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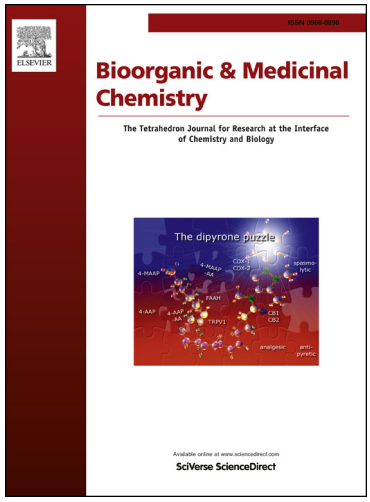

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Inhibition of carbonic anhydrase isoforms I, II, IV, VII and XII with carboxylates and sulfonamides incorporating phthalimide/phthalic anhydride scaffolds

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Abstract. We report a panel of carboxylates and sulfonamides incorporating phthalic anhydride and phthalimide moieties in their structure and their interaction with the metalloenzyme carbonic anhydrase (CA, EC 4.2.1.1). They were synthesized from substituted anthranilic acids and trimellitic anhydride chloride, followed by reaction with primary amines and were tested for the inhibition of five physiologically relevant CA isoforms, the human (h) hCA I, II, IV, VII and XII, some of which are involved in serious pathologies (CA II, IV and XII in glaucoma; CA VII in epilepsy; CA XII in some solid tumors). The carboxylic acids were generally poor inhibitors of isoforms hCA I, II and IV but were highly effective, low nanomolar inhibitors of hCA VII and XII. The sulfonamides inhibited all isoforms significantly, and some of them were sub-nanomolar hCA VII inhibitors, although their isoform selectivity was lower compared to the carboxylates. This study proves that carboxylic acids incorporating a phthalic anhydride/phthalimide based scaffold may lead to isoform-selective inhibitors by applying the tail approach, mostly used up until now for obtaining sulfonamide, sulfamide and sulfamate CA inhibitors.

Keywords: carbonic anhydrase; sulfonamide; carboxylic acid; isoform-selectivity

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1. Introduction

Primary sulfonamides (RSO_2NH_2) incorporating aromatic, heterocyclic, aliphatic or sugar R scaffolds, represent the most investigated class of inhibitors of the metalloenzyme carbonic anhydrase (CA, EC 4.2.1.1).[1-3] The reason for this is that CA inhibition with sulfonamides was already discovered in the '40s, the first such compounds entered in clinical use as diuretics and antiglaucoma drugs in the '50s, whereas more recently sulfonamide CA inhibitors (CAIs) proved to be useful for the management of a variety of disorders, such as obesity, epilepsy and other neurologic diseases, solid, metastatic tumors or neuropathic pain.[1-3] The complex pharmacology of the CAIs is due to the fact that a large number of human (h) isoforms are known, i.e., 15, numbered as hCA I - hCA XIV (but there are two V-type isoforms, hCA VA and VB), and because they possess different roles in various pathologies, as the ones mentioned above.[1-4] However, the principal drawback of this class of valuable drugs is related to their many side effects, due to the fact that most mammalian isoforms are rather well inhibited by the first and second generation sulfonamide CAIs, which are still nowadays in clinical use.[1-3] Thus, many efforts were registered ultimately for finding alternative chemotypes to the sulfonamides, and the carboxylic acids are among the most investigated such compounds.[3,4] Indeed, the carboxylates, (unlike the sulfonamides which inhibit CAs by coordinating to the Zn(II) ion from the enzyme active site and replacing the hydroxide ion acting as nucleophile in the catalysis)[1-3] were shown to possess a multitude of inhibition mechanisms.[1-4] Some of them, similarly to sulfonamides, directly coordinate to the Zn(II) ion, but other structurally similar carboxylic acids were shown to anchor to the zinc-coordinated water molecule/hydroxide ion, or occlude the entrance to the active site cavity, or even binding outside the active site.[4-7] Although at this moment it is impossible to forecast the mechanism by which a carboxylic acid will inhibit the CAs (except the

compounds formed from coumarins, which acting as prodrug CAIs undergo a hydrolysis within the active site with generation of derivatives of 2-hydroxy-cinnamic acid which all occlude the entrance to the active site)[5-7] their multiple binding modes to the enzyme certainly assure a variety of inhibitory profiles against the various CA isoforms, and thus a high level of isoform-selectivity. This is the reason why we continue our earlier investigation[8] on carboxylates *versus* sulfonamides as CAIs, reporting here the synthesis and inhibitory profile against five physiologically relevant isoforms (hCA I, II, IV, VII and XII) of a new series of such derivatives incorporating phthalimide/phthalic anhydride scaffolds.

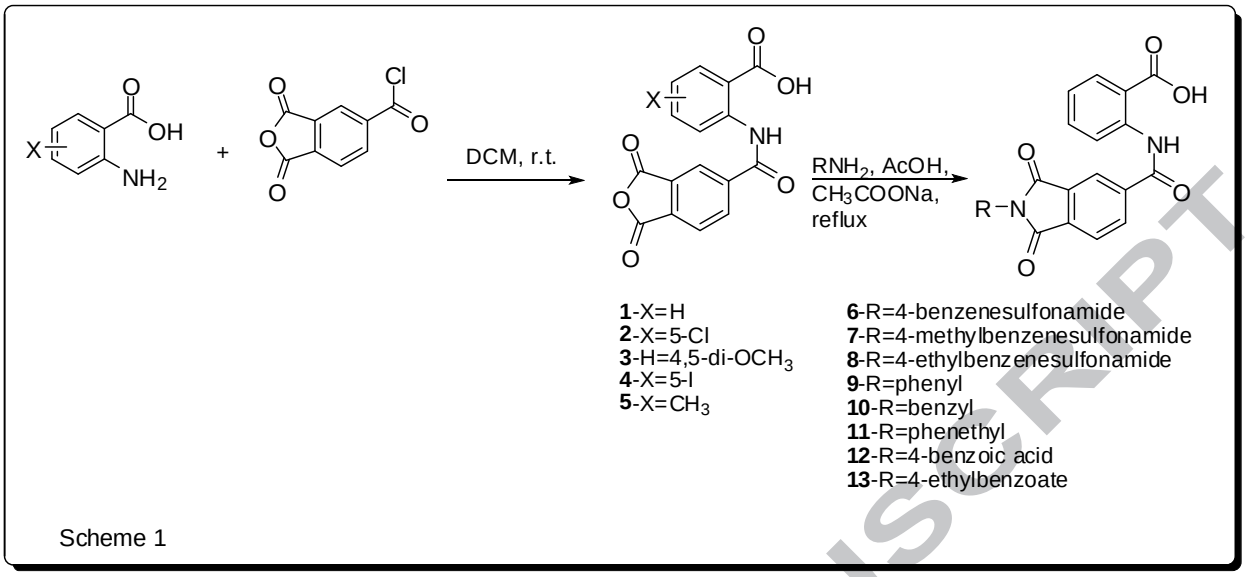
2. Result and discussion

2.1. Chemistry

The rationale for the drug design of the carboxylate/sulfonamide inhibitors reported here was the following one. The tail approach[9] was reported by one of these groups more than 15 years ago and allowed for the facile preparation of a large number of potent and isoform-selective classes of sulfonamide inhibitors.[9-13] Indeed, an initial drug design strategy based on appending "tails" (i.e., various moieties) of different size, shape or nature to pharmacophores incorporating scaffolds of derivatizable amino-hydroxy-substituted aromatic/heterocyclic sulfonamides has been proposed.[9] Thus, numerous sulfonamide CAIs possessing both high affinity and desired pharmacologic properties were obtained.[9-19] This approach, based on an "extension" of the aromatic/heterocyclic scaffolds through the anchoring tails has been thereafter explored for sulfamates, sulfamides and dithiocarbamates (as alternative zinc-binding groups (ZBGs) to the sulfonamide one, but much less to carboxylic acids). Furthermore, CAIs incorporating scaffolds belonging to the aliphatic or glycosidic chemical spaces were also explored in this way.[14,15]The advantage of the tail approach over other drug design strategies was thereafter explained at the

molecular level, after the report of many X-ray crystallographic structures of adducts of various CA isoforms with such inhibitors.[1-3,16-20] These studies demonstrated that the active site of most CA isoenzymes is a rather large conical cavity in which the Zn(II) ion is positioned at its bottom. The lining of the active site builds two adjacent very diverse halves, one entirely hydrophilic, the opposing one completely hydrophobic,[2,3,20]with the highest variability of amino acid residues between the different isoforms on the edge/entrance of the active site. This is exactly the region in which the tails of the inhibitors wereobserved,[20-23] explaining why these specific interactions between the inhibitor tail and amino acid residues at the entrance of the active site may lead to compounds showing selectivity for inhibiting isoforms with pharmacological applications.[1-4] Indeed, most of the isoform-selective inhibitors reported to date (except the coumarins)[5-7] were obtained by the tail approach.[9,20-23] Here we apply it for the preparation of compounds incorporating COOH and SO_2NH_2 moieties as ZBGs, considering the simple chemistry of phthalic anhydride/phthalimide (Scheme 1).

Thus, the substituted 2-(1,3-dioxo-1,3-dihydroisobenzofuran-5-carboxamido)benzoic acids (**1**-**5**) were obtained in 90-95% yield by reaction of anthranilic acid derivatives with trimellitic anhydride chloride in dichloromethane at room temperature. The resulting 2-(1,3-dioxo-1,3-dihydroisobenzofuran-5-carboxamido)benzoic acid (**1**) was treated with various primary amines in acetic acid in the presence of sodium acetate to give the corresponding 2-(1,3-dioxo-2-substituted phenylisoindoline-5-carboxamido)benzoic acids (**6**-**13**) in 76-85% yield (Scheme 1).



Scheme 1

Scheme 1: Preparation of compounds **1-13**.

Thus, the compounds **1-5** as well as **9-13** prepared as reported in Scheme 1, incorporate only COOH moieties as possible ZBG, whereas **6-8** incorporate both sulfamoyl and carboxylate as possible ZBGs.

2.2. CA inhibition

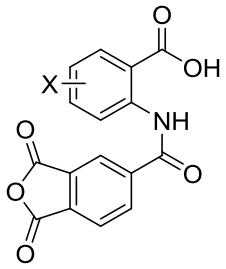
The compounds **1-13** reported here were investigated for their enzyme inhibitory action against five physiologically relevant CA isoforms, the human (h) hCA I, II, IV, VII and XII (Tables 1 and 2). Acetazolamide (5-acetamido-1,3,4-thiadiazole-2-sulfonamide) was used as standard drug in the assay.[24]

The following structure-activity relationship (SAR) can be drawn from the inhibition data shown in Table 1:

(i) Isoforms hCA I, II (cytosolic) and IV (membrane-bound) were poorly inhibited by the carboxylates **1-5** (K_Is in the micromolar range or > 10 μM), in contrast to the first generation

sulfonamide inhibitor acetazolamide which was effective against all of them with inhibition constants ranging between 12 and 250 nM (Table 1).

Table 1: Inhibition of human CA isoforms hCA I, II, IV, VII and XII with substituted 2-(1,3-dioxo-1,3-dihydroisobenzofuran-5-carboxamido)benzoic acid (**1**-**5**) and the standard sulfonamide inhibitor acetazolamide (**AAZ**) by a stopped flow CO_2hydrase assay.[24]

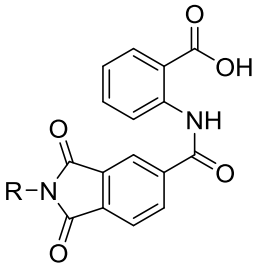


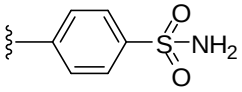
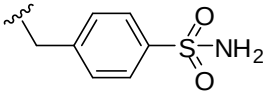
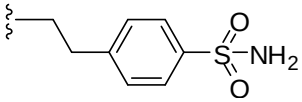
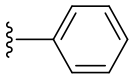
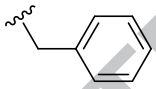
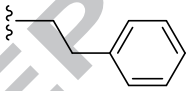
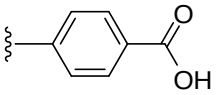
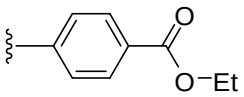
Compound	X	K_I (nM)				
		hCA I	hCA II	hCA IV	hCA VII	hCA XII
1	H	4140	>10000	494.4	3.9	228.4
2	5-Cl	3494	>10000	>10000	5.1	43.7
3	4,5-di-OCH_3	4368	>10000	>10000	2.9	46.5
4	5-I	>10000	>10000	>10000	3.3	57.4
5	5-CH_3	4753	>10000	526.7	3.5	40.8
AAZ	-	250	12	74	2.5	5.7

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

(ii) On the contrary, isoforms hCA VII (cytosolic) and XII (transmembrane) were effectively inhibited by these carboxylates, with K_Is in the range of 2.9 – 5.1 nM against hCA VII, and of 40.8 – 228.4 nM against hCA XII. For hCA VII the SAR is thus quite flat with all compounds highly effective inhibitors (similar to **AAZ**), whereas for hCA XII the unsubstituted derivative (at the anthranilic acid fragment of the molecule) such as compound **1** was the least effective inhibitor, with the derivatives **2-5** incorporating halogens, methoxy or methyl groups showing an enhanced activity (Table 1).

Table 2: Inhibition of human CA isoforms hCA I, II, IV, VII and XII with 2-(1,3-dioxo-2-substituted phenylisoindoline-5-carboxamido)benzoic acid (**6-13**) and the standard sulfonamide inhibitor acetazolamide (**AAZ**) by a stopped flow CO_2hydrase assay.[24]



Compound	R	K_I (nM)				
		hCA I	hCAII	hCA IV	hCA VII	hCA XII
6		33.6	8.9	184.4	0.46	44.4
7		41.3	10.5	72.7	0.35	28.5
8		46.8	13.8	495.6	0.31	4.1
9		>10000	>10000	>10000	4.3	51.9
10		2443	>10000	7109	3.2	27.3
11		3540	>10000	366.4	4.4	48.9
12		>10000	>10000	891.9	14.5	56.4
13		>10000	>10000	280.5	9.5	18.5
AAZ	-	250	12	74	2.5	5.7

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

The phthalimides **6-13** were tested for the inhibition of the same isoforms (Table 2). The following SAR can be observed from data of Table 2:

(iii) the sulfonamides **6-8** inhibited all five isoforms quite effectively (with few exceptions such as compounds **6** and **8** against hCA IV), usually in the low nanomolar or subnanomolar (for hCA VII) range. Thus, for these sulfonamides the tail approach applied here led to effective but rather non-selective inhibitors.

(iv) the carboxylates **9-13** on the other hand, similarly to compounds **1-5** discussed earlier show isoform selectivity. Indeed, these derivatives were poor inhibitors or did not inhibit significantly hCA I, II and IV (inhibition constants in the micromolar range), but they were highly effective as hCA VII inhibitors (K_Is in the range of 3.2 – 14.5 nM) and hCA XII inhibitors (K_Is in the range of4.1 – 56.4 nM). It is rather clear that the substitution pattern at the R moiety present in the starting amine is the main factor controlling potency, with the best hCA VII inhibitors incorporating phenyl, benzyl and phenethyl moieties, whereas the best hCA XII inhibitor containing ethyl benzoate (**13**) and benzyl group, **10** (Table 2).

3. Conclusions

A small panel of carboxylates and sulfonamides incorporating phthalic anhydride and phthalimide moieties in their structure were prepared by applying the tail approach for generating chemical diversity in the family of these classes of CAIs. The new derivatives were obtained from substituted anthranilic acids and trimellitic anhydride chloride, followed by reaction with primary amines, and were tested for the inhibition of five physiologically relevant isoforms, hCA I, II, IV, VII and XII. Some of these enzymes are involved in serious pathologies: CA II, IV and XII in glaucoma; CA VII in epilepsy; CA XII in some solid tumors. The carboxylic acid derivatives were generally poor inhibitors of isoforms hCA I, II and IV but were highly effective, low nanomolar inhibitors of hCA VII and XII. The sulfonamides inhibited all isoforms significantly, and some of them were sub-nanomolar hCAVII inhibitors, although their isoform selectivity was lower compared to the carboxylates. This study proved that carboxylic acids incorporating a phthalic anhydride/phthalimide based scaffold may lead to isoform-

selective CAIs by applying the tail approach, mostly used up until now for obtaining sulfonamide, sulfamide and sulfamate inhibitors.

4. Experimental

4.1. Chemistry

Melting points were recorded on Barnstead 9100 Electrothermal melting apparatus. IR spectra (KBr) were recorded on a FT-IR Perkin-Elmer spectrometer (ν cm^{-1}) at Research Center, King Saud University, Saudi Arabia. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on Bruker 500 MHz spectrometer using DMSO-d_6 as solvents at Research Center, King Saud University, Saudi Arabia. The chemical shifts are expressed in δ ppm using TMS as internal standard. Mass spectra were recorded on an Agilent 6320 Ion Trap mass spectrometers at Research Center, King Saud University, Saudi Arabia. Elemental analysis was carried out for C, H and N at the Research Centre of College of Pharmacy, King Saud University, Saudi Arabia and the results are within ±0.4% of the theoretical values. Solvent evaporation was performed under reduced pressure using Buchan Rotatory Evaporator. Thin layer chromatography was performed on precoated (0.25 mm) silica gel GF254 plates (E. Merck, Germany); compounds were detected with 254 nm UV lamp. Silica gel (60–230 mesh) was employed for routine column chromatography separations.

Substituted 2-(1,3-dioxo-1,3-dihydroisobenzofuran-5-carboxamido)benzoic acid (1-5)

A mixture of trimellitic anhydride chloride (2.15 g, 0.01 mol) and the appropriate anthranilic acid (0.01 mol) in dichloromethane (50 ml) was stirred at room temperature for 4-6 h. The obtained solid was filtered off, washed with dichloromethane and dried.

2-(1,3-Dioxo-1,3-dihydroisobenzofuran-5-carboxamido)benzoic acid (1)

Yield 92%, m.p. 285-287 ^{o}C; IR (KBr, cm^{-1}) ν:3250 (NH), 2855 (OH), 1777, 1755, 1693, (C=O); ^{1}H NMR (DMSO-d$_6$): δ 12.35-12.28 (m, 0.67H), 11.60 (m, 0.33H), 8.68-8.58 (m, 1H), 8.29-8.12 (m, 1H), 8.08-8.01 (m, 1H), 8.96-7.80 (m, 1H), 7.87-7.84 (m, 1H); 7.75-7.58 (m, 1H), 7.41-7.22 (m, 2H). MS: [M^{+} 311].

5-Chloro-2-(1,3-dioxo-1,3-dihydroisobenzofuran-5-carboxamido)benzoic acid (2)

Yield 95%, m.p. 294-295 ^{o}C; IR (KBr, cm^{-1}) ν: 3420 (NH), 1783, 1724, 1654 (C=O); ^{1}H NMR (DMSO-d$_6$): δ 9.69-8.65 (m, 1H), 8.53-8.47 (m, 1H), 8.43 (s, 1H), 8.18-8.11 (m, 1H), 8.06-8.00 (m, 2H), 7.63-7.59 (m, 1H). ^{13}C NMR (DMSO-d6): 120.1, 121.1, 123.7, 125.1, 126.9, 128.2, 129.9, 131.8, 132.5, 137.2, 139.4, 157.5, 162.2, 164.12, 167.88. MS: [M^{+} 345 and M^{+2} 347].

2-(1,3-Dioxo-1,3-dihydroisobenzofuran-5-carboxamido)-4,5-dimethoxybenzoic acid (3)

Yield 90%, m.p. 301-302 ^{o}C; IR (KBr, cm^{-1}) ν: 3245 (NH), 1774, 1776, 1648 (C=O); ^{1}H NMR (DMSO-d$_6$): δ 8.43-8.39 (m, 2H), 8.15-8.13 (m, 1H), 7.56-7.54 (m, 1H), 7.21 (s, 1H), 7.10 (s, 1H), 3.88 (s, 3H), 3.80 (s, 3H). MS: [M^{+} 371].

2-(1,3-Dioxo-1,3-dihydroisobenzofuran-5-carboxamido)-5-iodobenzoic acid (4)

Yield 94%, m.p. 278-280 ^{o}C; IR (KBr, cm^{-1}) ν: 3065 (OH), 1783, 1724, 1681 (C=O); ^{1}H NMR (DMSO-d$_6$): δ 12.27 (d, 1H, *J*=22.0 Hz), 8.44-8.38 (m, 2H), 8.34 (s, 1H), 8.27-8.11 (m, 2H), 7.96 (dd, 1H, J=1.5, 2.0 Hz), 7.37 (d, 1H, *J*= 8.0 Hz). MS: [M^{+} 437].

2-(1,3-Dioxo-1,3-dihydroisobenzofuran-5-carboxamido)-5-methylbenzoic acid (5)

Yield 91%, m.p. 298-300 ^{o}C; IR (KBr, cm^{-1}) ν:3142 (OH), 1785, 1718, 1684 (C=O); ^{1}H NMR (DMSO-d$_6$): δ 12.27 (s, 1H), 8.50 (d, 1H, *J*=8.5 Hz), 8.44-8.40 (m, 2H), 8.16 (d, 1H, *J*=8.0 Hz),

7.60 (d, 1H, *J*=8.0 Hz), 7.49-7.43 (m, 2H), 2.38 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 20.7, 118.1, 120.9, 124.7, 129.2, 130.8, 131.7, 132.8, 134.0, 134.6, 135.1, 138.4, 140.7, 163.1, 166.5, 167.0, 170.4. MS: [M^+ 432].

2-(1,3-Dioxo-2-substituted phenylisoindoline-5-carboxamido)benzoic acid (6-13)

A mixture of 2-(1,3-dioxo-1,3-dihydroisobenzofuran-5-carboxamido)benzoic acid (**1**) (612 mg, 2 mmol) and the appropriate amine (0.02 mmol) in glacial acetic acid (10 ml) in the presence of anhydrous sodium acetate (246 mg, 3 mmol) was heated for 10-12 h. The reaction mixture was cooled, the solvent was removed under vacuum, and the obtained solid was filtered, washed with water, dried and recrystallized with dichloromethane-ethanol (1:1).

2-(1,3-Dioxo-2-(4-sulfamoylphenyl)isoindoline-5-carboxamido)benzoic acid (6)

Yield 81%, m.p. 313-315 ^{o}C; IR (KBr, cm^{-1}) ν: 3328, 3245 (NH), 1779, 1661 (C=O); ^{1}H NMR (DMSO-d_6): δ 12.42 (s, 1H), 8.63 (d, 1H, *J*=8.5 Hz), 8.48-8.42 (m, 2H), 8.18 (d, 1H, *J*=8.0 Hz), 8.07 (d, 1H, *J*=1.5 Hz), 8.01 (d, 2H, *J*=8.5 Hz), 7.72-7.66 (m, 3H), 7.51 (s, 2H), 7.24 (t, 1H, J=7.5 Hz).^{13}C NMR (DMSO-d_6): δ 120.8, 121.8, 124.1, 126.8, 128.0, 131.7, 132.7, 134.3, 134.6, 134.7, 135.1, 140.5, 140.8, 143.9, 163.3, 166.4, 166.5. MS: [M^+ 465].

2-(1,3-Dioxo-2-(4-sulfamoylbenzyl)isoindoline-5-carboxamido)benzoic acid (7)

Yield 83%, m.p. 322-324 ^{o}C; IR (KBr, cm^{-1}) ν: 3391, 3253 (NH), 1781, 17334, 1654 (C=O); ^{1}H NMR (DMSO-d_6): δ 14.20 (s, 1H), 8.65 (d, 1H *J*=8.0 Hz), 8.42 (d, 1H, *J*=1.5 Hz), 8.37 (s, 1H), 8.09-8.06 (m, 3H), 7.80 (d, 2H, *J*=8.5 Hz), 7.55-7.52 (m, 3H), 7.36 (s, 2H), 7.18-7.15 (m, 1H), 4.88 (s, 2H).^{13}C NMR (DMSO-d_6): δ 41.2, 119.8, 121.7, 121.8, 123.4, 124.3, 126.4, 128.2, 131.7, 132.7, 133.9, 134.5, 140.8, 140.9, 141.0, 143.7, 163.0, 167.4, 167.5, 170.5. MS: [M^+ 479].

2-(1,3-Dioxo-2-(4-sulfamoylphenethyl)isoindoline-5-carboxamido)benzoic acid (8)

Yield 85%, m.p.300-301 ^{o}C; IR (KBr, cm^{-1}) ν: 3358, 3256 (NH), 3042 (OH), 1769, 1718, 1655 (C=O); ^{1}H NMR (DMSO-d$_6$): δ 12.28 (s, 1H), 8.60 (d, 1H, *J*=3.5 Hz), 8.34 (d, 1H, *J*=8.0 Hz), 8.27 (s, 1H), 8.02 (t, 2H, J=6.5 & 8.0 Hz), 7.74 (d, 2H, *J*=8.5 Hz), 7.67 (t, 1H, *J*=8.0), 7.44 (d, 2H, *J*=8.5 Hz), 7.33 (s, 2H), 7.24 (t, 1H, *J*=7.5 Hz), 3.89 (t, 2H, *J*=7.0 Hz), 3.03 (t, 2H, J=7.0 & 7.5 Hz).^{13}C NMR (DMSO-d$_6$): δ 33.9, 39.2, 118.0, 120.9, 121.4, 124.1, 124.2, 126.3, 129.7, 131.7, 132.6, 133.9, 134.5, 134.7, 140.2, 140.8, 142.8, 142.9, 163.3, 167.3, 167.4, 170.5. MS: [M^{+} 493].

2-(1,3-Dioxo-2-phenylisoindoline-5-carboxamido)benzoic acid (9)

Yield 80%, m.p. 307-309 ^{o}C; IR (KBr, cm^{-1}) ν:3105 (OH), 3412 (NH), 1780, 1702, 1655 (C=O); ^{1}H NMR (DMSO-d$_6$): δ , 12.36 (s, 1H), 8.62 (d, 1H, *J*=8.0 Hz), 8.42 (d, 1H, *J*=8.0 Hz), 8.38 (s, 1H), 8.14 (d, 2H, *J*=8.0 Hz), 8.05 (d, 1H, *J*=7.5 Hz), 7.67 (t, 1H, *J*=7.5 & 8.0 Hz), 7.56 (t, 2H, *J*=7.5 & 8.0 Hz), 7.49-7.46 (m, 3H), 7.25 (t, 1H, *J*=7.5 & 8.0 Hz).^{13}C NMR (DMSO-d$_6$): δ 117.8, 120.8, 121.6, 124.0, 124.6, 127.8, 128.7, 129.3, 131.7, 132.2, 132.7, 134.1, 134.6, 134.7, 140.3, 140.9, 163.3, 166.7, 170.5.MS: [M^{+} 386].

2-(2-Benzyl-1,3-dioxoisoindoline-5-carboxamido)benzoic acid (10)

Yield 82%, m.p. 270-272 ^{o}C; IR (KBr, cm^{-1}) ν:3421 (NH), 1771, 1717, 1654, (C=O); ^{1}H NMR (DMSO-d$_6$): δ 12.30 (s, 1H), 8.60 (d, 1H, *J*=8.5 Hz), 8.35 (d, 1H, *J*=8.0 Hz), 8.30 (s, 1H), 8.06 (d, 1H, *J*=8.0 Hz), 8.03 (d, 1H, *J*=8.0 Hz), 7.64 (t, 1H, *J*=8.0 Hz), 7.34-7.20 (m, 6H), 4.80 (s, 2H).^{13}C NMR (DMSO-d$_6$): δ 41.6, 117.8, 120.8, 121.5, 124.0, 124.3, 127.8, 127.9, 129.0, 131.7, 132.7, 134.0, 134.6, 134.7, 136.9, 140.2, 140.8, 163.2, 167.4, 170.5. MS: [M^{+} 400].

2-(1,3-Dioxo-2-phenethylisoindoline-5-carboxamido)benzoic acid (11)

Yield 85%, m.p. 255-257 ^{o}C; IR (KBr, cm^{-1}) ν:3421 (NH), 1793, 1734, 1684 (C=O); ^{1}H NMR (DMSO-d$_6$): δ 12.28 (s, 1H), 8.60 (d, 1H, *J*=8.0 Hz), 8.33 (d, 1H, *J*=8.0 Hz), 8.25 (s, 1H), 8.05 (d, 1H, *J*=8.0 Hz), 8.02 (d, 1H, J=7.5 Hz), 7.66 (t, 1H, *J*=7.5 & 8.0 Hz), 7.31-7.18 (m, 6H), 7.83 (t, 2H, *J*=7.5 & 9.0 Hz), 3.83 (t, 2H, *J*=7.5 Hz), 2.94 (t, 2H, *J*=7.0 & 7.5 Hz).^{13}C NMR (DMSO-d$_6$): δ 34.0, 40.5, 117.9, 120.8, 121.3, 124.1, 126.9, 127.0, 127.8, 128.9, 129.0, 129.2, 131.6, 132.6, 133.8, 134.5, 134.7, 138.6, 140.8, 163.3, 167.3, 170.4. MS: [M^{+} 414].

2-(2-(4-Carboxyphenyl)-1,3-dioxoisoindoline-5-carboxamido)benzoic acid (12)

Yield 76%, m.p. 330-331 ^{o}C; IR (KBr, cm^{-1}) ν:3032 (OH), 1778, 1734, 1699 (C=O), 3258 (NH); ^{1}H NMR (DMSO-d$_6$):δ 12.44 (s, 1H), 8.62 (d, 1H, *J*=8.0 Hz), 8.41 (d, 1H, *J*=7.5 Hz), 8.37 (s, 1H), 8.14 (d, 1H, *J*=8.0 Hz), 8.10 (d, 2H, *J*=8.0 Hz), 8.05 (d, 1H, *J*=8.0 Hz), 7.67-7.62 (m, 3H), 7.23 (t, 1H, *J*=7.5 Hz).^{13}C NMR (DMSO-d$_6$): δ 118.0, 120.7, 121.8, 124.0, 124.7, 127.4, 130.3, 130.6, 131.7, 132.6, 134.2, 134.5, 134.6, 136.0, 140.5, 140.8, 163.2, 166.3, 167.2, 170.5. MS: [M^{+} 430].

2-(2-(4-(Ethoxycarbonyl)phenyl)-1,3-dioxoisoindoline-5-carboxamido)benzoic acid (13)Yield 79%, m.p. 228-230 ^{o}C; IR (KBr, cm^{-1}) ν:3420 (NH), 1772, 1700, 1718, 1654 (C=O); ^{1}H NMR (DMSO-d$_6$): δ13.01 (s, 1H), 8.64 (d, 1H, *J*=8.0 Hz), 8.44 (d, 1H, *J*=78.0Hz), 8.40 (s, 1H), 8.14 (d, 1H, *J*=8.0 Hz), 8.12 (d, 2H, *J*=8.5 Hz), 8.07 (d, 1H, *J*=7.5 Hz), 7.71-7.61 (m, 3H), 7.22 (t, 1H, *J*=7.5 Hz), 4.36 (q, 2H, *J*=7.0 & 7.5 Hz), 1.30 (t, 3H, *J*=7.0 Hz).^{13}C NMR (DMSO-d$_6$): δ 14.6, 61.4, 121.9, 123.8, 124.7, 127.5, 127.8, 129.3, 129.6, 130.1, 130.6, 132.6, 134.0, 134.2, 134.4, 136.4, 140.7, 140.9, 163.1, 165.6, 166.3, 170.5. MS: [M^{+} 458].

4.2. Carbonic anhydrase inhibition

An Applied Photophysics stopped-flow instrument has been used for assaying the CA catalyzed CO_2 hydration activity.[24] 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 Hepes (pH 7.5) as buffer, and 20 mM Na_2SO_4 (for maintaining constant the ionic strength), following the initial rates of the CA-catalyzed CO_2 hydration reaction for a period of 10-100 s. The CO_2 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 0.01 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,[25-28]and represent the mean from at least three different determinations. All CA isofoms were recombinant ones obtained in-house as reported earlier.[25-28]

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Inhibition of carbonic anhydrase isoforms I, II, IV, VII and XII with carboxylates and sulfonamides incorporating phthalimide/phthalic anhydride scaffolds

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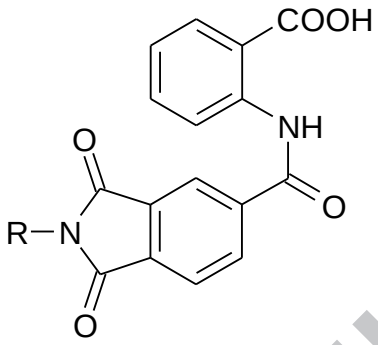

R = Ph, $PhCH_2$, $HOOC-C_6H_4$, $H_2NO_2S-C_6H_4$, etc.

K_I(hCA VII) = 0.31 - 14.5 nM; K_I(hCA XII) = 4.1 - 56.4 nM