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(*E*)-3-Arylidene-4-diazopyrrolidine-2,5-diones conveniently elaborated into cytotoxic compounds bearing primary sulfonamide and Michael acceptor moieties

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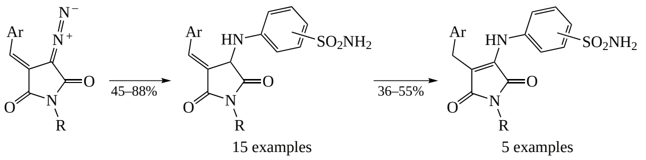
The earlier described (*E*)-3-arylidene-4-diazopyrrolidine-2,5-diones have been elaborated into two distinct series of compounds both bearing a primary sulfonamide moiety and an electrophilic 'Michael acceptor' motif. These compounds demonstrated cytotoxicity against colorectal cancer cell line HCT 116.



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Earlier we discovered[1] that $Rh_2(OAc)_2$-catalyzed coupling of one of (*E*)-3-arylidene-4-diazopyrrolidine-2,5-diones[2] **1** with either 3- or 4-aminobenzenesulfonamides delivered compounds **2a**,**b** (Figure 1). These compounds contained both the primary sulfonamide moiety (known to be important for inhibiting cancer-related isoforms of carbonic anhydrase, CA)[3] and an electrophilic 'Michael acceptor' motif which can sequester thioredoxin reductase (TrxR) enzyme.[4] Both enzymes, vital for cancer cell development and growth,[5] were shown to be inhibited by **2a**,**b**. However, the compounds showed moderate cytotoxic activity towards MDA-MB-231 or MCF-7 cancer cells. This motivated us to synthesize a series of potential dual CA/TrxX inhibitor both with exocyclic (**3**) and endocyclic (**2**) double bond (see Figure 1).

A large series of (*E*)-3-arylidene-4-diazopyrrolidine-2,5-diones **1** were already available from our previous efforts.[2(*a*)]

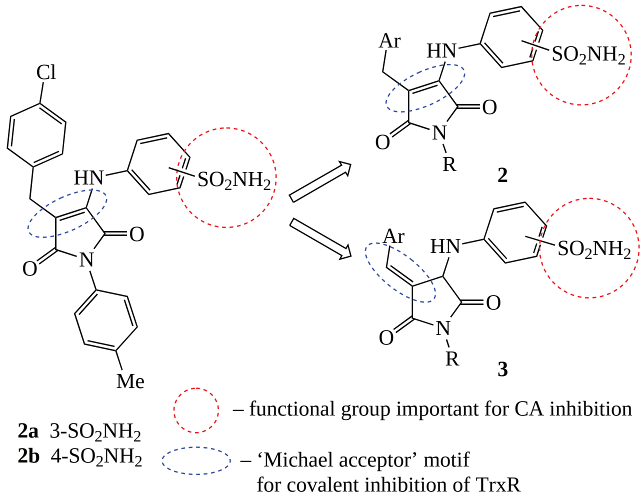


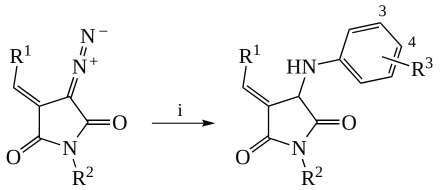
Figure 1 Prior findings (**2a**,**b**) and focus of the present research (**2, 3**).

When conducting the Rh^{II}-catalyzed coupling with either 3- or 4-aminobenzenesulfonamide under standard conditions (*i.e.* prolonged heating overnight), a mixture of products of types **2** and **3** was always isolated. Our idea was to obtain compounds **3** first and then isomerize them to compounds **2**. This was achieved by lowering the reaction time to only 1 h whereupon a large set of *exo*-arylidene compounds **3a**–**o** was obtained in good to excellent yields (Scheme 1).[†] The geometry of the double bond had been unequivocally established previously.[2(*a*)]

Quite surprisingly, prolongation of the processing (see Scheme 1) even up to 72 h did not cause full isomerization of **3** to **2**. In order to synthesize a smaller, maleimide set of compounds **2** from the *exo*-arylidene set **3**, somewhat forcing conditions had to be applied to itaconimides **3** isolated prior to the reaction. Heating selected compounds **3d**,**h**,**k**,**l**,**o** in DMF at 100 °C over 12 h led to a clean (although moderately yielding) conversion to their maleimide counterparts **2** (Scheme 2).[‡] Note that compounds **3** resisted isomerization under acid- or base-catalyzed conditions.

[†] *General procedure for the preparation of compounds* **3a**–**o**. Aminobenzenesulfonamide (1 mmol, 80 mg) was dissolved by refluxing in 4 : 3 mixture of toluene/1,4-dioxane (4.7 ml). Diazo compound **1** (1 mmol) and the catalyst $Rh_2(OAc)_4$ (1 mol%) were introduced. Evolution of N_2 gas was observed. The reaction mixture was stirred at 110 °C for 1 h, the solvent was distilled off, and the resulting compounds **2** were purified by column chromatography on silica gel using and appropriate gradient of either MeOH/chloroform or DCM/ethyl acetate.

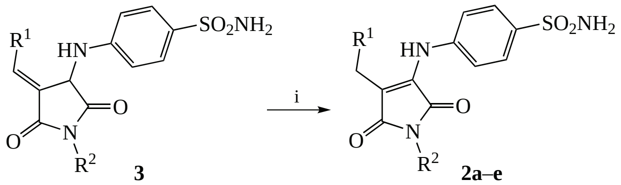
[‡] *General procedure for the preparation of compounds* **2a**–**e**. The corresponding compound **3** (1 mmol) was dissolved in DMF (2 ml) and stirred at 100 °C for 12 h. The reaction mixture was poured into distilled water (50 ml) and extracted with ethyl acetate (3 × 30 ml). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Compounds **2** were purified by column chromatography on silica gel using an appropriate gradient of methanol in chloroform.



1 **3a–n**

a R^1 = Ph, R^2 = 4-$\mathrm{MeOC_6H_4}$, R^3 = 4-$\mathrm{SO_2NH_2}$, 77%
b R^1 = Ph, R^2 = 4-$\mathrm{MeOC_6H_4}$, R^3 = 3-$\mathrm{SO_2NH_2}$, 88%
c R^1 = R^2 = Ph, R^3 = 4-$\mathrm{SO_2NH_2}$, 77%
d R^1 = Ph, R^2 = 4-$\mathrm{CF_3C_6H_4}$, R^3 = 4-$\mathrm{SO_2NH_2}$, 78%
e R^1 = 2-thienyl, R^2 = 4-$\mathrm{MeOC_6H_4}$, R^3 = 4-$\mathrm{SO_2NH_2}$, 82%
f R^1 = 3-thienyl, R^2 = 4-$\mathrm{CF_3C_6H_4}$, R^3 = 4-$\mathrm{SO_2NH_2}$, 48%
g R^1 = 2-$\mathrm{MeOC_6H_4}$, R^2 = Ph, R^3 = 3-$\mathrm{SO_2NH_2}$, 45%
h R^1 = 2-$\mathrm{MeOC_6H_4}$, R^2 = Ph, R^3 = 4-$\mathrm{SO_2NH_2}$, 78%
i R^1 = 4-$\mathrm{MeOC_6H_4}$, R^2 = Ph, R^3 = 4-$\mathrm{SO_2NH_2}$, 78%
j R^1 = 4-$\mathrm{MeC_6H_4}$, R^2 = Ph, R^3 = 4-$\mathrm{SO_2NH_2}$, 73%
k R^1 = 3-$\mathrm{MeC_6H_4}$, R^2 = Ph, R^3 = 4-$\mathrm{SO_2NH_2}$, 80%
l R^1 = 4-$\mathrm{ClC_6H_4}$, R^2 = Ph, R^3 = 4-$\mathrm{SO_2NH_2}$, 71%
m R^1 = 4-$\mathrm{ClC_6H_4}$, R^2 = 4-$\mathrm{MeC_6H_4}$, R^3 = 4-$\mathrm{SO_2NH_2}$, 59%
n R^1 = 4-$\mathrm{ClC_6H_4}$, R^2 = 4-$\mathrm{MeC_6H_4}$, R^3 = 3-$\mathrm{SO_2NH_2}$, 66%
o R^1 = 4-$\mathrm{FC_6H_4}$, R^2 = Ph, R^3 = 4-$\mathrm{SO_2NH_2}$, 85%

Scheme 1 *Reagents and conditions*: i, 3- or 4-$\mathrm{H_2NC_6H_4SO_2NH_2}$, toluene/1,4-dioxane (4 : 3), compound **1**, $\mathrm{Rh_2(OAc)_4}$ (1 mol%).



3 **2a–e**

a R^1 = 2-$\mathrm{MeOC_6H_4}$, R^2 = Ph, 42%
b R^1 = 3-$\mathrm{MeC_6H_4}$, R^2 = Ph, 53%
c R^1 = 4-$\mathrm{ClC_6H_4}$, R^2 = Ph, 55%
d R^1 = 4-$\mathrm{FC_6H_4}$, R^2 = Ph, 53%
e R^1 = Ph, R^2 = 4-$\mathrm{CF_3C_6H_4}$, 36%

Scheme 2 *Reagents and conditions:* i, DMF, 100 °C, 12 h.

The preliminary study of cytotoxicity profile of compounds of series **2** and **3** showed a moderate activity of these compounds against colon cancer cell line HCT 116[6] (Table 1).

Table 1 Cytotoxicity of sulfonamide ‘Michael acceptors’ **2** and **3** against colon cancer cell line HCT 116 (72 h incubation).

Compound	IC_{50}/μM	Compound	IC_{50}/μM
3a	>100	**3k**	90.1 ± 29.1
3b	>100	**3l**	38.8 ± 4.1
3c	98.6 ± 18.6	**3m**	31.2 ± 4.3
3d	57.2 ± 8.7	**3n**	31.2 ± 3.3
3e	99.8 ± 15.3	**3o**	70.3 ± 6.6
3f	31.8 ± 4.1	**2a**	>100
3g	79.0 ± 13.7	**2b**	62.0 ± 20.7
3h	>100	**2c**	59.4 ± 18.5
3i	>100	**2d**	45.7 ± 10.9
3j	>100	**2e**	34.6 ± 2.1

In summary, we have described the synthesis of potentially dual inhibitors of two enzymes – carbonic anhydrase (CA) and thrioredoxin reductase (TrxR) – that are crucial for the survival of cancer cells. The synthesis stemmed from the earlier described (*E*)-3-arylidene-4-diazopyrrolidine-2,5-diones[2] which were coupled (*via* the respective Rh^{II} carbene) with 3- and 4-aminobenzenesulfonamides. Selected *exo*-arylidene products were transformed into maleimide counterparts by heating in DMF. Both series demonstrated double-digit micromolar activity against colon cancer cell line HCT 116 and are currently evaluated for inhibition of CA and TrxR enzymes as well as cytotoxicity against other human cancer cell lines. The results of these studies will be reported in due course.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.03.007.

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