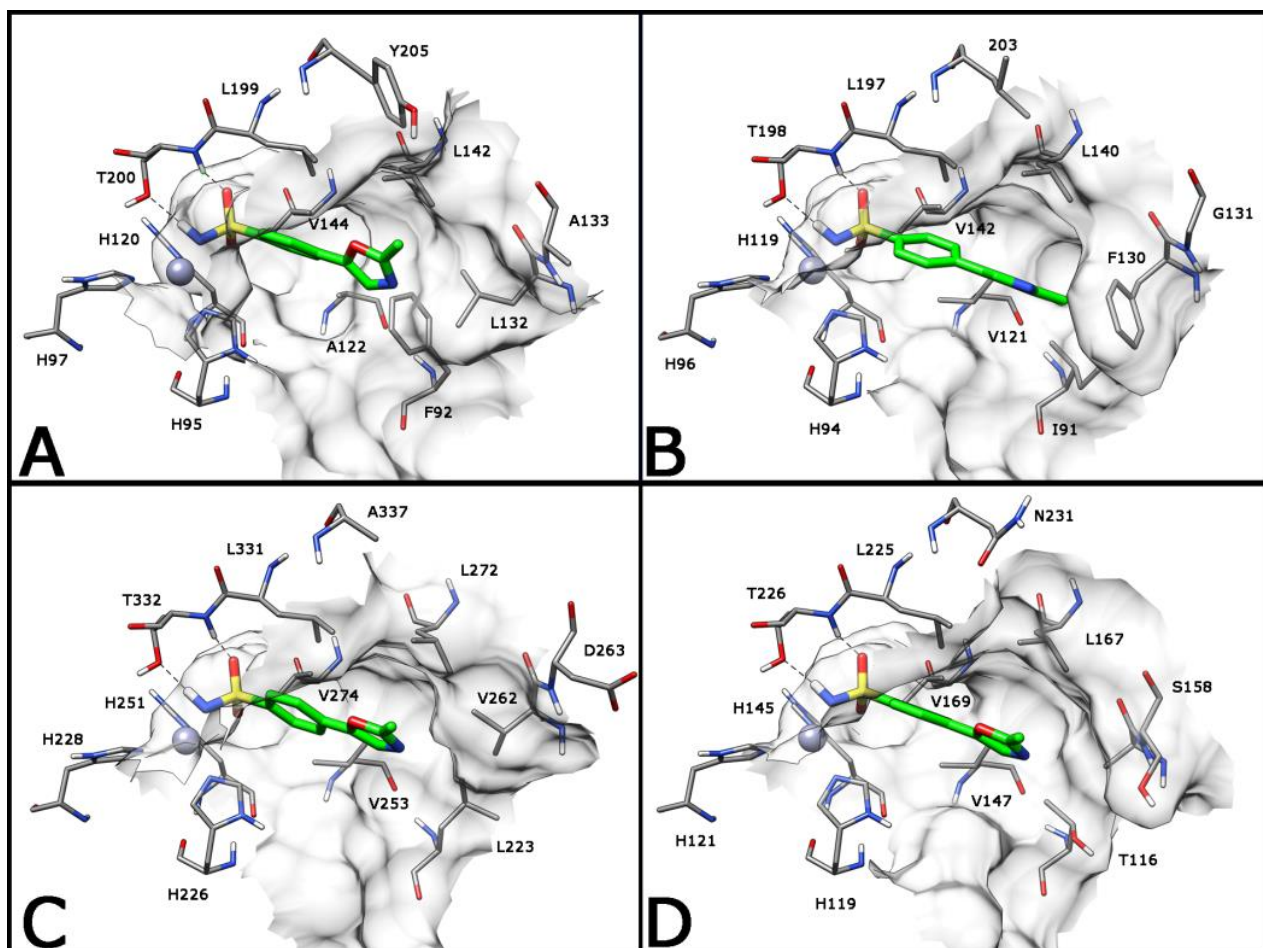
10i		79.9	0.02	15.2	64.4
10j		0.09	0.03	28.0	9.2

2.3 Docking studies

When the inhibitory activity of compound **9a** toward the panel of four CAs was compared with that of compound **10a**, a striking, nearly 10,000-fold difference in the inhibition of CA I was noted. The two compounds differ only with regard to the substitution in the 1,3-oxazole ring and display similar activity patterns on the other three enzymes. This observation led us to perform *in silico* docking experiments in order to determine what a likely binding pose and the crucial interactions of compound **9a** in the CA II active site could be (vs. the other three isoforms) and what causes the drastic change in the CA I potency when the methyl group is replaced with pyrrolidinocarbonyl substituent (to give **10a**).

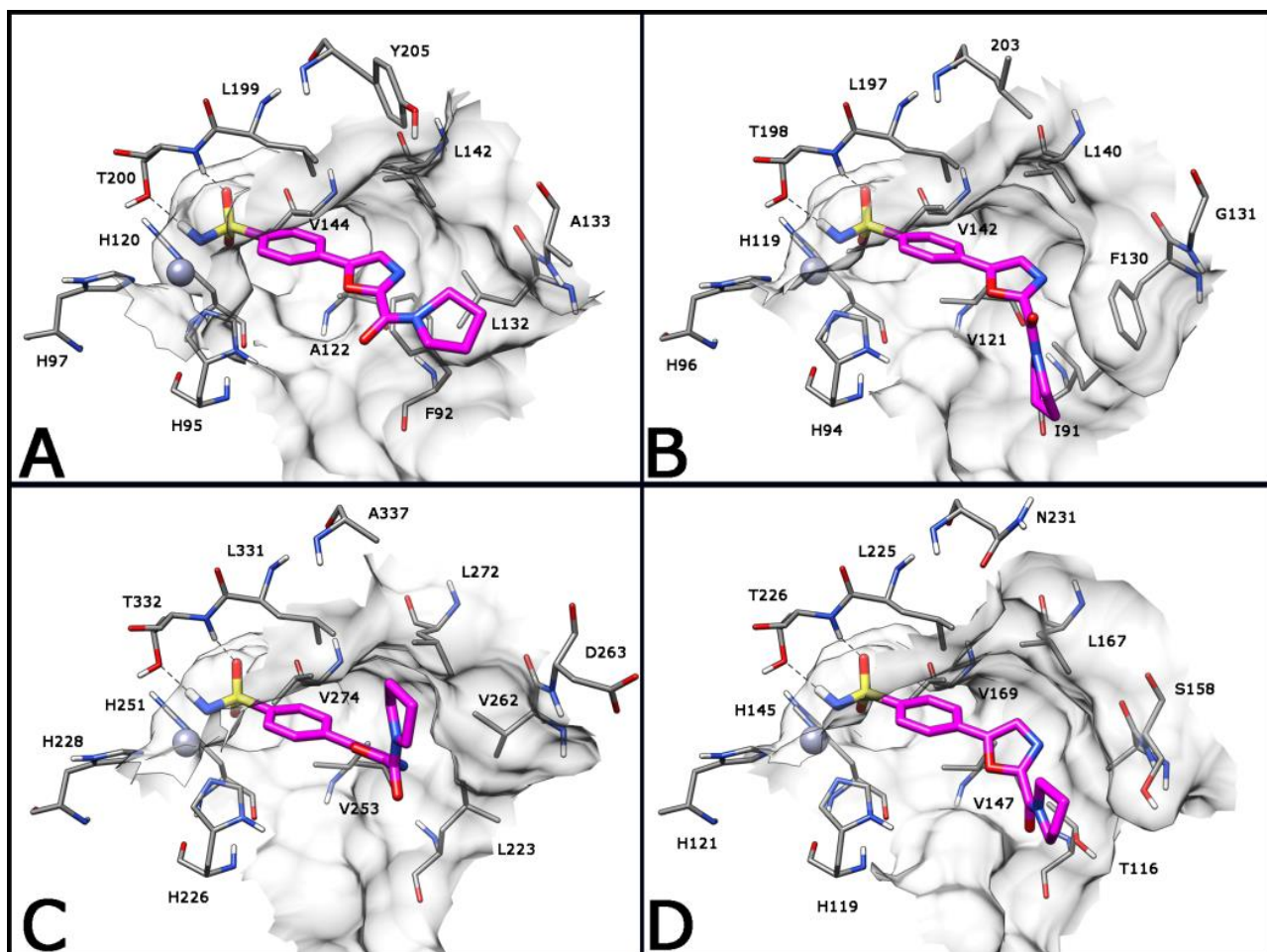
Figure 4 shows the docking of compound **9a** into the active sites of CA I, CA II, CA IX and CA XII. In all four cases, the sulphonamide group acts as a ZBG and forms hydrogen bonds to the protein backbone and the hydroxy group of T196 (CA II numbering), whereas the phenyl ring shows lipophilic interactions with the conserved A/V119, L138, V140, L195. In the CA I, IX and XII isoforms, which are weakly inhibited by **9a**, the 1,3-oxazole ring itself is not involved in any important interactions and the methyl group is directed toward the solvent-exposed region of the binding site. Contrary to this picture, in the CA II, the methyl group is disposed into a lipophilic cleft delimited by the non-conserved I89 and T128. It is this interaction that could be responsible for the activity bias of **9a** toward CA II.

Figure 4. Docking of compound **9a** into CA I (A), CA II (B), CA IX (C), and CA XII (D).



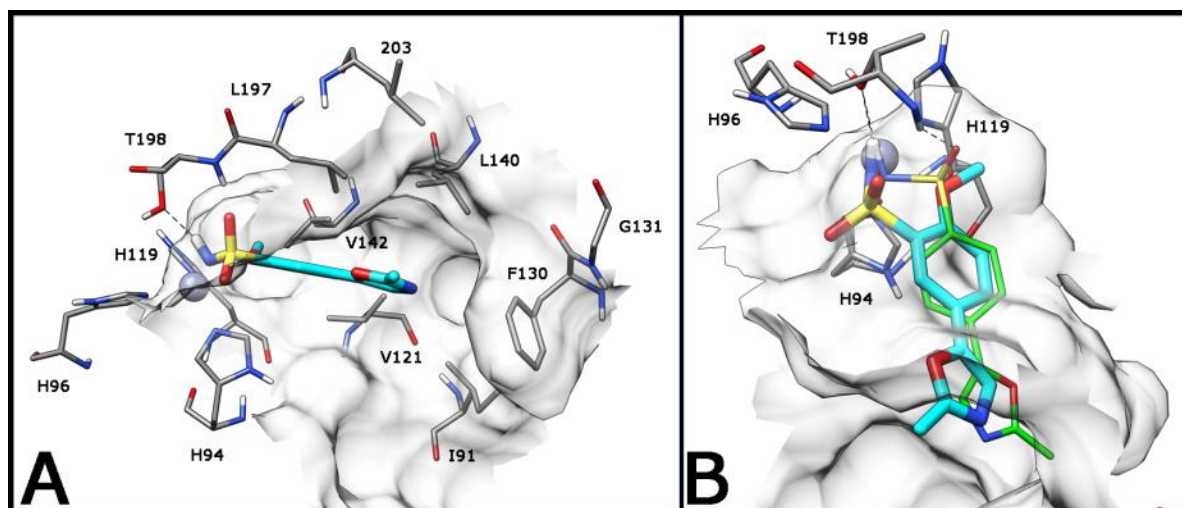
When docked into CA II, compound **10a** shows a very similar pose to that of compound **9a**, with the pyrrolidine moiety forming strong lipophilic interactions with I89 and F128. Contrary to this situation, due to the mutation of I89 and F128 with F89 and L129, respectively, the pyrrolidine group is rotated about 90 ° and forms lipophilic interactions with L129 and A130 in CA I. This is the likely cause for the observed 10 pM inhibition of the latter isoform. In CA IX, the pyrrolidine moiety is directed toward the solvent-exposed area, while in CA XII it is in proximity to the hydroxy group of S128, displaying no important interaction (Figure 5).

Figure 5. Docking of compound **10a** into CA I (A), CA II (B), CA IX (C), and CA XII (D).



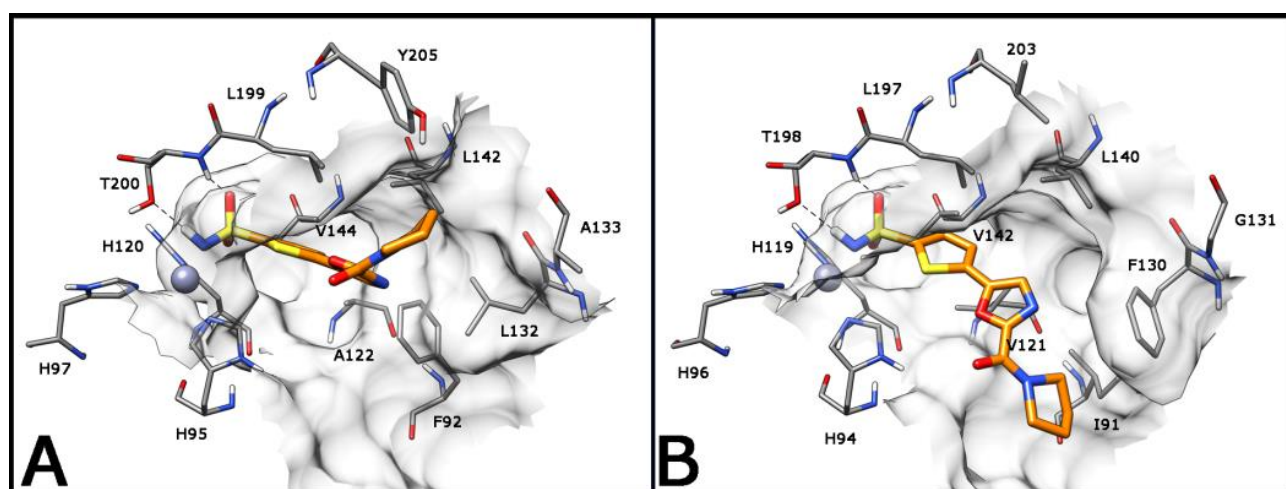
The next question we sought to address using *in silico* docking, was the drastic loss of potency (specifically, vs. CA II) generally observed in the 1,3-phenylidene-linked compounds compared to their 1,4-phenylidene-linked counterparts (cf. **9a** and **9g**). As shown in Figure 6A, **9g** displays an unusual coordination to the zinc ion with a loss of the hydrogen bond to the nitrogen backbone of T196, due to the ‘bent’ shape of the 1,3-phenylidene linker and the presence of the methoxy group. The difference in the crucial anchoring to the zinc ion between **9g** and **9a** (Figure 6B) is the likely cause of the ~100,000-fold difference in the activity of these compounds toward CA II.

Figure 6. Docking of compound **9g** into CA II (A) and the overlay of **9g** (sky blue) and **9a** (green) in the active site of CA II showing the difference in Zn ion coordination.



Further, we were interested in comparing the *p*-phenylidene linked compounds to their 2,5-thiophene counterparts (the two aromatic groups are considered isosteres of each other).¹⁸ The pronounced difference in CA inhibition profile becomes apparent if compounds **10a** and **10g** are compared. **10a** (a *p*-phenylidene-linked compound) is a potent inhibitor of both CA I and CA II. However, **10g** (the 2,5-thiophene-linked analog) is >4000 times less potent toward CA I while continuing to provide picomolar inhibition of CA II. The docking of the docking of **10g** to the active site of the two enzymes (Figure 7) shows that the pyrrolidine portion in the compound still maintains the lipophilic interactions with I89 and F128 (the same interactions were observed for **10a** – see Figure 5). Differently, in the CA I active site, the analogous lipophilic interactions with L129 and A130 are lost, which is the likely cause for the observed drop in potency.

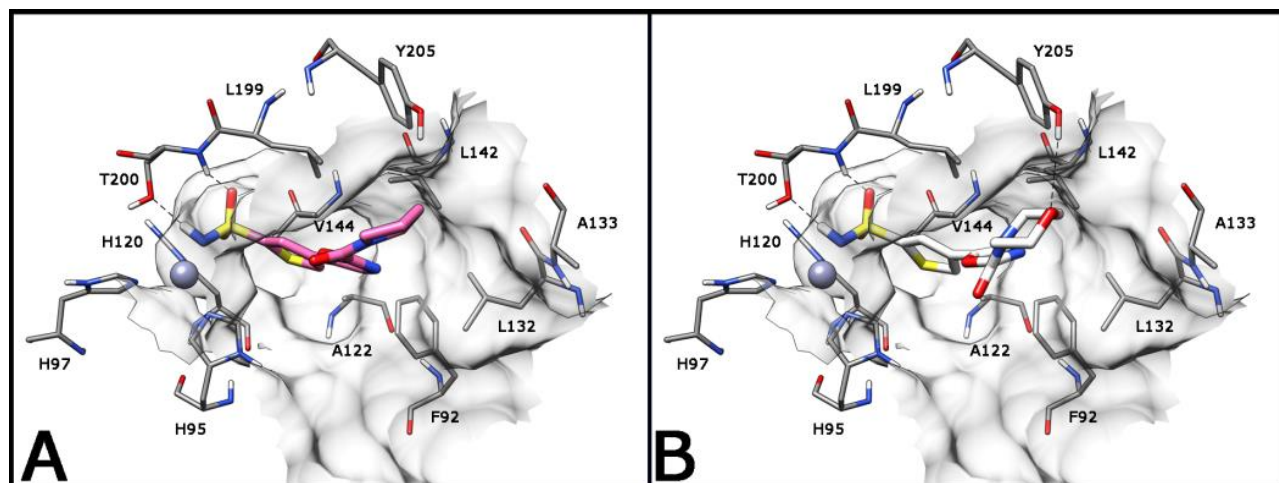
Figure 7. Docking of compound **10g** into CA I (A) and CA II (B).



Finally, we sought to understand the reason for the utter sensitivity of the CA I inhibitory potency observed in the 2,4-thiophene-linked subseries. Indeed, compounds **10i** and **10j** provide nearly identical inhibition of CA II while their CA I potency differs >800-fold. The CA I docking pose of

compound **10i** (Figure 8A) turned out to be very similar to that of compound **10g** (Figure 7A), with the pyrrolidine ring pointing toward the solvent-exposed region of the binding site, which correlates with similar CA I potencies of the two compounds. When the pyrrolidine motif in **10i** is replaced with morpholine (to give **10j**), it doesn't alter the docking pose of the compound (**10j**); however, a weak hydrogen bond between the morpholine oxygen and Y202 (Figure 8B), which is the likely reason for the observed restoration of CA I potency.

Figure 8. Docking of compounds **10i** (A) and **10j** (B) into CA I.



3. Conclusions

In this article, we presented the design, synthesis and biological evaluation of novel diaryl sulphonamides as inhibitors of human carbonic anhydrases. The twenty five compounds employed in this study were designed to enable a variation in the topology of the sulphonamide zinc-binding group (relative to the diaryl moiety). More importantly, the compounds incorporated a set of lipophilic as well as polar appendages in order to act as probes for the ‘bipolar’ architecture of the CA active site. Some of the 1,3-oxazole containing compounds described herein, displayed a remarkable, picomolar inhibitory potency toward CA II and CA I isoforms and an informative SAR pattern, which will be very useful in designing the next generation, optimized CA inhibitors around this chemotype (and, potentially, other diaryl scaffolds). Several front-runner compounds (**9a**, **10a**, **10e**, **10h**, **10i**) were selected for further studies as drug leads, based on their potency (mostly, against CA II, which is a clinically validated target) as well as selectivity. The results of these studies as well as further SAR-guided optimization of this series will be reported in due course.

4. Experimental protocols

All reactions were carried out in oven-dried glassware in atmosphere of nitrogen. Melting points were measured with a BuchiB-520 melting point apparatus and are uncorrected. Thin-layer chromatography was carried out on Silufol UV-254 silica gel plates using an appropriate mixture of ethyl acetate and hexane. Compounds were visualized with short-wavelength UV light. ¹H NMR and ¹³C NMR spectra were recorded on Bruker MSL-300 spectrometers in DMSO-*d*₆ using TMS as an internal standard. Elemental analyses were obtained at Research Institute for Chemical Crop Protection (Moscow, Russia) using Carlo ErbaStrumentazione 1106 analyzer. Mass spectra were recorded using Shimadzu LCMS-2020 system with electron impact (EI) ionization. All reagents and solvents were obtained from commercial sources and used without purification.

4.1. Synthesis

4.1.1. General procedure 1 (GP1): preparation of 1,3-oxazoles 5a-f and 5j-o

An appropriate α -acylamino precursor (13.0 mmol) was added to 94% sulphuric acid. The reaction mixture was heated at 80 °C under stirring for 1.5 h, cooled to room temperature and poured into ice water (100 mL). The solution was neutralized with 28% aqueous ammonia and extracted with ethyl acetate (150 mL). The organic extract was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford desired analytically pure 1,3-oxazoles **5**.

4.1.2. General procedure 2 (GP2): preparation of 1,3-oxazoles 5g-i

An appropriate α -acylamino precursor (10.0 mmol) was added to phosphorus (V) oxychloride (130 mol). The reaction mixture was heated at 80 °C under stirring for 1.5 h, cooled to room temperature and poured over crushed ice. The precipitate formed was filtered off, washed with water, air-dried and further crystallized from acetonitrile to give desired analytically pure 1,3-oxazoles **5**.

4.1.3. 2-Methyl-5-Phenyl-1,3-oxazole (5a)

Yellow solid, m.p. 126–128°C, yield 82%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.21 (s, 1H, H_{oxazole}), 7.80 (d, J = 7.2 Hz, 2H, 2,6-H_{Ar}), 7.43 (t, J = 7.2 Hz, 2H, 3,5-H_{Ar}), 7.40 (t, J = 7.2 Hz, 1H, 4-H_{Ar}), 2.47 (s, 3H, CH₃); MS m/z (relative intensity) 159 (M⁺, 100), 118 (15), 117 (68), 116 (38), 105 (47), 89 (46), 90 (50), 76 (36), 77(42), 78(22), 63 (34), 43 (29), 39 (42), 32 (12); anal. calcd for C₁₀H₉NO (159.19): C, 75.45; H, 5.70; N, 8.80; found: C, 75.31; H, 5.60; N, 8.83.

4.1.4. 2-Cyclopropyl-5-phenyl-1,3-oxazole (5b)

Yellow solid, m.p. 123–125°C, yield 79%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.64 (d, J = 7.2 Hz, 2H, 2,6-H_{Ar}), 7.49 (s, 1H, H_{oxazole}), 7.43 (t, J = 7.2 Hz, 2H, 3,5-H_{Ar}), 7.32 (t, J = 7.2 Hz, 1H, 4-H_{Ar}), 2.16 (m, 1H, CH_{cyclopropyl}), 1.05 (m, 2H, H_{cyclopropyl}), 1.00 (m, 2H, H_{cyclopropyl}); MS m/z (relative intensity) 185 (M⁺, 100), 118 (15), 117 (42), 116 (23), 105 (62), 89 (60), 90 (73), 76 (12), 77(62), 78(23), 63 (14), 62 (23), 51 (45), 50 (42), 43 (26), 39 (42), 32 (32); anal. calcd for C₁₂H₁₁NO (185.23): C, 77.81; H, 5.99; N, 7.56; found: C, 77.73; H, 6.08; N, 7.53.

4.1.5. 2-Cyclobutyl-5-phenyl-1,3-oxazole (5c)

Yellow solid, m.p. 105–107°C, yield 73%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.66 (d, *J* = 7.2 Hz, 2H, 2,6-H_{Ar}), 7.56 (s, 1H, H_{oxazole}), 7.44 (t, *J* = 7.2 Hz, 2H, 3,5-H_{Ar}), 7.34 (t, *J* = 7.2 Hz, 1H, 4-H_{Ar}), 3.69 (m, 1H, CH_{cyclobutyl}), 2.36 (m, 2H, H_{cyclobutyl}), 2.33 (m, 2H, H_{cyclobutyl}), 2.07 (m, 1H, H_{cyclobutyl}), 1.92 (m, 1H, H_{cyclobutyl}); MS *m/z* (relative intensity) 199 (M⁺, 100), 145 (12), 118 (75), 89 (35), 90 (75), 76 (47), 77(86), 78(24), 63 (35), 62 (43), 51 (47), 50 (62), 43 (33), 39 (39), 32 (21); anal. calcd for C₁₃H₁₃NO (199.25): C, 78.36; H, 6.58; N, 7.03; found: C, 78.30; H, 6.53; N, 7.05.

4.1.6. 2-Methyl-5-(4-methylphenyl)-1,3-oxazole (5d)

Yellow solid, m.p. 110–112°C, yield 65%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.90 (s, 1H, H_{oxazole}), 7.69 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.29 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 2.34 (s, 3H, CH₃), 1.33 (s, 3H, CH₃); MS *m/z* (relative intensity) 173 (M⁺, 100), 131 (30), 130 (54), 119 (42), 132 (62), 116 (42), 115 (35), 104 (42), 103 (48), 77 (58), 77 (41), 67 (32), 65 (32), 43 (42), 39 (34), 32 (42); anal. calcd for C₁₁H₁₁NO (173.22): C, 76.27; H, 6.40; N, 8.09; found: C, 76.19; H, 6.41; N, 8.11.

4.1.7. 2-Cyclopropyl-5-(4-methylphenyl)-1,3-oxazole (5e)

Yellow solid, m.p. 122–124°C, yield 48%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.52 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.41 (s, 1H, H_{oxazole}), 7.24 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 2.32 (s, 3H, CH₃), 2.14 (m, 1H, CH_{cyclopropyl}), 1.05 (m, 2H, H_{cyclopropyl}), 1.00 (m, 1H, H_{cyclopropyl}); MS *m/z* (relative intensity) 199 (M⁺, 100), 131 (21), 130 (42), 119 (45), 117 (23), 116 (45), 115 (62), 104 (41), 103 (42), 77 (41), 77 (32), 67 (12), 65 (42), 43 (45), 39 (62), 32 (62); anal. calcd for C₁₃H₁₃NO (199.25): C, 78.37; H, 6.58; N, 7.03; found: C, 78.28; H, 6.58; N, 7.00.

4.1.8. 2-Cyclobutyl-5-(4-methylphenyl)-1,3-oxazole (5f)

Yellow solid, m.p. 82–84°C, yield 56%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.56 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.48 (s, 1H, H_{oxazole}), 7.26 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 3.68 (m, 1H, CH_{cyclobutyl}), 3.32 (s, 3H, CH₃), 2.35 (m, 2H, H_{cyclobutyl}), 2.33 (m, 2H, H_{cyclobutyl}), 2.05 (m, 1H, H_{cyclobutyl}), 1.93 (m, 1H, H_{cyclobutyl}); MS *m/z* (relative intensity) 213 (M⁺, 100), 159 (57), 131 (35), 130 (46), 119 (47), 117 (86), 116 (36), 115 (75), 104 (37), 77 (24), 67 (13), 65 (53), 43 (59), 39 (64), 32 (50); anal. calcd for C₁₄H₁₅NO (213.28): C, 78.84; H, 7.09; N, 6.57; found: C, 78.80; H, 7.20; N, 6.56.

4.1.9. 5-(4-Methoxyphenyl)-2-methyl-1,3-oxazole (5g)

Yellow solid, m.p. 115–117°C, yield 83%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.97 (s, 1H, H_{oxazole}), 7.57 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.03 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 3.79 (s, 3H, OCH₃), 2.45 (s, 3H, CH₃); MS *m/z* (relative intensity) 189 (M⁺, 100), 160 (53), 146 (24), 135 (86), 133 (24), 132 (67), 77 (24), 76 (54), 39 (54), 32 (24); anal. calcd for C₁₁H₁₁NO₂ (189.22): C, 69.82; H, 5.86; N, 7.40; found: C, 69.88; H, 5.91; N, 7.41.

4.1.10. 2-Cyclopropyl-5-(4-methoxyphenyl)-1,3-oxazole (5h)

Yellow solid, m.p. 102–104°C, yield 75%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.55 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.41 (s, 1H, H_{oxazole}), 7.01 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 3.70 (s, 3H, OCH₃), 2.13 (m, 1H, CH_{cyclopropyl}), 1.05 (m, 2H, H_{cyclopropyl}), 1.00 (m, 2H, H_{cyclopropyl}); MS *m/z* (relative intensity) 215 (M⁺, 100), 160 (35), 146 (42), 135 (16), 133 (76), 132 (83), 104 (28), 103 (29), 91 (31), 77 (21), 76 (23), 39 (27), 32 (41); anal. calcd for C₁₃H₁₃NO₂ (215.25): C, 72.54; H, 6.09; N, 6.51; found: C, 72.53; H, 6.02; N, 6.47.

4.1.11. 2-Cyclobutyl-5-(4-methoxyphenyl)-1,3-oxazole (5i)

Yellow solid, m.p. 113–115°C, yield 72%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.58 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.41 (s, 1H, H_{oxazole}), 7.11 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 3.60 (s, 3H, OCH₃), 3.65 (m, 1H, CH_{cyclobutyl}), 2.34 (m, 2H, H_{cyclobutyl}), 2.32 (m, 2H, H_{cyclobutyl}), 2.07 (m, 1H, H_{cyclobutyl}), 1.92 (m, 1H, H_{cyclobutyl}); MS *m/z* (relative intensity) 229 (M⁺, 100), 175 (41), 160 (24), 146 (41), 135 (15), 133 (52), 132 (25), 104 (31), 103 (25), 91 (42), 77 (24), 76 (63), 65 (57), 43 (12), 39 (54), 32 (12); anal. calcd for C₁₄H₁₅NO₂ (229.28): C, 73.34; H, 6.59; N, 6.11; found: C, 73.30; H, 6.55; N, 6.01.

4.1.12. 2-Methyl-5-(thiophen-2-yl)-1,3-oxazole (5j)

Brown solid, m.p. 98–100°C, yield 64%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.61 (dd, *J*₃₋₄ = 4.9 Hz, *J*₃₋₅ = 1.3 Hz, 1H, 3-H_{thiophene}), 7.39 (dd, *J*₄₋₅ = 3.6 Hz, *J*₃₋₅ = 1.3 Hz, 1H, 5-H_{thiophene}), 7.33 (s, 1H, H_{oxazole}), 7.14 (dd, *J*₃₋₄ = 4.9 Hz, *J*₄₋₅ = 3.6 Hz, 1H, 4-H_{thiophene}), 2.45 (s, 3H, CH₃); MS *m/z* (relative intensity) 165 (M⁺, 100), 123 (32), 122 (42), 111 (56), 109 (21), 108 (6), 97 (15), 70 (16), 69 (42), 58 (17), 57 (18), 45 (42), 39 (62), 38 (32), 32 (42), 30 (32); anal. calcd for C₈H₇NOS (165.22): C, 58.16; H, 4.27; N, 8.48; found: C, 58.02; H, 4.23; N, 8.45.

4.1.13. 2-Cyclopropyl-5-(thiophen-2-yl)-1,3-oxazole (5k)

Brown solid, m.p. 99–102°C, yield 73%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.60 (dd, *J*₃₋₄ = 4.9 Hz, *J*₃₋₅ = 1.3 Hz, 1H, 3-H_{thiophene}), 7.36 (dd, *J*₄₋₅ = 3.6 Hz, *J*₃₋₅ = 1.3 Hz, 1H, 5-H_{thiophene}), 7.30 (s, 1H, H_{oxazole}), 7.13 (dd, *J*₃₋₄ = 4.9 Hz, *J*₄₋₅ = 3.6 Hz, 1H, 4-H_{thiophene}), 2.14 (m, 1H, CH_{cyclopropyl}), 1.05 (m, 2H, H_{cyclopropyl}), 0.97 (m, 2H, H_{cyclopropyl}); MS *m/z* (relative intensity) 191 (M⁺, 100), 151 (52), 123 (12), 109 (39), 108 (46), 97 (35), 96 (53), 70 (12), 69 (35), 45 (76), 39 (34), 38 (97), 32 (65), 30 (45); anal. calcd for C₁₀H₉NOS (191.25): C, 62.80; H, 4.74; N, 7.32; found: C, 62.71; H, 4.80; N, 7.35.

4.1.14. 2-Cyclobutyl-5-(thiophen-2-yl)-1,3-oxazole (5l)

Brown solid, m.p. 92–105°C, yield 74%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.61 (dd, *J*₃₋₄ = 4.9 Hz, *J*₃₋₅ = 1.3 Hz, 1H, 3-H_{thiophene}), 7.40 (dd, *J*₄₋₅ = 3.6 Hz, *J*₃₋₅ = 1.3 Hz, 1H, 5-H_{thiophene}), 7.37 (s, 1H, H_{oxazole}), 7.14 (dd, *J*₃₋₄ = 4.9 Hz, *J*₄₋₅ = 3.6 Hz, 1H, 4-H_{thiophene}), 3.66 (m, 1H, CH_{cyclobutyl}), 2.34 (m, 2H, H_{cyclobutyl}), 2.32 (m, 2H, H_{cyclobutyl}), 2.05 (m, 1H, H_{cyclobutyl}), 1.90 (m, 1H, H_{cyclobutyl}); MS *m/z* (relative intensity) 205 (M⁺, 100), 151 (36), 123 (56), 122 (76), 111 (69), 109 (40), 69 (35), 58 (97),

57 (59), 45 (36), 39 (28), 38 (42), 32 (47), 30 (53); anal. calcd for C₁₁H₁₁NOS (205.28): C, 64.37; H, 5.40; N, 6.82; found: C, 64.32; H, 5.33; N, 6.85.

4.1.15. 2-Methyl-5-(thiophen-3-yl)-1,3-oxazole (5m)

Brown solid, m.p. 100–102°C, yield 68%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.74 (d, *J*₂₋₄ = 2.4 Hz, 1H, 2-H_{thiophene}), 7.67 (dd, *J*₂₋₄ = 5.1 Hz, *J*₄₋₅ = 2.4 Hz, 1H, 4-H_{thiophene}), 7.41 (d, *J*₄₋₅ = 2.4 Hz, 1H, 5-H_{thiophene}), 7.32 (s, 1H, H_{oxazole}), 2.45 (s, 3H, CH₃); MS *m/z* (relative intensity) 165 (M⁺, 100), 123 (42), 122 (41), 111 (23), 109 (21), 108 (42), 97 (16), 83 (22), 84 (23), 70(41), 69 (23), 45 (41), 39 (69), 38 (15), 32 (41), 30 (15); anal. calcd for C₈H₇NOS (165.22): C, 58.16; H, 4.27; N, 8.48; found: C, 58.09; H, 4.22; N, 8.47.

4.1.16. 2-Cyclopropyl-5-(thiophen-3-yl)-1,3-oxazole (5n)

Brown solid, m.p. 78–80°C, yield 67%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.72 (dd, *J*₂₋₄ = 3.0 Hz, *J*₂₋₅ = 1.2 Hz, 1H, 2-H_{thiophene}), 7.62 (dd, *J*₂₋₄ = 5.0 Hz, *J*₄₋₅ = 3.0 Hz, 1H, 4-H_{thiophene}), 7.40 (dd, *J*₄₋₅ = 5.0 Hz, *J*₂₋₅ = 1.2 Hz, 1H, 5-H_{thiophene}), 7.29 (s, 1H, H_{oxazole}), 2.13 (m, 1H, CH_{cyclopropyl}), 1.04 (m, 2H, H_{cyclopropyl}), 0.98 (m, 2H, H_{cyclopropyl}); MS *m/z* (relative intensity) 191 (M⁺, 100), 151 (35), 123 (35), 108 (83), 97 (13), 83 (45), 84 (64), 70 (34), 69 (75), 45 (35), 39 (65), 32 (44), 30 (35); anal. calcd for C₁₀H₉NOS (191.25): C, 62.80; H, 4.74; N, 7.32; found: C, 62.65; H, 4.79; N, 7.26.

4.1.17. 2-Cyclobutyl-5-(thiophen-3-yl)-1,3-oxazole (5o)

Brown solid, m.p. 92–105°C, yield 81%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.76 (dd, *J*₂₋₄ = 3.0 Hz, *J*₂₋₅ = 1.2 Hz, 1H, 2-H_{thiophene}), 7.67 (dd, *J*₂₋₄ = 5.0 Hz, *J*₄₋₅ = 3.0 Hz, 1H, 4-H_{thiophene}), 7.43 (dd, *J*₄₋₅ = 5.0 Hz, *J*₂₋₅ = 1.2 Hz, 1H, 5-H_{thiophene}), 7.36 (s, 1H, H_{oxazole}), 4.61 (m, 1H, CH_{cyclobutyl}), 2.34 (m, 4H, H_{cyclobutyl}), 2.03 (m, 1H, H_{cyclobutyl}), 1.92 (m, 1H, H_{cyclobutyl}); MS *m/z* (relative intensity) 205 (M⁺, 100), 151 (53), 123 (35), 122 (53), 111 (24), 84 (35), 70(36), 69 (46), 45 (64), 39 (83), 38 (14), 32 (46), 30 (68); anal. calcd for C₁₁H₁₁NOS (205.28): C, 64.36; H, 5.40; N, 6.82; found: C, 64.20; H, 5.32; N, 6.79.

4.1.18. General procedure 3 (GP3): preparation of 1,3-oxazoles 6a-j

The cyclodehydration step was carried out as described in GP3. The 1,3-oxazoles **5p-t** were promptly added to pyrrolidine or morpholine (100 mmol). The reaction mixture was heated at 50 °C under stirring for 2.5 h and cooled to room temperature. Water (150 mL) was added. The precipitate formed was filtered off, washed with water, air-dried and further crystallized from isopropyl alcohol to give desired analytically pure 1,3-oxazoles **6**.

4.1.19. (5-phenyl-1,3-oxazol-2-yl) (pyrrolidin-1-yl)methanone (6a)

Brown solid, m.p. 127–130°C, yield 85% (amidation step); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.80 (s, 1H, H_{oxazole}), 7.79 (d, *J* = 7.2 Hz, 2H, 2,6-H_{Ar}), 7.49 (t, *J* = 7.2 Hz, 2H, 3,5-H_{Ar}), 7.41 (t, *J* = 7.2 Hz, 1H, 4-H_{Ar}), 3.96 (t, *J* = 6.7 Hz, 2H, H_{pyrrolidine}), 3.55 (t, *J* = 6.7 Hz, 2H, H_{pyrrolidine}), 1.94 (t, *J* = 6.7 Hz, 4H, H_{pyrrolidine}); MS *m/z* (relative intensity) 242 (M⁺, 28), 116 (31), 105 (14), 102

(30), 98 (17), 89 (19), 77 (28), 70 (100), 56 (33), 55 (40), 42 (33), 41 (38), 39 (25), 29 (11); anal. calcd for C₁₄H₁₄N₂O₂ (242.28): C, 69.40; H, 5.82; N, 11.56; found: C, 69.36; H, 5.76; N, 11.49.

4.1.20. Morpholin-4-yl(5-phenyl-1,3-oxazol-2-yl)methanone (6b)

Brown solid, m.p. 93–96°C, yield 79% (amidation step); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.81 (s, 1H, H_{oxazole}), 7.79 (d, *J* = 7.2 Hz, 2H, 2,6-H_{Ar}), 7.50 (t, *J* = 7.2 Hz, 2H, 3,5-H_A), 7.42 (t, *J* = 7.2 Hz, 1H, 4-H_{Ar}), 4.12 (m, 2H, H_{morpholine}), 3.69 (m, 6H, H_{morpholine}); MS *m/z* (relative intensity) 258 (M⁺, 18), 172 (31), 171 (25), 116 (57), 114 (12), 105 (19), 102 (30), 89 (23), 86 (100), 77 (35), 70 (30), 63 (12), 56 (57), 42 (42), 41 (12), 39 (13), 30 (16), 29 (38); anal. calcd for C₁₄H₁₄N₂O₃ (258.28): C, 65.11; H, 5.46; N, 10.85; found: C, 65.01; H, 5.46; N, 10.87.

4.1.21. [5-(4-Methylphenyl)-1,3-oxazol-2-yl](pyrrolidin-1-yl)methanone (6c)

Yellow solid, m.p. 168–170°C, yield 82% (amidation step); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.83 (s, 1H, H_{oxazole}), 7.68 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.32 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 3.91 (m, 2H, H_{pyrrolidine}), 3.51 (m, 2H, H_{pyrrolidine}), 2.35 (s, 3H, CH₃), 1.89 (m, 4H, H_{pyrrolidine}); MS *m/z* (relative intensity) 256 (M⁺, 10), 130 (20), 119 (8), 116 (15), 115 (12), 98 (11), 91 (15), 77 (10), 70 (100), 56 (24), 55 (27), 42 (40), 41 (42), 39 (22), 29 (7); anal. calcd for C₁₅H₁₆N₂O₂ (256.31): C, 70.29; H, 6.29; N, 10.93; found: C, 70.20; H, 6.35; N, 10.94.

4.1.22. [5-(4-Methylphenyl)-1,3-oxazol-2-yl](morpholin-4-yl)methanone (6d)

Yellow solid, m.p. 157–159°C, yield 83% (amidation step); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.83 (s, 1H, H_{oxazole}), 7.68 (d, *J* = 7.9 Hz, 2H, H_{Ar}), 7.33 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 4.07 (m, 2H, H_{morpholine}), 3.67 (m, 6H, H_{morpholine}), 2.35 (s, 3H, CH₃); MS *m/z* (relative intensity) 272 (M⁺, 10), 186 (34), 185(34), 130 (60), 119 (17), 116 (33), 103 (19), 89 (9), 86 (100), 77 (17), 70(32), 63 (9), 56 (49), 42 (40), 41 (12), 39 (13), 30 (13), 29 (28); anal. calcd for C₁₅H₁₆N₂O₂ (272.31): C, 66.16; H, 5.92; N, 10.29; found: C, 66.08; H, 5.97; N, 10.28.

4.1.23. [5-(4-Methoxyphenyl)-1,3-oxazol-2-yl](pyrrolidin-1-yl)methanone (6e)

Yellow solid, m.p. 110–112°C, yield 79% (amidation step); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.72 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 7.64 (s, 1H, H_{oxazole}), 7.03 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 3.95 (m, 2H, H_{pyrrolidine}), 3.83 (s, 3H, OCH₃), 3.54 (m, 2H, H_{pyrrolidine}), 1.94 (m, 4H, H_{pyrrolidine}); MS *m/z* (relative intensity) 272 (M⁺, 21), 146 (15), 132 (15), 98 (13), 77 (6), 70 (100), 56 (19), 55 (25), 42 (23), 41 (22), 39 (10), 29 (7); anal. calcd for C₁₅H₁₆N₂O₃ (272.31): C, 66.16; H, 5.92; N, 10.29; found: C, 65.99; H, 5.92; N, 10.32.

4.1.24. [5-(4-Methoxyphenyl)-1,3-oxazol-2-yl](morpholin-4-yl)methanone (6f)

Yellow solid, m.p. 88–90°C, yield 79% (amidation step); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.72 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 7.67 (s, 1H, H_{oxazole}), 7.04 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 4.13 (m, 2H, H_{morpholine}), 3.89 (s, 3H, OCH₃), 3.68 (m, 6H, H_{morpholine}); MS *m/z* (relative intensity) 288 (M⁺, 28), 202 (14), 201 (18), 145 (39), 135 (11), 132 (29), 114 (11), 89 (7), 86 (100), 77 (11), 70 (31), 63 (6),

56 (47), 42 (28), 41 (7), 32 (16), 30 (9), 29 (26); anal. calcd for C₁₅H₁₆N₂O₄ (288.31): C, 62.49; H, 5.59; N, 9.72; found: C, 62.43; H, 5.63; N, 9.75.

4.1.25. Pyrrolidin-1-yl[5-(thiophen-2-yl)-1,3-oxazol-2-yl]methanone (6g)

Brown solid, m.p. 121–123°C, yield 80% (amidation step); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.74 (dd, *J*₃₋₄ = 4.9 Hz, *J*₃₋₅ = 1.0 Hz, 1H, 3-H_{thiophene}), 7.72 (s, 1H, H_{oxazole}), 7.58 (dd, *J*₄₋₅ = 3.6 Hz, *J*₃₋₅ = 1.0 Hz, 1H, 5-H_{thiophene}), 7.21 (dd, *J*₃₋₄ = 4.9 Hz, *J*₄₋₅ = 3.6 Hz, 1H, 4-H_{thiophene}), 3.90 (m, 2H, H_{pyrrolidine}), 3.50 (m, 2H, H_{pyrrolidine}), 1.88 (m, 4H, H_{pyrrolidine}); MS *m/z* (relative intensity) 248 (M⁺, 21), 122 (30), 111 (15), 108 (15), 98 (19), 70 (100), 56 (38), 55 (39), 45 (18), 42 (52), 41 (58), 39 (42), 29 (12); anal. calcd for C₁₂H₁₂N₂O₂S (248.31): C, 58.05; H, 4.87; N, 11.28; found: C, 57.97; H, 4.92; N, 11.30.

4.1.26. Morpholin-4-yl[5-(thiophen-2-yl)-1,3-oxazol-2-yl]methanone (6h)

Brown solid, m.p. 60–70°C, yield 73% (amidation step); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.74 (dd, *J*₃₋₄ = 4.9 Hz, *J*₃₋₅ = 1.0 Hz, 1H, 3-H_{thiophene}), 7.72 (s, 1H, H_{oxazole}), 7.59 (dd, *J*₄₋₅ = 3.6 Hz, *J*₃₋₅ = 1.0 Hz, 1H, 5-H_{thiophene}), 7.21 (dd, *J*₃₋₄ = 4.9 Hz, *J*₄₋₅ = 3.6 Hz, 1H, 4-H_{thiophene}), 4.06 (m, 2H, H_{morpholine}), 3.66 (m, 6H, H_{morpholine}); MS *m/z* (relative intensity) 264 (M⁺, 19), 178 (21), 177 (21), 122 (69), 114 (18), 111 (22), 108 (26), 95 (13), 86 (100), 70 (51), 69 (23), 58(15), 57(12), 56 (82), 45 (34), 42 (62), 41 (20), 39 (25), 30 (23), 29 (55); anal. calcd for C₁₂H₁₂N₂O₃S (264.31): C, 54.53; H, 4.58; N, 10.60; found: C, 54.41; H, 4.65; N, 10.53.

4.1.27. Pyrrolidin-1-yl[5-(thiophen-3-yl)-1,3-oxazol-2-yl]methanone (6i)

Brown solid, m.p. 134–136°C, yield 78% (amidation step); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.97 (s, 1H, H_{thiophene}), 7.73 (s, 1H, H_{thiophene}), 7.71 (s, 1H, H_{oxazole}), 7.52 (s, 1H, H_{thiophene}), 3.90 (m, 2H, H_{pyrrolidine}), 3.51 (m, 2H, H_{pyrrolidine}), 1.88 (m, 4H, H_{pyrrolidine}); MS *m/z* (relative intensity) 248 (M⁺, 19), 122 (25), 111 (16), 108 (17), 98 (16), 70 (100), 56 (29), 55 (31), 45 (20), 42 (36), 41 (40), 39 (30), 29 (9); anal. calcd for C₁₂H₁₂N₂O₂S (248.31): C, 58.05; H, 4.87; N, 11.28; found: C, 58.00; H, 4.92; N, 11.19.

4.1.28. Morpholin-4-yl[5-(thiophen-3-yl)-1,3-oxazol-2-yl]methanone (6j)

Brown solid, m.p. 103–105°C, yield 80% (amidation step); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.98 (s, 1H, H_{thiophene}), 7.74 (s, 1H, H_{thiophene}), 7.71 (s, 1H, H_{oxazole}), 7.52 (s, 1H, H_{thiophene}), 4.05 (m, 2H, H_{morpholine}), 3.66 (m, 6H, H_{morpholine}); MS *m/z* (relative intensity) 264 (M⁺, 26), 178 (32), 177 (29), 122 (57), 114 (15), 111 (23), 108 (33), 95 (8), 86 (100), 70 (53), 69 (9), 58 (11), 57(7), 56 (44), 45 (37), 42 (56), 41 (11), 39 (24), 30 (13), 29 (27); anal. calcd for C₁₂H₁₂N₂O₃S (264.31): C, 54.53; H, 4.58; N, 10.60; found: C, 54.50; H, 4.53; N, 10.66.

4.1.29. General procedure 4 (GP4): preparation of sulfonamides 9a-o and 10a-j

The starting 1,3-oxazole **5** or **6** (6.0 mmol) was added portion-wise to a cooled mixture of chlorosulfonic acid (60 mmol) and thionyl chloride (6.0 mmol). The resulting mixture was heated at

60°C for 2 h, cooled to room temperature and poured over crushed ice. The precipitate formed was filtered off, washed with water and dissolved in chloroform (100 mL). The solution was washed with 5% aqueous potassium carbonate, dried over anhydrous calcium chloride, filtered and concentrated. The residue was flash-chromatographed on silica gel using an appropriate gradient of ethyl acetate in hexanes as eluent. The intermediate sulfonyl chloride (**7** or **8**) was obtained as a viscous, slowly crystallizing oil. A portion of it (1.25 mmol) was dissolved in 1,4-dioxane (2.5 mL) and treated with 25% aqueous ammonia (0.56 mL, 7.5 mmol). The resulting mixture was heated at 75 °C for 2 h. The volatiles were removed in vacuo and the residue was treated with water (10 mL). The resulting precipitate was filtered off and crystallized from isopropyl alcohol to give sulfonamides **9** or **10**. The yield of sulfonamides is reported for two consecutive steps (sulfochlorination and sulfonamide synthesis).

4.1.30. 4-(2-Methyl-1,3-oxazol-5-yl)benzenesulfonamide (**9a**)

White solid, m.p. 221–224°C (*i*-PrOH), yield 72%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.88 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.84 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.70 (s, 1H, H_{oxazole}), 7.40 (s, 2H, NH₂), 2.49 (s, 3H, CH₃); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 162.64, 149.96, 144.04, 131.42, 127.39, 125.54, 124.71, 14.60; MS *m/z* (relative intensity) 238 (M⁺, 100), 174 (21), 158 (19), 130 (10), 120 (5), 103 (7), 77 (7), 76 (7), 63 (7), 54 (9), 50 (5), 43 (5), 27 (5); anal. calcd for C₁₀H₁₀N₂O₃S (238.27): C, 50.41; H, 4.23; N, 11.76; found: C, 50.36; H, 4.23; N, 11.80.

4.1.31. 4-(2-Cyclopropyl-1,3-oxazol-5-yl)benzenesulfonamide (**9b**)

White solid, m.p. 181–184°C (*i*-PrOH), yield 83%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.87 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.84 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.66 (s, 1H, H_{oxazole}), 7.39 (s, 2H, NH₂), 2.18 (m, 1H, CH_{cyclopropyl}), 1.06 (m, 4H, H_{cyclopropyl}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 162.46, 150.04, 144.16, 131.48, 127.39, 125.50, 124.66, 21.10, 9.90, 9.84; MS *m/z* (relative intensity) 264 (M⁺, 100), 263 (18), 238 (12), 200 (6), 184 (11), 129 (13), 128 (9), 89 (18), 80 (14), 77 (5), 76 (8), 75 (5), 63 (6), 53 (11), 52 (5), 51 (5), 50 (5), 41 (7), 39 (8), 27 (7); anal. calcd for C₁₂H₁₂N₂O₃S (264.31): C, 54.53; H, 4.58; N, 10.60; found: C, 54.48; H, 4.58; N, 10.62.

4.1.32. 4-(2-Cyclobutyl-1,3-oxazol-5-yl)benzenesulfonamide (**9c**)

White solid, m.p. 192–195°C (*i*-PrOH), yield 64%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.89 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.86 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.73 (s, 1H, H_{oxazole}), 7.40 (s, 2H, NH₂), 3.72 (quin, *J* = 8.3 Hz, 1H, CH_{cyclobutyl}), 2.18 (m, 4H, H_{cyclobutyl}), 2.06 (m, 1H, H_{cyclobutyl}), 1.94 (m, 1H, H_{cyclobutyl}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 167.98, 149.76, 144.09, 131.48, 127.38, 125.48, 124.81, 38.30, 33.20, 27.69, 18.99; MS *m/z* (relative intensity) 278 (M⁺, 30), 252 (6), 251 (16), 250 (100), 186 (9), 170 (13), 115 (8), 89 (15), 39 (8), 27 (5); anal. calcd for C₁₃H₁₄N₂O₃S (278.33): C, 56.10; H, 5.07; N, 10.06; found: C, 56.02; H, 5.08; N, 10.09.

4.1.33. 2-Methyl-5-(2-methyl-1,3-oxazol-5-yl)benzenesulfonamide (**9d**)

White solid, m.p. 195–198°C (*i*-PrOH), yield 71%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.10 (s, 1H, X-H_{Ar}), 7.77 (d, *J* = 7.7 Hz, 1H, B-H_{Ar}), 7.56 (s, 1H, H_{oxazole}), 7.47 (s, 2H, NH₂), 7.46 (d, *J* = 7.7 Hz, 1H, A-H_{Ar}), 2.60 (s, 3H, CH₃); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 161.96, 150.07, 143.74, 136.56, 133.95, 127.56, 126.52, 123.91, 122.86, 20.54, 14.54; MS *m/z* (relative intensity) 252 (M⁺, 76), 172 (27), 171 (100), 143 (10), 116 (23), 115 (21), 103 (17), 102 (25), 89 (16), 77 (21), 63 (11), 54 (14), 51 (10), 43 (11), 27 (9); anal. calcd for C₁₁H₁₂N₂O₃S (252.29): C, 52.37; H, 4.79; N, 11.10; found: C, 52.31; H, 4.79; N, 11.12.

4.1.34. 5-(2-Cyclopropyl-1,3-oxazol-5-yl)-2-methylbenzenesulfonamide (9e)

White solid, m.p. 175–177°C (*i*-PrOH), yield 80%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.07 (d, *J*_{BX} = 1.1 Hz, 1H, X-H_{Ar}), 7.75 (dd, *J*_{AB} = 8.1 Hz, *J*_{BX} = 1.1 Hz, 1H, B-H_{Ar}), 7.53 (s, 1H, H_{oxazole}), 7.47 (s, 2H, NH₂), 7.45 (d, *J*_{AB} = 8.1 Hz, 1H, A-H_{Ar}), 2.60 (s, 3H, CH₃), 2.18 (m, 1H, CH_{cyclopropyl}), 1.08 (m, 2H, H_{cyclopropyl}), 1.01 (m, 2H, H_{cyclopropyl}); ¹³C NMR (DMSO-*d*₆) δ ppm 166.32, 149.40, 143.74, 136.39, 133.92, 127.45, 126.52, 123.93, 122.74, 67.25, 20.55, 9.40, 9.04; MS *m/z* (relative intensity) 278 (M⁺, 100), 277 (10), 198 (21), 197 (91), 168 (13), 142 (13), 141 (24), 128 (15), 115 (11), 103 (16), 102 (19), 90 (12), 89 (26), 80 (24), 77 (26), 63 (15), 53 (26), 52 (13), 51 (14), 41 (20), 39 (21), 27 (19); anal. calcd for C₁₃H₁₄N₂O₃S (278.33): C, 56.10; H, 5.07; N, 10.06; found: C, 56.00; H, 5.07; N, 10.10.

4.1.35. 5-(2-Cyclobutyl-1,3-oxazol-5-yl)-2-methylbenzenesulfonamide (9f)

White solid, m.p. 170–173°C (*i*-PrOH), yield 75%; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.12 (d, *J*_{BX} = 1.2 Hz, 1H, X-H_{Ar}), 7.82 (dd, *J*_{AB} = 7.9, *J*_{BX} = 1.2 Hz, 1H, B-H_{Ar}), 7.63 (s, 1H, H_{oxazole}), 7.51 (m, 2H, NH₂), 7.48 (d, *J*_{AB} = 7.9 Hz, 1H, A-H_{Ar}), 3.73 (m, 1H, CH_{cyclobutyl}), 2.62 (s, 3H, CH₃), 2.38 (m, 4H, H_{cyclobutyl}), 2.07 (m, 1H, H_{cyclobutyl}), 1.95 (m, 1H, H_{cyclobutyl}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 165.91, 149.75, 143.55, 136.59, 133.48, 127.62, 126.31, 123.94, 122.52, 33.00, 26.98, 20.55, 19.01; MS *m/z* (relative intensity) 292 (M⁺, 43), 291 (9), 266 (6), 265 (15), 264 (100), 184 (16), 183 (79), 154 (6), 128 (13), 103 (5), 102 (7), 89 (6), 77 (8), 39 (7); anal. calcd for C₁₄H₁₆N₂O₃S (292.36): C, 57.52; H, 5.52; N, 9.58; found: C, 57.48; H, 5.52; N, 9.60.

4.1.36. 2-Methoxy-5-(2-methyl-1,3-oxazol-5-yl)benzenesulfonamide (9g)

White solid, m.p. 215–217°C (*i*-PrOH), yield 75%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.90 (d, *J*_{BX} = 1.9 Hz, 1H, X-H_{Ar}), 7.83 (dd, *J*_{AB} = 8.6, Hz, *J*_{BX} = 1.9 Hz, 1H, B-H_{Ar}), 7.41 (s, 1H, H_{oxazole}), 7.31 (d, *J*_{AB} = 8.6 Hz, 1H, A-H_{Ar}), 7.17 (s, 2H, NH₂), 3.94 (s, 3H, OCH₃), 2.50 (c, 3H, CH₃); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 165.74, 156.54, 149.38, 132.76, 129.79, 124.14, 122.00, 120.77, 114.45, 57.38, 12.46; MS *m/z* (relative intensity) 268 (M⁺, 100), 190 (5), 189 (12), 162 (6), 161 (6), 131 (7), 119 (5), 118 (6), 104 (7), 103 (5), 91 (5), 89 (17), 77 (6), 76 (11), 75 (6), 63 (8), 54 (8), 43 (10), 36 (7), 27 (5), 15 (7); anal. calcd for C₁₁H₁₂N₂O₄S (268.29): C, 49.25; H, 4.51; N, 10.44; found: C, 49.15; H, 4.51; N, 10.46.

4.1.37. 5-(2-Cyclopropyl-1,3-oxazol-5-yl)-2-methoxybenzenesulfonamide (9h)

White solid, m.p. 211–215°C (*i*-PrOH), yield 68%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.94 (d, *J*_{BX} = 1.8 Hz, 1H, X-H_{Ar}), 7.84 (dd, *J*_{AB} = 8.6 Hz, *J*_{BX} = 1.8 Hz, 1H, B-H_{Ar}), 7.45 (s, 1H, H_{oxazole}), 7.29 (d, *J*_{AB} = 8.6 Hz, 1H, A-H_{Ar}), 7.18 (s, 2H, NH₂), 3.94 (s, 3H, OCH₃), 2.17 (m, 1H, CH_{cyclopropyl}), 1.06 (m, 2H, H_{cyclopropyl}), 0.99 (m, 2H, H_{cyclopropyl}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 165.82, 156.51, 149.37, 132.72, 129.77, 123.65, 122.74, 120.71, 114.40, 67.23, 57.24, 9.37, 8.95; MS *m/z* (relative intensity) 294 (M⁺, 100), 293 (7), 279 (5), 215 (6), 129 (5), 128 (8), 115 (7), 89 (7), 80 (7), 76 (7), 53 (7), 41 (6), 39 (6), 27 (6); anal. calcd for C₁₃H₁₄N₂O₄S (294.33): C, 53.05; H, 4.79; N, 9.52; found: C, 52.96; H, 4.80; N, 9.54.

4.1.38. 5-(2-Cyclobutyl-1,3-oxazol-5-yl)-2-methoxybenzenesulfonamide (9i)

White solid, m.p. 175–177°C (*i*-PrOH), yield 69%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.97 (d, *J*_{BX} = 2.0 Hz, 1H, X-H_{Ar}), 7.88 (dd, *J*_{AB} = 8.7 Hz, *J*_{BX} = 2.0 Hz, 1H, B-H_{Ar}), 7.52 (s, 1H, H_{oxazole}), 7.31 (d, *J*_{AB} = 8.7 Hz, 1H, A-H_{Ar}), 7.18 (s, 2H, NH₂), 3.94 (s, 3H, OCH₃), 3.70 (m, 1H, CH_{cyclobutyl}), 2.35 (m, 4H, H_{cyclobutyl}), 2.04 (m, 1H, H_{cyclobutyl}), 1.93 (m, 1H, H_{cyclobutyl}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 166.84, 156.63, 149.84, 132.70, 129.97, 123.80, 122.68, 120.72, 114.42, 57.24, 33.14, 27.69, 18.99; MS *m/z* (relative intensity) 308 (M⁺, 25), 282 (5), 281 (14), 280 (100), 225 (6), 201 (7), 115 (5), 89 (11), 76 (7), 55 (6), 39 (9), 27 (7); anal. calcd for C₁₄H₁₆N₂O₄S (308.36): C, 54.53; H, 5.23; N, 9.08; found: C, 54.49; H, 5.23; N, 9.08.

4.1.39. 5-(2-Methyl-1,3-oxazol-5-yl)thiophene-2-sulfonamide (9j)

White solid, m.p. 154–157°C (*i*-PrOH), yield 76%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.78 (s, 2H, NH₂), 7.55 (s, 1H, H_{oxazole}), 7.54 (d, *J* = 4.0 Hz, 1H, H_{thiophene}), 7.38 (d, *J* = 4.0 Hz, 1H, H_{thiophene}), 2.48 (s, 3H, CH₃); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 162.26, 145.31, 134.09, 131.76, 125.03, 124.57, 14.48; MS *m/z* (relative intensity) 244 (M⁺, 100), 189 (25), 180 (12), 164 (7), 152 (16), 136 (12), 111 (6), 110 (8), 109 (59), 95 (37), 93 (7), 83 (6), 82 (15), 69 (12), 64 (7), 54 (20), 53 (7), 52 (5), 45 (16), 43 (25), 39 (6), 38 (5), 27 (11), 26 (6), 15 (5); anal. calcd for C₈H₈N₂O₃S₂ (244.29): C, 39.33; H, 3.30; N, 11.47; found: C, 39.28; H, 3.30; N, 11.45.

4.1.40. 5-(2-Cyclopropyl-1,3-oxazol-5-yl)thiophene-2-sulfonamide (9k)

White solid, m.p. 140–142°C (*i*-PrOH), yield 69%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.79 (s, 2H, NH₂), 7.55 (s, 1H, H_{oxazole}), 7.53 (s, 1H, H_{thiophene}), 7.45 (s, 1H, H_{thiophene}), 2.16 (m, 1H, CH_{cyclopropyl}), 1.08 (m, 2H, H_{cyclopropyl}), 1.02 (m, 2H, H_{cyclopropyl}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 162.19, 145.34, 133.97, 131.24, 125.24, 124.20, 65.83, 10.49, 10.05; MS *m/z* (relative intensity) 270 (M⁺, 100), 269 (16), 268 (16), 244 (10), 190 (19), 162 (7), 135 (55), 134 (19), 123 (5), 98 (7), 95 (14), 91 (10), 82 (16), 80 (21), 69 (7), 54 (5), 53 (23), 52 (9), 51 (10), 45 (11), 41 (16), 39 (17), 38 (10), 29 (9), 27 (23), 26 (7), 15 (7); anal. calcd for C₁₀H₁₀N₂O₃S₂ (270.33): C, 44.43; H, 3.73; N, 10.36; found: C, 44.35; H, 3.73; N, 10.32.

4.1.41. 5-(2-Cyclobutyl-1,3-oxazol-5-yl)thiophene-2-sulfonamide (9l)

White solid, m.p. 149–152°C (*i*-PrOH), yield 78%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.78 (s, 2H, NH₂), 7.59 (s, 1H, H_{oxazole}), 7.54 (d, *J* = 4.0 Hz, 1H, H_{thiophene}), 7.40 (d, *J* = 4.0 Hz, 1H, H_{thiophene}), 3.69 (quin, *J* = 8.33 Hz, 1H, CH_{cyclobutyl}), 2.35 (m, 4H, H_{cyclobutyl}), 2.04 (m, 1H, H_{cyclobutyl}), 1.93 (m, 1H, H_{cyclobutyl}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 167.59, 145.37, 145.11, 134.12, 131.72, 124.96, 124.69, 33.02, 27.66, 18.98; MS *m/z* (relative intensity) 284 (M⁺, 33), 283 (5), 258 (12), 257 (14), 256 (100), 201 (12), 192 (5), 164 (7), 148 (7), 121 (18), 95 (15), 94 (5), 66 (6), 64 (5), 55 (11), 45 (7), 39 (11), 29 (6), 27 (10); anal. calcd for C₁₁H₁₂N₂O₃S₂ (284.36): C, 46.46; H, 4.25; N, 9.85; found: C, 46.43; H, 4.25; N, 9.87.

4.1.42. 4-(2-Methyl-1,3-oxazol-5-yl)thiophene-2-sulfonamide (9m)

White solid, m.p. 182–185°C (*i*-PrOH), yield 81%; ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 7.98 (d, *J* = 1.3 Hz, 1H, H_{thiophene}), 7.84 (d, *J* = 1.3 Hz, 1H, H_{thiophene}), 7.76 (s, 2H, NH₂), 7.47 (s, 1H, H_{oxazole}), 2.46 (s, 3H, CH₃); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 165.80, 148.18, 146.39, 129.21, 127.57, 125.27, 123.84, 9.01; MS *m/z* (relative intensity) 244 (M⁺, 100), 216 (8), 190 (7), 189 (28), 175 (9), 173 (16), 164 (6), 136 (14), 125 (11), 123 (7), 110 (7), 109 (22), 108 (7), 97 (7), 95 (32), 93 (7), 83 (5), 82 (19), 81 (5), 69 (12), 64 (9), 54 (26), 53 (8), 52 (7), 51 (7), 50 (5), 45 (26), 43 (18), 39 (8), 38 (8), 27 (16), 26 (7), 15 (5); anal. calcd for C₈H₈N₂O₃S₂ (244.29): C, 39.33; H, 3.30; N, 11.47; found: C, 39.32; H, 3.30; N, 11.50.

4.1.43. 4-(2-Cyclopropyl-1,3-oxazol-5-yl)thiophene-2-sulfonamide (9n)

White solid, m.p. 150–153°C (*i*-PrOH), yield 75%; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.98 (d, *J* = 1.2 Hz, 1H, H_{thiophene}), 7.85 (d, *J* = 1.2 Hz, 1H, H_{thiophene}), 7.79 (s, 2H, NH₂), 7.46 (s, 1H, H_{oxazole}), 2.17 (m, 1H, CH_{cyclopropyl}), 1.08 (m, 2H, H_{cyclopropyl}), 1.01 (m, 2H, H_{cyclopropyl}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 165.80, 148.18, 146.39, 129.21, 127.57, 125.27, 123.84, 67.23, 9.37, 9.01; MS *m/z* (relative intensity) 270 (M⁺, 100), 269 (16), 268 (13), 244 (11), 241 (5), 190 (14), 189 (5), 162 (6), 136 (5), 135 (41), 134 (14), 133 (6), 123 (6), 110 (5), 98 (5), 95 (18), 91 (11), 83 (5), 82 (15), 81 (5), 80 (19), 69 (12), 64 (8), 54 (11), 53 (26), 52 (14), 51 (11), 50 (7), 45 (19), 43 (6), 41 (19), 39 (25), 38 (8), 29 (11), 27 (26), 26 (6), 15 (6); anal. calcd for C₁₀H₁₀N₂O₃S₂ (270.33): C, 44.43; H, 3.73; N, 10.36; found: C, 44.40; H, 3.73; N, 10.35.

4.1.44. 4-(2-Cyclobutyl-1,3-oxazol-5-yl)thiophene-2-sulfonamide (9o)

White solid, m.p. 169–173°C (*i*-PrOH), yield 70%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.00 (d, *J* = 1.5 Hz, 1H, H_{thiophene}), 7.85 (d, *J* = 1.5 Hz, 1H, H_{thiophene}), 7.76 (s, 2H, NH₂), 7.51 (s, 1H, H_{oxazole}), 3.68 (m, 1H, CH_{cyclobutyl}), 2.34 (m, 4H, H_{cyclobutyl}), 2.04 (m, 1H, H_{cyclobutyl}), 1.92 (m, 1H, H_{cyclobutyl}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 166.85, 148.22, 146.85, 129.25, 127.67, 125.61, 123.77, 33.10, 27.66, 18.98; MS *m/z* (relative intensity) 284 (M⁺, 31), 283 (7), 258 (12), 257 (14), 256 (100), 228 (6), 201 (18), 148 (7), 121 (21), 95 (13), 82 (8), 66 (8), 64 (6), 55 (9), 53 (5), 45

(11), 41 (5), 39 (17), 29 (8), 27 (11); anal. calcd for C₁₁H₁₂N₂O₃S₂ (284.36): C, 46.46; H, 4.25; N, 9.85; found: C, 46.45; H, 4.26; N, 9.84.

4.1.45. 4-[2-(Pyrrolidin-1-ylcarbonyl)-1,3-oxazol-5-yl]benzenesulfonamide (10a)

White solid, m.p. 265–267°C (*i*-PrOH), yield 65%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.06 (s, 1H, H_{oxazole}), 7.99 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.84 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.46 (s, 2H, NH₂), 3.93 (t, *J* = 6.7 Hz, 2H, H_{pyrrolidine}), 3.53 (t, *J* = 6.7 Hz, 2H, H_{pyrrolidine}), 1.93 (m, 2H, H_{pyrrolidine}), 1.87 (m, 2H, H_{pyrrolidine}); ¹³C NMR (75 MHz, DMSO-*d*₆) δ ppm 155.50, 154.24, 150.77, 144.79, 130.06, 127.10, 125.77, 125.43, 49.03, 47.38, 26.39, 23.83; MS *m/z* (relative intensity) 321 (M⁺, 22), 98 (11), 70 (100), 56 (14), 55 (20), 42 (5), 41 (5); anal. calcd for C₁₄H₁₅N₃O₄S (321.36): C, 52.33; H, 4.70; N, 13.08; found: C, 52.32; H, 4.71; N, 13.10.

4.1.46. 4-[2-(Morpholin-4-ylcarbonyl)-1,3-oxazol-5-yl]benzenesulfonamide (10b)

White solid, m.p. 190–193°C (*i*-PrOH), yield 70%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.05 (s, 1H, H_{oxazole}), 7.98 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.94 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.45 (br. s., 2H, NH₂), 4.05 (m, 2H, H_{morpholin}), 3.67 (m, 6H, H_{morpholine}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 155.58, 154.83, 151.26, 145.23, 130.35, 127.51, 125.86, 125.76, 67.19, 66.84, 47.93, 43.53; MS *m/z* (relative intensity) 337 (M⁺, 5), 251 (16), 250 (21), 181 (8), 131 (6), 115 (6), 114 (12), 87 (6), 86 (100), 72 (5), 70 (24), 56 (18), 42 (16), 29 (5); anal. calcd for C₁₄H₁₅N₃O₅S (337.36): C, 49.85; H, 4.48; N, 12.46; found: C, 49.80; H, 4.49; N, 12.40.

4.1.47. 2-Methyl-5-[2-(pyrrolidin-1-ylcarbonyl)-1,3-oxazol-5-yl]benzenesulfonamide (10c)

White solid, m.p. 247–250°C (*i*-PrOH), yield 63%; ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.24 (d, *J*_{BX} = 1.2 Hz, 1H, X-H_{Ar}), 7.98 (s, 1H, H_{oxazole}), 7.94 (dd, *J*_{AB} = 7.9, Hz, *J*_{BX} = 1.2 Hz, 1H, B-H_{Ar}), 7.56 (s, 2H, NH₂), 7.55 (d, *J*_{AB} = 8.6 Hz, 1H, A-H_{Ar}), 3.94 (t, *J* = 6.7 Hz, 2H, H_{pyrrolidin}), 3.55 (t, *J* = 6.7 Hz, 2H, H_{pyrrolidin}), 2.66 (s, 3H, OCH₃), 1.95 (m, 2H, H_{pyrrolidine}), 1.89 (m, 2H, H_{pyrrolidine}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 155.73, 153.99, 151.37, 143.69, 137.81, 134.38, 128.58, 125.47, 124.16, 123.79, 49.12, 47.07, 26.56, 24.23, 20.69; MS *m/z* (relative intensity) 335 (M⁺, 23), 98 (13), 70 (100), 56 (12), 55 (20), 44 (5); anal. calcd for C₁₅H₁₇N₃O₄S (335.38): C, 53.72; H, 5.11; N, 12.53; found: C, 53.58; H, 5.11; N, 12.55.

4.1.48. 2-Methyl-5-[2-(morpholin-4-ylcarbonyl)-1,3-oxazol-5-yl]benzenesulfonamide (10d)

White solid, m.p. 239–242°C (*i*-PrOH), yield 61%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.21 (d, *J*_{BX} = 1.7 Hz, 1H, X-H_{Ar}), 7.92 (s, 1H, H_{oxazole}), 7.91 (dd, *J*_{AB} = 7.9, Hz, *J*_{BX} = 1.2 Hz, 1H, B-H_{Ar}), 7.54 (d, *J*_{AB} = 8.6 Hz, 1H, A-H_{Ar}), 7.53 (s, 2H, NH₂), 4.07 (m, 2H, H_{morpholine}), 3.67 (m, 6H, H_{morpholine}), 2.63 (s, 3H, CH₃); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 155.58, 154.36, 151.44, 143.93, 138.07, 134.17, 128.58, 125.47, 124.38, 123.79, 67.19, 66.85, 47.93, 43.53, 20.66; MS *m/z* (relative intensity) 351 (M⁺, 19), 266 (6), 265 (24), 264 (35), 252 (6), 130 (8), 128 (6), 114 (20), 87

(5), 86 (100), 70 (23), 56 (13), 42 (12); anal. calcd for C₁₅H₁₇N₃O₅S (351.38): C, 51.27; H, 4.88; N, 11.96; found: C, 51.25; H, 4.88; N, 11.97.

4.1.49. 2-Methoxy-5-[2-(pyrrolidin-1-ylcarbonyl)-1,3-oxazol-5-yl]benzenesulfonamide (10e)

White solid, m.p. 275–278°C (*i*-PrOH), yield 69%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.09 (s, 1H, X-H_{Ar}), 8.00 (d, *J* = 8.4 Hz, 1H, B-H_{Ar}), 7.89 (s, 1H, H_{oxazole}), 7.38 (d, *J* = 8.4 Hz, 1H, A-H_{Ar}), 7.24 (br. s., 2H, NH₂), 3.97 (s, 3H, OCH₃), 3.92 (t, *J* = 6.4 Hz, 2H, H_{pyrrolidine}), 3.52 (t, *J* = 6.4 Hz, 2H, H_{pyrrolidine}), 1.89 (m, 4H, H_{pyrrolidine}); ¹³C NMR (75 MHz, DMSO-*d*₆) δ ppm 157.10, 154.68, 154.29, 151.04, 132.55, 130.52, 124.34, 123.32, 119.19, 114.22, 56.95, 49.03, 47.34, 26.42, 23.82; MS *m/z* (relative intensity) 351 (M⁺, 10), 211 (6), 98 (15), 70 (100), 56 (13), 55 (25), 29 (5); anal. calcd for C₁₅H₁₇N₃O₅S (351.38): C, 51.27; H, 4.88; N, 11.96; found: C, 51.21; H, 4.88; N, 11.95.

4.1.50. 2-Methoxy-5-[2-(morpholin-4-ylcarbonyl)-1,3-oxazol-5-yl]benzenesulfonamide (10f)

White solid, m.p. 198–201°C (*i*-PrOH), yield 72%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.09 (d, *J*_{BX} = 2.2 Hz, 1H, X-H_{Ar}), 8.00 (dd, *J*_{AB} = 8.7, *J*_{BX} = 2.2 Hz, 1H, B-H_{Ar}), 7.89 (s, 1H, H_{oxazole}), 7.38 (d, *J*_{AB} = 8.77 Hz, 1H, A-H_{Ar}), 7.23 (br. s., 2H, NH₂), 4.08 (m, 2H, H_{morpholine}), 3.97 (s, 3H, OCH₃), 3.67 (m, 6H, H_{morpholine}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 157.53, 155.56, 153.96, 151.52, 132.90, 130.95, 124.75, 123.30, 119.46, 114.62, 67.19, 66.87, 57.36, 47.91, 43.52; MS *m/z* (relative intensity) 367 (M⁺, 31), 282 (7), 281 (26), 280 (49), 268 (8), 254 (7), 225 (14), 211 (16), 114 (16), 87 (5), 86 (100), 70 (28), 56 (11), 44 (5), 42 (11); anal. calcd for C₁₅H₁₇N₃O₆S (367.38): C, 49.04; H, 4.66; N, 11.44; found: C, 49.00; H, 4.67; N, 11.45.

4.1.51. 5-[2-(Pyrrolidin-1-ylcarbonyl)-1,3-oxazol-5-yl]thiophene-2-sulfonamide (10g)

White solid, m.p. 226–229°C (*i*-PrOH), yield 70%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.92 (s, 1H, H_{oxazole}), 7.86 (s, 2H, NH₂), 7.60 (d, *J* = 3.8 Hz, 1H, H_{thiophene}), 7.58 (d, *J* = 3.8 Hz, 1H, H_{thiophene}), 3.90 (t, *J* = 6.7 Hz, 2H, H_{pyrrolidine}), 3.51 (t, *J* = 6.7 Hz, 2H, H_{pyrrolidine}), 1.90 (m, 4H, H_{pyrrolidine}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 155.27, 154.34, 147.03, 146.63, 132.82, 131.83, 126.72, 125.62, 49.45, 47.82, 26.81, 24.23; MS *m/z* (relative intensity) 327 (M⁺, 12), 98 (24), 71 (7), 70 (100), 56 (24), 55 (39), 42 (7), 41 (6); anal. calcd for C₁₂H₁₃N₃O₄S₂ (327.38): C, 44.03; H, 4.00; N, 12.84; found: C, 43.98; H, 4.01; N, 12.85.

4.1.52. 5-[2-(Morpholin-4-ylcarbonyl)-1,3-oxazol-5-yl]thiophene-2-sulfonamide (10h)

White solid, m.p. 188–191°C (*i*-PrOH), yield 73%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.91 (s, 1H, H_{oxazole}), 7.86 (s, 2H, NH₂), 7.60 (d, *J* = 3.8 Hz, 1H, H_{thiophene}), 7.58 (d, *J* = 3.8 Hz, 1H, H_{thiophene}), 4.03 (m, 2H, H_{morpholine}), 3.66 (m, 6H, H_{morpholine}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 155.27, 154.22, 147.09, 146.70, 132.67, 131.82, 126.81, 125.19, 67.14, 66.82, 47.93, 43.53; MS *m/z* (relative intensity) 343 (M⁺, 12), 258 (6), 257 (17), 256 (30), 201 (7), 187 (11), 137 (6), 114 (22), 86 (100), 72 (6), 70 (40), 64 (8), 56 (21), 45 (6), 42 (25), 29 (6); anal. calcd for C₁₂H₁₃N₃O₅S₂ (343.38): C, 41.97; H, 3.82; N, 12.24; found: C, 41.95; H, 3.82; N, 12.26.

4.1.53. 4-[2-(Pyrrolidin-1-ylcarbonyl)-1,3-oxazol-5-yl]thiophene-2-sulfonamide (10i)

White solid, m.p. 268–271°C (*i*-PrOH), yield 64%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.20 (d, *J* = 1.2 Hz, 1H, H_{thiophene}), 7.96 (d, *J* = 1.2 Hz, 1H, H_{thiophene}), 7.81 (s, 1H, H_{oxazole}), 7.86 (s, 2H, NH₂), 3.91 (t, *J* = 6.7 Hz, 2H, H_{pyrrolidine}), 3.51 (t, *J* = 6.7 Hz, 2H, H_{pyrrolidine}), 1.89 (m, 4H, H_{pyrrolidine}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 154.94, 154.59, 148.63, 148.21, 127.94, 124.75, 49.47, 47.79, 26.82, 24.24; MS *m/z* (relative intensity) 327 (M⁺, 1), 187 (9), 98 (14), 70 (100), 56 (17), 55 (25), 42 (6), 41 (5); anal. calcd for C₁₂H₁₃N₃O₄S₂ (327.38): C, 44.03; H, 4.00; N, 12.84; found: C, 44.01; H, 4.00; N, 12.82.

4.1.54. 4-[2-(Morpholin-4-ylcarbonyl)-1,3-oxazol-5-yl]thiophene-2-sulfonamide (10j)

White solid, m.p. 226–229°C (*i*-PrOH), yield 68%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.20 (d, *J* = 1.2 Hz, 1H, H_{thiophene}), 7.96 (d, *J* = 1.2 Hz, 1H, H_{thiophene}), 7.81 (s, 1H, H_{oxazole}), 7.86 (s, 2H, NH₂), 4.05 (m, 2H, H_{morpholine}), 3.67 (m, 6H, H_{morpholine}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm 155.50, 153.85, 148.66, 148.27, 128.11, 127.94, 124.31, 67.19, 66.85, 47.91, 43.52; MS *m/z* (relative intensity) 343 (M⁺, 8), 258 (6), 257 (21), 256 (28), 201 (16), 187 (13), 114 (14), 86 (100), 70 (33), 56 (18), 45 (7), 42 (21), 29 (5); anal. calcd for C₁₂H₁₃N₃O₅S₂ (343.38): C, 41.97; H, 3.82; N, 12.24; found: C, 41.92; H, 3.82; N, 12.28.

4.2. Carbonic anhydrase inhibition assay

An Applied Photophysics stopped-flow instrument has been used for assaying the CA catalyzed CO₂ hydration activity [23]. Phenol red (at a concentration of 0.2 mM) has been used as indicator, working at the absorbance maximum of 557 nm, with 20 mM Tris (pH 8.3) as buffer, and 20 mM Na₂SO₄ (for maintaining constant the ionic strength), following the initial rates of the CA-catalyzed CO₂ hydration reaction for a period of 10–100 s. The CO₂ concentrations ranged from 1.7 to 17 mM for the determination of the kinetic parameters and inhibition constants. For each inhibitor at least six traces of the initial 5–10% of the reaction have been used for determining the initial velocity. The uncatalyzed rates were determined in the same manner and subtracted from the total observed rates. Stock solutions of inhibitor (0.1 mM) were prepared in distilled-deionized water and dilutions up to 0.005 nM were done thereafter with the assay buffer. Inhibitor and enzyme solutions were preincubated together for 15 min at room temperature prior to assay, in order to allow for the formation of the E–I complex. The inhibition constants were obtained by non-linear least-squares methods using PRISM 3 and the Cheng–Prusoff equation, as reported earlier, and represent the mean from at least three different determinations. All CA isoforms were recombinant ones obtained in-house [24]b), [24]c), [24]d), [24], [24]a).

4.3. Docking studies

The crystal structures of *hCA I* (pdb code 1AZM) [25], *hCA II* (pdb code 2AW1) [26], *hCA IX* (pdb code 3IAI) [27], and *hCA XII* (pdb code 1JD0) [28] were taken from the Protein Data Bank [29]. After adding hydrogen atoms and removing complexed ligands, the four proteins were minimized using Amber 11 software [30] and parm03 force field at 300 K. The four proteins were placed in a rectangular parallelepiped water box, an explicit solvent model for water, TIP3P, was used and the complexes were solvated with a 10 Å water cap. Sodium ions were added as counter ions to neutralize the system. Two steps of minimization were then carried out; in the first stage, we kept the protein fixed with a position restraint of 500 kcal/mol•Å² and we solely minimized the positions of the water molecules. In the second stage, we minimized the entire system through 5000 steps of steepest descent followed by conjugate gradient until a convergence of 0.05 kcal/Å•mol. The region of interest used by the docking program GOLD version 5.1 was defined in order to contain the residues within 15 Å from the original position of the ligand in the X-ray structure. Metal coordination in GOLD is modeled as ‘pseudohydrogen bonding’ in which metals can be considered to bind to H-bond acceptors and the metal will compete with H-bond donors for interaction. The catalytic zinc ion was set to have a tetrahedral coordination geometry. The ‘allow early termination’ option was deactivated, while the possibility for the ligand to flip ring corners was activated. The remaining GOLD default parameters were used, and the ligands were submitted to 30 genetic algorithm runs. The docking analysis was carried out using the ChemScore fitness function imposing the formation of an H bond between the ligands and the hydroxy group of the highly conserved residue T192 (CA II sequence numbering) [31], [31](a), [31](b). Cluster analysis was performed on the results using an rmsd tolerance of 2.0 Å and the best docked conformation was taken into account.

Acknowledgements

This research was supported by the Russian Scientific Fund (project grant 14-50-00069).

Appendix A. Supplementary data.

Supplementary data related to this article can be found at <http://dx.doi.org/...>

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