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# A new synthesis of difluoromethanesulfonamides–a novel pharmacophore for carbonic anhydrase inhibition†

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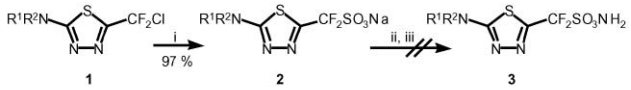
**Preparation of the key intermediate carboxydifluoromethanesulfonamide provides direct synthetic access to a wide range of novel difluoromethanesulfonamides, including the acetazolamide analogue (2-ethanoylamino-1,3,4-thiadiazol-5-yl)-difluoromethanesulfonamide. Their water solubility and stability, ether partition coefficient, p$K_a$ and submicromolar dissociation constants for human carbonic anhydrase isozyme II (HCA II) make them promising candidates for topical glaucoma therapy.**

To date, virtually all sulfonamide compounds evaluated as carbonic anhydrase inhibitors, CAIs, share the common structural feature of a primary sulfonamide group ($SO_2NH_2$) attached to a substituted or unsubstituted aromatic or heteroaromatic moiety ($ArSO_2NH_2$). Acetazolamide has long been the CAI of choice for glaucoma therapy despite its poor water solubility. Consequently, there has been a systematic search for CAIs with improved water solubility as agents for the topical treatment of glaucoma.[1] The inherent problem is the three-way balance between the acidity of the sulfonamide function, the water solubility and the lipophilicity[2] needed to provide the requisite bioavailability. Thus, while trifluoromethanesulfonamide has been found to be one of the most potent inhibitors of carbonic anhydrase isozyme II (CA II) and is very water soluble, toxicity and limited bioavailability have denied its clinical development.[3] Moreover, its use as a lead compound has been held back by the problems of synthesis of α-fluoro-sulfonamides.[4]

The inhibitory potency of $CF_3SO_2NH_2$ has been attributed in part to its very strongly acidic sulfonamide, p$K_a$ 6.3. Given that $CH_3SO_2NH_2$, p$K_a$ 10.3, is a poor CA inhibitor, the difference in activity must be a direct result of the electronegativity of the $CF_3$ group and thereby satisfies one of the established prime requirements[5] for an effective CAI, namely a sulfonamide function of low p$K_a$. We therefore sought to link a proven heterocyclic pharmacophore, Het, with the difluoromethylenesulfonamide group, $-CF_2SO_2NH_2$, to generate a novel range of CA II inhibitors of general structure $HetCF_2SO_2NH_2$. In this work, we have employed the 1,3,4-thiadiazole to provide the Het function for a number of viable CAIs.[1]

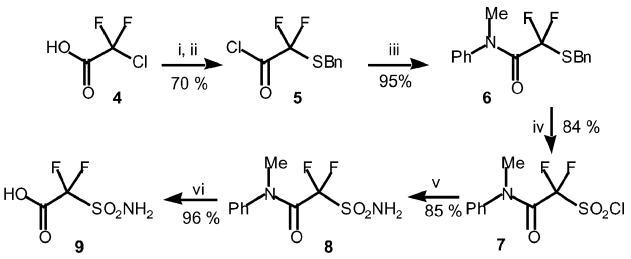
We have recently achieved the first successful syntheses of aryldifluoromethanesulfonamides by direct fluorination of arylmethanesulfonamides.[4] We next sought to develop a method that would be more general for a range of functionalised heterocyclic methanesulfonamides, especially in the amino-1,3,4-thiadiazole series. Our initial approach involved the synthesis of 5-chlorodifluoromethyl-2-amino-1,3,4-thiadiazole **1a** and its derivatives and their sulfonylation to **2** leading to the difluoromethanesulfonamides **3**. The sulfonylation was accomplished in good yield for a range of amine-substituted thiadiazoles **2a–e** using aqueous sodium bisulfite (Scheme 1). Unfortunately, all efforts to convert these sulfonic acids or their salts into the respective sulfonamides using electrophilic agents ($SOCl_2$, $POCl_3$, $PCl_5$, $Tf_2O$, *etc.*) followed by liquid ammonia treatment failed. Reports of the transformation of simple difluoromethanesulfonic acids into sulfonamides *via* sulfonyl chlorides are limited.[6]




**a**, R¹=R² =H; **b**, R¹=R²=Me; **c**, R¹=H, R²=Me; **d**, R¹=H, R²=Ac; **e**, R¹=Me, R²=Ac.

**Scheme 1** *Reagents and conditions*: i) $Na_2SO_3$ aq., dioxane, rt, 5 h; ii) $POCl_3$ *etc.*; iii) $NH_3$, −78 °C.

We therefore chose to approach the desired synthesis by constructing the heterocyclic ring onto a preformed difluoromethanesulfonamide entity. Retrosynthetic analysis identified carboxydifluoromethanesulfonamide **9** as a suitable intermediate and we accomplished its synthesis in six steps and 46% overall yield from inexpensive chlorodifluoroethanoic acid **4** (Scheme 2).[7] The carboxyl group of **9** shows normal reactivity, being converted into its methyl ester in 90% yield on heating with methanolic HCl.




**Scheme 2** *Reagents and conditions*: i) $PhCH_2SNa$, dioxane; ii) $POCl_3$ *etc.*; iii) PhNHMe, −78 °C; iv) $Cl_2$–AcOH–$H_2O$, 0 °C, 1 h; v) $NH_3$ (liq.), 2 h; vi) HCl conc., reflux, 16 h.

More significantly, **9** was condensed with thiosemicarbazide in the presence of phosphoryl chloride to give (2-amino-1,3,4-thiadiazolyl)-difluoromethanesulfonamide† **3** in 33% yield. The amino function of **3** was readily converted into the acetamide **10** (the difluoromethylene homologue of acetazolamide) and the trifluoroacetamide **11** by treatment with the corresponding carboxylic anhydride (Scheme 3).

In other studies, attention has been focused on achieving water solubility by the incorporation of charged functions in the acyl side chain of acetazolamide, including aminoacyl functions[8] and carboxylic acids.[9] We therefore prepared a further six derivatives of **3** incorporating glycyl **12**, β-alanyl **13**, succinyl **14** and 3-chloropropionyl **15** functions to provide additional

† Electronic supplementary information (ESI) available: characterisation of all compounds by HRMS or combustion analysis and by $^1H$, $^{13}C$, and $^{19}F$ NMR. See http://www.rsc.org/suppdata/ob/b4/b416642f/

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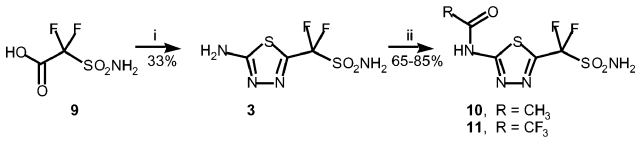

**Scheme 3** *Reagents and conditions*: i) $NH_2CSNHNH_2$, $POCl_3$, 70 °C, 3 h; ii) $(RCO)_2O$, rt, 12 h.

thiadiazolyl-α,α-difluoromethanesulfonamides (Fig. 1) along with carboxamidodifluoromethanesulfonamide **16**.

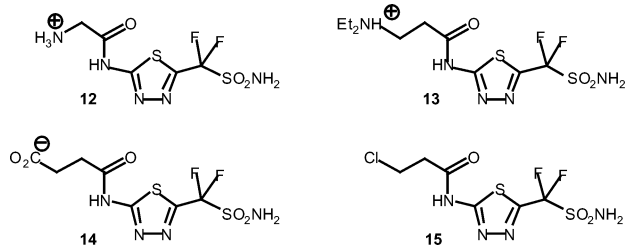

**Fig. 1** *N*-2-Substituted thiadiazolyldifluoromethanesulfonamides.

Sulfonamide p$K_a$ values were determined by potentiometric titration for trifluoromethanesulfonamide and compounds **8–16** (25 °C, 0.1 M salt) and overlapping p$K_a$s were deconvoluted using Kaleidagraph™ (Table 1). For the thiadiazoles **10** and **14**, p$K_a$s were also determined spectroscopically from UV scans using various buffers in the range pH 5–10, especially to discriminate between the ionisations of sulfonamide and carboxamide functions. Clearly, insertion of the $CF_2$ group next to the sulfonamide markedly enhances its acidity (Table 1). A $\Delta pK_a$ increment of +2.2 for acetazolamide (relative to **10**) was matched by similar increments for other thiadiazolesulfonamides of +2.2 for glyazolamide[10] (relative to **12**), +1.9 for betazolamide (relative to 13) and +2.3 for chlorpropazolamide (relative to **15**). These are well in line with the incremental effects of α-fluorination on sulfonamide p$K_a$ values for $CH_3SO_2NH_2$ (10.8), $CFH_2SO_2NH_2$ (9.32),[11] $CF_2HSO_2NH_2$ (8.06)[11] and $CF_3SO_2NH_2$ (6.3).

Water solubilities were determined spectroscopically in phosphate buffered saline, PBS, at pH 7.2 and 25 °C for the thiadiazoles and gravimetrically for other sulfonamides. The data (Table 1) shows that the marked hydrophobic character of fluoromethylene groups does not have an adverse effect on water solubility of the α,α-difluoromethanesulfonamides. Indeed, many of these compounds have solubilities suitable for their application as topical agents in aqueous solution.

Ether partition coefficients were measured for equilibria between diethyl ether and PBS at 25 °C and pH 7.2 and corrected for ionisation of the sulfonamide, with the zwitterionic forms of **12** and **13** and the carboxylate of **9** and **14** taken as uncharged species (Table 1). They show a 300-fold range but with several values close to unity, especially for the most powerful CA inhibitors.

Dissociation constants of inhibitors for human CA II were measured by a fluorimetric competition method[12] accurate to 0.5%. $K_d$ values for these novel α,α-difluoromethanesulfonamides range from 15 to 210 nM (Table 1), which bracket the value of 50 nM for difluoromethanesulfonamide.[3] No other alkanesulfonamides remotely approach such affinity for CA II.[1]

For comparison, the desfluoro-isostere of **10** has $K_d$ 2.5 μM, that is a 12-fold increase resulting from the loss of the two fluorines adjacent to the sulfonamide.

Taken together, the results described here show that the difluoromethanesulfonamide group delivers high affinity ligands for CA II and it can be considered a new sulfonamide pharmacophore of general potential. Its major significance is that it effectively uncouples the desired sulfonamide acidity and drug lipophilicity for CAI activity that hitherto have been achieved only with arenesulfonamides and heteroarenesulfonamides.[1,3] Moreover, it can readily be incorporated into other glaucoma agents, such as ethoxzolamide and methazolamide,[1] and it may well have potential for incorporation into analogues of other sulfonamide therapeutic agents.

Maren has established a near linear inverse correlation between sulfonamide p$K_a$ and log$K_i$ for CA II over five decades.[5] Most importantly, the identification of other binding affinities in the non-sulfonamide moiety has enabled the successful development of anti-glaucoma drugs with over 100-fold improved affinity for CA II over that predicted from their sulfonamide p$K_a$.[5] Of the compounds described here, **3**, **14**, and **15** identify opportunities for such further progress in the use of α,α-difluoroalkanesulfonamides as CAI agents.

Finally, it is noteworthy that the observed affinities of these difluoromethanesulfonamides for CA II relate well to those of a family of 2-(aryloxy)-ethyl sulfamates, $ArOCH_2CH_2OSO_2NH_2$, the best of which have $K_i$ values in the 5 to 50 nM range.[13] This comparison suggests that in the sulfonamide series, as for the phosphonic acids, the $CF_2$ group can be considered as an isopolar and isosteric surrogate for oxygen.[14]

## Acknowledgements

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**Table 1** Some properties of fluoromethanesulfonamides

| Sulfonamide | p$K_a$ | Water sol[a]/wv% | $P_{ether}$ (pH 7.2) | $K_d$ (CAI)/nM |
|---|---|---|---|---|
| Acetazolamide | 8.9 | 0.17 | 0.10 | 9.3 |
| Dorzolamide | 8.4 | 2.17 | 2.0[b] | 8.0[c] |
| $CF_3SO_2NH_2$ | 6.3 | > 10 | 0.003 | <2 |
| **3** | 6.8 | 2.83 | 0.72 | 15.1 |
| **8** | 7.2 | 0.07 | 5.39 | 186 |
| **9** $HOCOCF_2SO_2NH_2$ | 8.3 | > 10 | 0.03 | n.d. |
| **10** | 6.7 | 0.21 | 1.08 | 208 |
| **11** | 6.5 | 0.66 | 1.37 | 150 |
| **12** | 6.8 | > 10 | 0.075 | 122 |
| **13** | 6.9 | 1.30 | 1.05 | 117 |
| **14** | 6.7 | > 10 | 0.33 | 45.4 |
| **15** | 6.8 | 0.36 | 0.98 | 31.7 |
| **16** $H_2NCOCF_2SO_2NH_2$ | 7.0 | > 5 | 0.3 | 40 |

[a] Determined at pH 7.2. [b] $P_{chloroform}$ reported[1]. [c] $K_d$ value reported.[1]

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