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Synthesis of tetrahydrobenzoxazepine acetals with electron-withdrawing groups on the nitrogen atom. Novel scaffolds endowed with anticancer activity against breast cancer cells

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Abstract—Synthetic approaches that have led to (*RS*)-3-methoxy-*N*-substituded-1,2,3,5-tetrahydro-4,1-benzoxazepines with different electron-withdrawing groups, and (*RS*)-2-methoxy-*N*-trifluoroacetyl-2,3,4,5-tetrahydro-1,4-benzoxazepine are described. These novel synthons that were designed to be used as scaffolds for the preparation of new *O*,*N*-acetals as anticancer agents, unexpectedly proved to show antiproliferative activity against the MCF-7 breast cancer cell line. It has been found that substituents on the nitrogen atom have an influence on biological activity. In particular, the presence of a trifluoroacetyl moiety on the nitrogen atom leads to amides displaying interesting in vitro antitumour activities.

1. Introduction

3-Methoxy-2,3-dihydro-5*H*-1,4-benzodioxepins (**1**–**3**) have been used as starting synthons for the preparation of 5-FU derivatives (**4**–**6**, Fig. 1).[1] On the other hand, the reaction between 2-(hydroxymethyl)phenyloxyacetaldehyde dimethyl acetals with 5-FU was subsequently studied.[2] In contrast to 5-FU,[3] the benzannelated 5-FU *O*,*N*-acetals[1] and corresponding open analogues[2] have proved to be non-toxic. Moreover, the bioisosteric benzannelated seven-membered *O*,*N*-acetal **7** (Fig. 1) is particularly useful in stimulating the apoptotic process in breast cancer cells.[1] This was an outstanding biological result because there are few commonly used agents which elicit apoptosis in breast cancer cells, these including paclitaxel (Taxol®), cyclophosphamide, doxorubicin and cytosine arabinoside.[4–6] Nevertheless, their toxicity implies a serious drawback for their therapeutic use and the search of new derivatives possessing even better apoptotic properties and fewer toxic side effects are being diligently sought throughout the scientific community.

Over the years isosteric replacement of oxygen by the nitrogen atom has proved to be one of the most useful tools for medicinal chemistry.[7] The presence of a nitrogen atom provides a new substitution position, the modulation of lipophilicity being possible by the appropriate selection of the nitrogen group. Eleven years ago we described the preparation of acyclic nucleoside analogues,[8] by the tin(IV) chloride-catalysed ring opening of alkoxy-1,4-diheteroepanes with several silylated 5-substituted pyrimidine bases generated in situ. In the case of 7-isopropoxy-1,4-oxazepane **8** (Fig. 1) we noticed that better yields were obtained when the nitrogen atom was substituted by an electron-withdrawing group (such as a tosyl group).

With all this background and as part of an Anticancer Drug Programme we are interested in the preparation of the heterocycles **9a**–**f** and **10** (Fig. 1) that can be useful intermediates for the synthesis of novel bioactive

Keywords: Acetals; Antitumour compounds; Medium-ring heterocycles; Mitsunobu reactions.

Abbreviations: DEAD, diethyl azodicarboxylate; DIAD, diisopropyl azodicarboxylate; DMF, *N*,*N*-dimethylformamide; 5-FU, 5-fluorouracil; MTBD, 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TBAF, tetrabutylammonium fluoride; THF, tetrahydrofuran; TEA, triethylamine; TFAA, trifluoroacetic anhydride.

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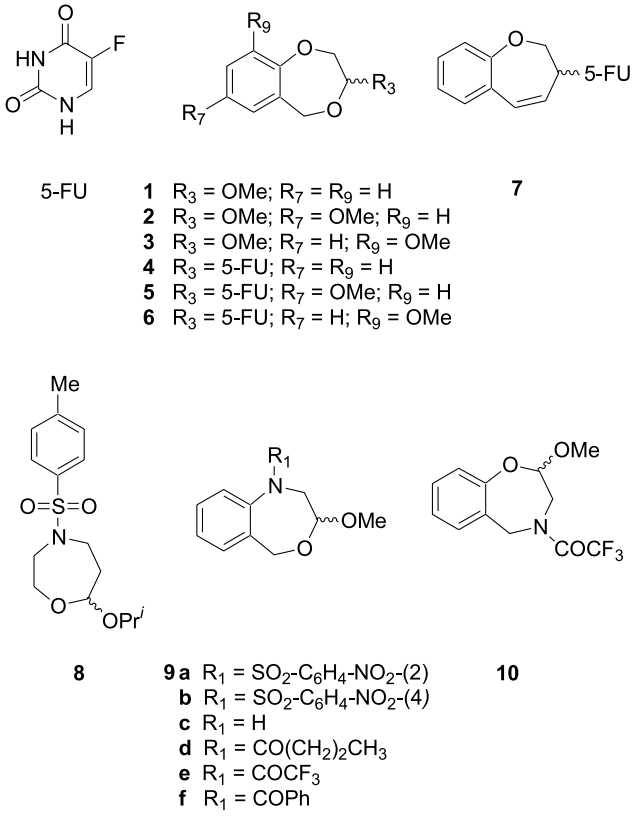


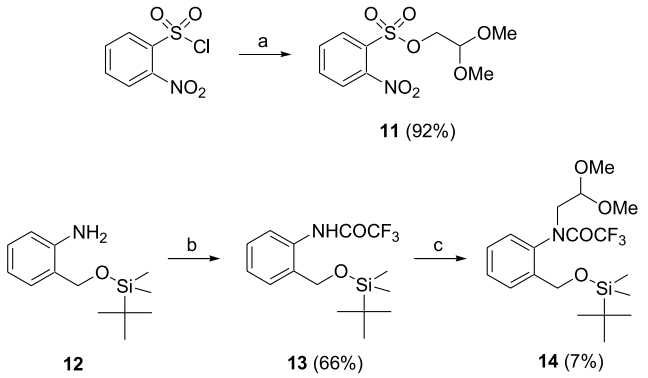
Figure 1.

compounds. In fact, these intermediates were also explored for antitumour activity against the MCF-7 breast cancer cell line. The biological properties of the target molecules **9a–f** and **10** were compared with that of their bioisostere analogue **1** to emphasize the significance of the *N*-substituted fragment in the benzannelated seven-membered acetalic scaffold.

2. Results and discussion

2.1. Synthesis of (*RS*)-3-methoxy-*N*-substituted-1,2,3,5-tetrahydro-4,1-benzoxazepines (9a–f)

All the attempts to alkylate the nitrogen atom of the 2-(hydroxymetyl)aniline with the bromoacetaldehyde dimethyl acetal failed, even when the alcohol group was protected (data not shown). Accordingly, another alkylating strategy was designed (Scheme 1). The formation of 2,2-dimethoxyethyl-2-nitrobenzenesulfonate **11** makes the carbon bearing the sulfonate group adequately electrophilic, which facilitates the attack by a not excessively strong nucleophile. The protection of the hydroxy group of 2-aminobenzyl alcohol with the *tert*-butyldimethylsilanyl group gave **12**,[9] which was trifluoroacetylated by 1-(trifluoroacetyl)benzotriazole[10] to yield **13** (66%). The attack by **11** on the conjugate base of the trifluoroacetanilide moiety could give rise to **14** in the presence of the non-nucleophilic guanidine-like base MTBD. The reaction proceeded neither at rt nor at 40 °C. Compound **14** was obtained when the temperature was raised to 100 °C in a low yield (7%). We think this may be due to an elimination process leading to 1,1-dimethoxyethene and concomitant

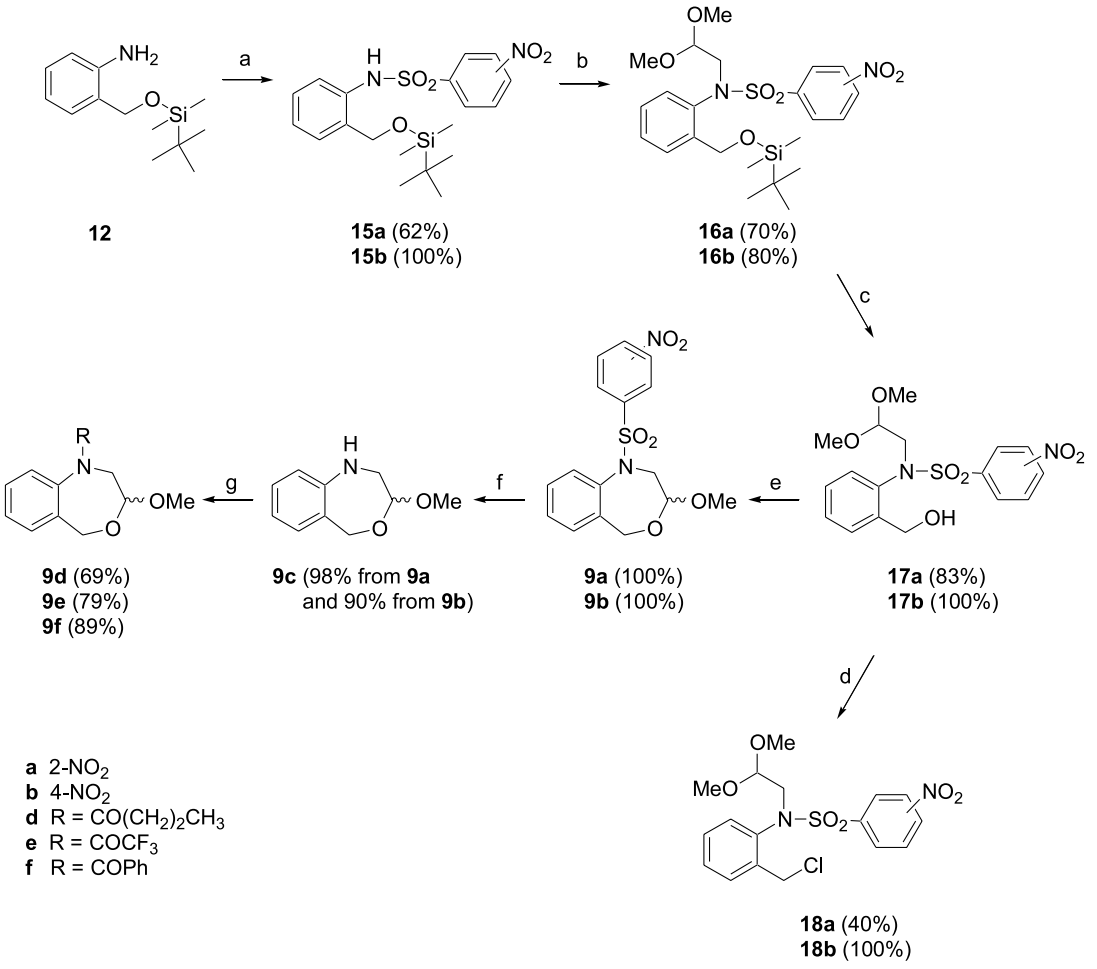


Scheme 1. Reagents and conditions: (a) hydroxyacetaldehyde dimethyl acetal (1 equiv), TEA (1 equiv), anhydrous CH_2Cl_2, 0 °C→rt, 3 h under argon; (b) 1-(trifluoroacetyl)benzotriazole (2.5 equiv), anhydrous THF, rt, 3 h; (c) **11** (1 equiv), MTBD (1 equiv), anhydrous DMF, 100 °C, 24 h under argon.

formation of the sulfonate salt of the base. Due to this low yield, a new synthetic approach needed to be investigated.

The following third strategy was the most rewarding and the synthesis of derivatives **9a–f** was accomplished as outlined in Scheme 2. The Mitsunobu reaction is a versatile method for the conversion of aliphatic alcohols into alkylating agents in situ and under mild conditions.[11] It has been demonstrated that a successful Mitsunobu displacement depends not on the nucleophilicity of the incoming nucleophile but rather on the pK_a associated with the N–H bond.[12] Thus, an 'activating group' (a powerful electron-withdrawing moiety) for the amino fragment is needed, such as the 2- or 4-nitrobenzenesulfonyl function. Attempts of amide alkylation such as the trifluoroacetamide derivative failed. The incapacity of the trifluoroacetamide **13** to participate in the Mitsunobu reaction could be explained by its insufficient acidity, although several alkylation reactions on aromatic trifluoroacetamides have been reported by means of the Mitsunobu reaction.[13–16] The silanyl protecting group probably sterically influenced the outcome of the reaction. Herein we have protected the aniline nitrogen atom as 2- and 4-nitrobenzenesulfonamides. A benzannelated seven-membered secondary amine was obtained (**9c**) after alkylation, deprotection and subsequent cyclization. This synthon could be transformed to a wide range of terciary amides. After protection of the hydroxyl group by the *tert*-butyldimethylsilanyl group (**12**), the synthesis of sulfonamides **15a** and **15b** was accomplished under the conditions of Fukuyama et al.[17] The Mitsunobu conditions were applied to **15a** and hydroxyacetaldehyde dimethyl acetal[18] to give **16a** in a 70% yield. It is worth emphasizing that the yield of **16a** depends greatly on the temperature of the reaction (Scheme 2). When the optimized temperature conditions were applied to **15b**, **16b** was obtained in a 80% yield. After deprotection of the silanyl group of **16a** (and **16b**) with TBAF in THF, **17a** was obtained in a 83% yield (and **17b** in a 100% yield). Compounds **17a** and **17b** quantitatively afforded the cyclic compounds **9a** and **9b**, respectively, using boron trifluoride diethyl etherate as previously reported.[19]

Other conditions were also used for the synthesis of **9a** and **9b**. Such seven-membered acetals were formed after a



Scheme 2. Reagents and conditions: (a) (2)-O_2N-C_6H_4-SO_2Cl (1.1 equiv), TEA (1.5 equiv), CH_2Cl_2, reflux, 24 h, for **15a**; (4)-O_2N-C_6H_4-SO_2Cl (0.5 equiv), CH_2Cl_2, rt, 3 h, for **15b**; (b) $HOCH_2CH(OMe)_2$ (1 equiv), DIAD (1.1 equiv), PPh_3 (1.2 equiv), anhydrous THF, 21 h; the yield of **16a** depends greatly on the reaction temperature: at rt it is 19%, increases up to 70% at 30 °C and goes down to 40% when the temperature is 40 °C; (c) TBAF (1 equiv), THF, rt, 1 h; (d) PhP_3 (1 equiv), CCl_4, 110 °C, 30 min; (e) $BF_3 \cdot OEt_2$ (2 equiv), anhydrous Et_2O, rt, 7 days for **9a**; when these conditions were used to obtain **9b**, the yield was 67%; *p*-H_3C-C_6H_4-SO_3H (0.03 equiv), anhydrous toluene, 110 °C, 2 h under argon for **9a** and **9b**; (f) PhSH (1.1 equiv), K_2CO_3 (3 equiv), DMF, rt, 1 h; (g) $CH_3(CH_2)_2COCl$ (2 equiv), TEA (3 equiv), anhydrous CH_2Cl_2, rt, 17 h under argon, for **9d**; TFAA (2 equiv), TEA (3 equiv), anhydrous CH_2Cl_2, rt, 18 h under argon for **9e**; PhCOCl (2 equiv), TEA (3 equiv), anhydrous CH_2Cl_2, 0–5 °C, 3 h under argon for **9f**.

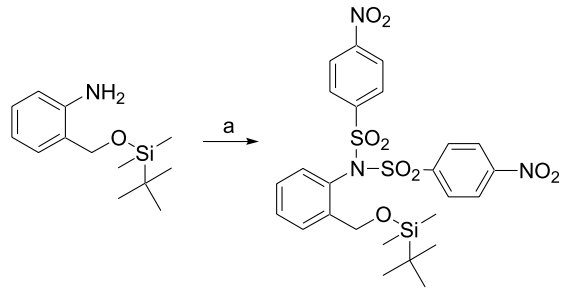
p-toluenesulfonic acid-mediated cyclization from the acyclic acetals **17a** and **17b**, using anhydrous toluene as solvent. We tried to carry out the cyclization process on **17a** (and on **17b**) under the neutral and mild conditions mediated by the triphenylphosphine/carbon tetrachloride system[20] but the process failed and the substitution of the hydroxy group by the chlorine took place to afford **18a** (and **18b**). **17a** and **17b** present bulky groups that limit their conformational motions, making them rigid structures. The oxygen atoms of the acetalic groups cannot act as nucleophiles against the benzylic position (with the triphenylphosphine ether) due to steric hindering.[†]

Finally, the elimination of the sulfonamide group was carried out by treatment with thiophenol[17] and potassium carbonate in DMF to yield the secondary cyclic amine **9c** (98% from **9a**, and 90% from **9b**). Amine **9c** seems to be rather unreactive towards non-activated anhydrides. Acyl chlorides or TFAA were used to conduct the acetylation process that afforded amides **9d** (69%), **9e** (79%), and **9f** (89%). The three amides **9d–f** showed duplicity of all the signals in their ^1H NMR spectra. Such a phenomenon has been studied at length and considered to be due to the existence of a barrier to rotation in amides.[21]

Product **15b** (Scheme 2) was obtained using a two-fold excess of the 2-aminobenzyl silanyl ether **12**. The conditions under which this reaction was carried out were most important for the preparation of **15b**. In fact, the disubstituted derivative **19** was isolated when the reaction is conducted using TEA as a hydrochloride acid scavenger or 1.1 equiv of the sulfonyl chloride was added (Scheme 3).

A plausible explanation implies the previous ionization of the sulfonamide hydrogen atom of **15b** to give a $^-NSO_2$ anion which reacts more rapidly than the starting amine to give **19**. The disulfonimides have been stated[22] to be by-products in reactions of sulfonyl halides with primary amines and ammonia. The 2-nitro group might sterically hinder the $^-NSO_2$ anion and the analogous side product was not isolated.

[†] Hydrogen atoms of the methylene groups of both compounds (**17a** and **17b**) are diastereotopic protons (J_{gem}=12.6–14.1 Hz).

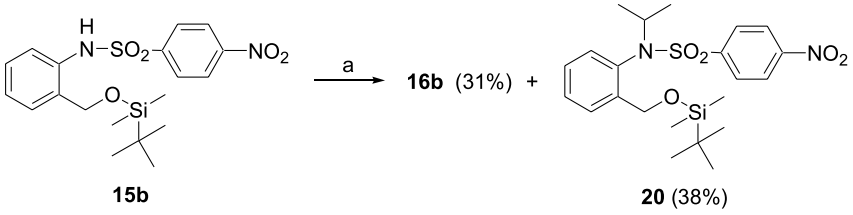


Scheme 3. Reagents and conditions: (a) (4)-O_2N-C_6H_4-SO_2Cl (1.1 equiv), TEA (1.5 equiv), anhydrous CH_2Cl_2, rt, 5 h. When, 0.5 equiv of (4)-O_2N-C_6H_4-SO_2Cl was used, see Scheme 2 (conversion **12**→**15b**).

value is similar to the barrier to rotation around the C_{CO-N} bond in *N*,*N*-dimethylacetamide.[21]

2.3. Structural characteristics of the seven-membered acetals 9a–f and 10

The structures of all derivatives were ascertained by their spectroscopic data (^1H, ^{13}C NMR, MS) and elemental analyses. In compounds **9a–f** ($CDCl_3$ solutions) the acetalic hydrogen atom (H-3) appears between δ 4.67–4.78 ppm as double of doublets (dd). The H-5 atoms are in all cases diastereotopic and compounds **9a–f** show a J_{gem} in the range 13.70–14.30 Hz. Regarding the ^{13}C NMR spectra, the acetalic C-3 atoms of **9a–f** appear at δ 99.03–102.28 ppm. In the case



Scheme 4. Reagents and conditions: (a) $HOCH_2CH(OMe)_2$ (4.3 equiv), DIAD (1.2 equiv), PPh_3 (1.2 equiv), anhydrous THF, rt, 18 h; when 1.2 equiv of $HOCH_2CH(OMe)_2$ were used, see Scheme 2 (conversion **15b**→**16b**).

Alternative conditions to obtain compound **16b** were also investigated (Scheme 4). Thus, addition of an excess of hydroxyacetaldehyde dimethyl acetal (4.3 equiv) afforded the expected acetal **16b** (31%) but the isopropyl alkylated derivative **20** (38%) was also formed. Such a compound could be interpreted by the transesterification reaction of hydroxyacetaldehyde dimethyl acetal with DIAD with the concomitant leaving of isopropanol. A similar process had been previously reported for DEAD but not when DIAD was used.[23]

2.2. Synthesis of (*RS*)-*N*-trifluoroacetyl-2-methoxy-2,3,4,5-tetrahydro-1,4-benzoxazepine (10)

Compound **10** was synthesized as depicted in Scheme 5. Secondary amine **21** was obtained by a reductive alkylation from 2-hydroxybenzaldehyde and aminoacetaldehyde dimethyl acetal. The secondary amine **21** was transformed into the trifluoroacetamide **22** (72%) under the neutral conditions supplied by trifluoroacetylbenzotriazol.[10] Finally, the cyclization process was carried out as previously reported[19] and yielded **10**. The acyclic and cyclic compounds **22** and **10** showed duplicity in their ^1H NMR signals. The hydrogen atoms of the benzyl group had a $\Delta G_c^{\ddagger}$ value of 18.5 kcal/mol using the Eyring equation[24] at a coalescence temperature (T_c) of 80 °C for **22**.[‡] Such a

[‡] The rate constant (k_c) and the free energy of activation ($\Delta G_c^{\ddagger}$) at the coalescence temperature (T_c) were calculated using Gutowsky (1) and Eyring (2) equations, respectively. $\Delta\nu$ is the limiting frequency separation. For Eqs. 1 and 2, see Ref. 24.

$$k_c = \frac{\pi(\Delta\nu)}{\sqrt{2}} \qquad \text{Gutowsky equation (1)}$$

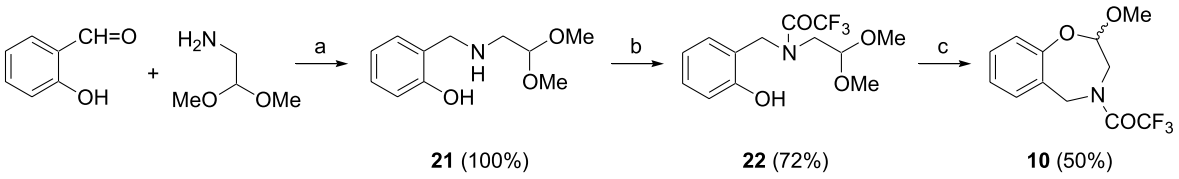
$$\Delta G_c^{\ddagger} = 191.2T_c(10.32 + \log T_c - \log k_c) \qquad \text{Eyring equation (2)}$$

of **10** ($CDCl_3$ solutions) the acetalic proton appears at δ 4.73 ppm as a dd (J=7.8, 2.3 Hz) for one isomer (which represents the 63% of the mixture) and δ 4.79 ppm as a dd (J=7.1, 2.2 Hz) for the other one (37%). Moreover, exactly as it occurred to **9a–f**, the benzilic protons are diastereotopic and resonate at δ 4.91 and 4.35 ppm as doublets (J=14.4 Hz) for the major isomer and at δ 4.73 and 4.57 ppm as doublets (J=15.5 Hz) for the minor one.

2.4. Antiproliferative activity against the MCF-7 human breast cancer cell line for compounds 9a–f,10 and 1

Breast cancer is the second most frequent cancer in the world (1.05 million cases), and is by far the most common malignant disease in women (22% of all new cancer cases). The ratio of mortality to incidence is about 36% worldwide, and breast cancer ranks fifth as a cause of death from cancer overall (although it is the leading cause of cancer mortality in women - the 370 000 annual deaths represent 13.9% of cancer death in women).[25] The MCF-7 human breast cancer cell line had been used as an excellent experimental model to improve the efficacy of different therapies before its use in patients.[26,27] Compounds **9a–f**,**10** and **1** were assayed for their in vitro antiproliferative activity against the MCF-7 cell line and the results are summarized in Table 1. The two most potent compounds are **9e** (IC_{50}=27.39±0.71 μM) and **10** (IC_{50}=27.85±0.64 μM), which bear a trifluoroacetyl group on their nitrogen atom. On the other hand, it is worth pointing out that all the nitrogen-containing acetals (**9a–f**,**10**) are better anticancer agents than the oxygen-containing acetal **1**. This seems to emphasize the importance of the presence of the nitrogen atom on the benzannelated seven-membered rings (biophore).[§]

[§] A biophore may consist of a single feature or a family of chemically similar features.



Scheme 5. Reagents and conditions: (a) (i) EtOH, 78 °C, 5 h, (ii) $NaBH_4$ (2.5 equiv), anhydrous MeOH, 65 °C, 75 min; (b) 1-(trifluoroacetyl)benzotriazole (2.5 equiv), THF, rt, 3 h; (c) $BF_3 \cdot OEt_2$ (2 equiv), anhydrous Et_2O, rt, 5 days.

Table 1. Antiproliferative activities for the compounds against the MCF-7 breast cancer cell line

	9a	9b	9c	9d	9e	9f	10	1
IC_{50} (μM)[a]	51.78±0.21	44.80±0.37	81.05±2.86	39.84±5.35	27.39±0.71	36.70±0.78	27.85±0.64	151.28±16.3

[a] See Ref. 29. The data are means±SEM of three independent determinations.

3. Conclusion

We have developed a new synthetic strategy for the preparation of previously unreported seven-membered acetals such as *N*-substituted-3-methoxy-1,2,3,5-tetrahydro-4,1-benzoxazepines and 2-methoxy-*N*-trifluoroacetyl-2,3,4,5-tetrahydro-1,4-benzoxazepine. These new bicyclic cores may be promising intermediates in the synthesis of new anticancer agents. **9c** is appropriate for the synthesis of an array of target structures for structure–activity relationship studies. An additional point of diversity can now be rapidly introduced on the nitrogen atom of the benzannelated nitrogen-containing acetals utilizing readily available building blocks.

4. Experimental

4.1. Chemistry

Melting points (mp) were taken in open capillaries on an Electrothermal melting point apparatus and are uncorrected. All moisture-sensitive reactions were performed in flame-dried glassware equipped with rubber septa under a positive pressure of dry argon. Organic extracts were dried over $MgSO_4$ and Na_2SO_4. Thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254}, the spots being developed at the UV light. The FLASH 40 chromatography module and the prepacked cartridge systems were supplied by Biotage UK Limited, 15 Harforde Court. Foxholes Business Park, John Tate Rd. Hertford, England SG13 7NM. ^1H and ^{13}C NMR spectra were recorded on a Bruker at 300.13 and 400.13 MHz, and at 75.78 and 100.03 MHz, respectively in $CDCl_3$ and in DMSO-d_6 solutions. Chemical shifts were measured in δ and referenced to $CDCl_3$ (7.25 ppm for ^1H NMR and 77.20 ppm for ^{13}C NMR) and to DMSO-d_6 (2.50 ppm for ^1H NMR and 39.50 ppm for ^{13}C NMR). The mass spectra (MS) were obtained using a Micromass Platform II spectrometer at 70 eV, carrying out injection through a Carlo Erba GC 8000 chromatograph in a splitless mode for capillary columns. The accurate mass determination was carried out in an AutoSpec-Q mass spectrometer arranged in an EBE geometry (Micromass Instruments, Manchester, UK) and equipped with a liquid secondary ion mass spectra (LSIMS) source. The instrument was operated at 8 kV of accelerating voltage and Cs^+ cations were used as primary ions. Solvents were obtained dry as follows: THF was distilled from benzophenone ketyl, CH_2Cl_2 was refluxed over, and distilled from P_2O_5 and then stored over molecular sieves (3 Å), CH_3OH from Mg. Anhydrous DMF was purchased from Sigma-Aldrich Quimica S. A.

4.1.1. 2,2-Dimethoxyethyl-2-nitrobenzenesulfonate (11). A solution of hydroxyacetaldehyde dimethyl acetal (1 equiv) in dried CH_2Cl_2 (3 mL/mmol of hydroxyacetaldehyde dimethyl acetal) was prepared under argon. After cooling to 0 °C, 2-nitrobenzenesulfonile chloride (1 equiv) was added as a solid in one portion, followed by TEA (1 equiv). The reaction mixture was then allowed to warm at rt and stirred under argon for 3 h after which CH_2Cl_2 was added and the solution was washed with water. The final organic layer was dried (Na_2SO_4) and the solvent evaporated under vacuum. Purification by flash chromatography (elution with CH_2Cl_2) afforded **11** as a yellow liquid (92% yield). ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.12 (dd, J= 7.9 Hz, 1H), 7.84–7.70 (m, 3H), 4.60 [t, J_{CH-CH2}=5.3 Hz, 1H, C*H*$(OCH_3)_2$], 4.22 (d, 2H, CH_2), 3.36 [s, 6H, $(OCH_3)_2$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 134.93, 132.38, 131.43, 124.93 (C_3, C_4, C_5, C_6), 129.72 (C_1), 101.09 [*C*H$(OCH_3)_2$], 69.62 (*C*H_2), 54.73 [$(OCH_3)_2$]. LSIMS *m/z* (relative intensity) 316 (7), 315 (14), 314 $[M+Na)^+$, 100], 307 (8), 289 (7), 279 (5), 260 (25), 237 (46), 226 (7), 215 (4), 214 (10). HR LSIMS *m/z* calcd for $C_{10}H_{13}NO_7SNa$ $(M+Na)^+$: 314.0310, found: 314.0309.

4.1.2. *N*-[2-(*tert*-Butyldimethylsilanyloxymethyl)phenyl]-2,2,2-trifluoroacetamide (13). A solution of **12**[9] (1 equiv) and 1-(trifluoroacetyl)benzotriazole[10] (2.5 equiv) in THF (3 mL/mmol of **12**) was prepared and allowed to stir at rt for 3 h. The solvent was then removed under vacuum and the residue purified by flash chromatography (elution mixture EtOAc/hexane 1/100 in flash 40 chromatography). **13** was obtained as a yellow liquid in 66% yield. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 10.15 (bs, 1H, N*H*), 8.22, (d, J=8.12 Hz, 1H), 7.36 (m, 1H), 7.17–7.11 (m, 2H), 4.80 (s, 2H, CH_2), 0.89 [s, 9H, $(CH_3)_3C$], 0.10 (s, 6H, $(CH_3)_2Si$]. ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 135.77, 129.43 (C_1, C_2), 128.98, 127.92, 125.50, 121.76 (C_5, C_6, C_7, C_8), 115.69 (q, J_{C-F}=290.0 Hz, *C*F_3), 65.61 (*C*H_2), 25.66 [$(CH_3)_3C$], 18.26 [$(CH_3)_3C$], −5.44 [$(CH_3)_2Si$]. LSIMS *m/z* (relative intensity) 358 (8), 357 (18), 356 $[M+Na)^+$, 100], 355 (7). HR LSIMS *m/z* calcd for $C_{15}H_{22}NO_2F_3SiNa$ $(M+Na)^+$: 356.1270, found: 356.1268.

4.1.3. *N*-[2-(*tert*-Butyldimethylsilanyloxymethyl)phenyl]-*N*-(2,2-dimethoxyethyl)-2,2,2-trifluoroacetamide (14). The base MTBD (1 equiv) was added dropwise, at rt, to a solution of **13** (1 equiv) in dried DMF (3 mL/mmol of **13**) prepared under argon. The mixture was stirred at rt for 1 h, after which a solution of sulfonate **11** (1 equiv) in dried DMF (3 mL/mmol of **11**) was added. The temperature was then raised to 100 °C. After 24 h stirring under argon, water and CH_2Cl_2 were added to the cooled reaction mixture and the organic layer was subjected to several washes with water. The final organic layer was dried (Na_2SO_4) and the solvent removed under vacuum. The residue was chromatographed on silica flash by gradient elution mixtures (EtOAc/hexane 1/150→1/100) to afford **14** as a yellow liquid in 7% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.18 (t, 1H), 7.01 (d, 1H), 6.65 (m, 2H), 4.66 (s, 2H, OCH_2), 4.62 [t, 1H, $CH(OCH_3)_2$], 3.41 [s, 6H, $(OCH_3)_2$], 3.28 (d, 2H, NCH_2), 0.89 [s, 9H, $(CH_3)_3C$], 0.06 [s, 6H, $(CH_3)_2Si$].

4.1.4. *N*-[2-(*tert*-Butyldimethylsilanyloxymethyl)phenyl]-2-nitrobenzenesulfonamide (15a). To a solution of **12**[9] in CH_2Cl_2 (3 mL/mmol of **12**) at rt, was added solid 2-nitrobenzenesulfonyl chloride (1.1 equiv) followed by TEA (1.5 equiv). After stirring for 24 h at 30 °C, the mixture was diluted with CH_2Cl_2 and the resulting organic layer was washed with water, dried on Na_2SO_4 and the solvent evaporated under vacuum. **15a** was purified by flash chromatography (gradient elution EtOAc/hexane 1/100→1/8) and obtained as a yellow, low melting point solid (mp 83.0–83.9 °C) in 62% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.70 (bs, 1H, N*H*), 7.90 (dd, J=7.8, 1.5 Hz, $1H_{sulfonamide}$), 7.82 (dd, J=7.9, 1.4 Hz, $1H_{sulfonamide}$), 7.68 (ddd, $J_1=J_2$=7.7 Hz, J_3=1.5 Hz, $1H_{sulfonamide}$), 7.61–7.54 (m, 2H), 7.28–7.23 (m, 1H), 7.12–7.08 (m, 2H), 4.58 (s, 2H, CH_2), 0.91 [s, 9H, $(CH_3)_3C$], 0.07 (s, 6H, $(CH_3)_2Si$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 148.04, 135.58 ($C_{2\ sulfonamide}$, C_{1}), 133.81, 132.45 ($C_{4\ sulfonamide}$, $C_{5\ sulfonamide}$), 133.63, 132.61 ($C_{1\ sulfonamide}$, C_2), 131.26, 128.71, 128.28 125.54, 125.14 ($C_{3\ sulfonamide}$, $C_{6\ sulfonamide}$, C_3, C_4, C_5, C_6), 64.32 (CH_2), 25.87 [$(CH_3)_3C$], 18.36 [$(CH_3)_3C$], −5.30 [$(CH_3)_2Si$]. LSIMS *m/z* (relative intensity) 448 (2), 447 (13), 446 (27), 445 [$(M+Na)^+$, 100], 423 [$(M+H)^+$, 14], 421 (6), 367 (6), 366 (12), 365 (50), 329 (17), 313 (11), 292 (11), 291 (70). HR LSIMS *m/z* calcd for $C_{19}H_{26}N_2O_5SSiNa$ $(M+Na)^+$: 445.1229, found: 445.1230.

4.1.5. *N*-[2-(*tert*-Butyldimethylsilanyloxymethyl)phenyl]-4-nitrobenzenesulfonamide (15b). Small portions 4-nitrobenzenesulfonyl chloride (0.5 equiv) were added to a solution of **12**[9] (1 equiv) in dried CH_2Cl_2 (3 mL/mmol of **12**). After 3 h stirring at rt the reaction mixture was washed 3 times with water. The final organic layer was dried on Na_2SO_4 and evaporated under vacuum. Purification by flash chromatography (gradient elution mixtures EtOAc/hexane 1/50→1/20) afforded **15b** as a white solid (mp 103.6–103.8 °C) in quantitative yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.69 (s, 1H, N*H*), 8.27 (d, $J_{6-5\ sulfonamide}=J_{3-2\ sulfonamide}$= 8.8 Hz, 2H, $H_{3,5\ sulfonamide}$), 7.95 (d, 2H, $H_{2,6\ sulfonamide}$), 7.56 (dd, J=8.1, 0.9 Hz, 1H), 7.29 (ddd, $J_1=J_2$=7.7 Hz, J_3= 1.6 Hz, 1H), 7.08 (ddd, $J_1=J_2$=7.5 Hz, J_3=1.2 Hz, 1H), 7.00 (dd, J=7.6, 1.6 Hz, 1H), 4.36 (s, 2H, CH_2), 0.92 [s, 9H, $(CH_3)_3C$], 0.08 [s, 6H, $(CH_3)_2Si$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 150.23 ($C_{4\ sulfonamide}$), 146.14, 136.18 ($C_{1\ sulfonamide}$, C_1), 130.54 (C_2), 129.18, 128.24, 125.36, 122.22 (C_3, C_4, C_5, C_6), 128.24 ($C_{2\ sulfonamide}$, $C_{6\ sulfonamide}$), 124.27 ($C_{3\ sulfonamide}$, $C_{5\ sulfonamide}$), 65.25 (CH_2), 25.80 [$(CH_3)_3C$], 18.19 [$(CH_3)_3C$], −5.38 [$(CH_3)_2Si$]. LSIMS *m/z* (relative intensity) 448 (12), 447 (17), 446 (22), 445 [$(M+Na)^+$, 100], HR LSIMS *m/z* calcd for $C_{19}H_{26}N_2O_5SSiNa$ $(M+Na)^+$: 445.1229, found: 445.1229.

4.1.6. *N*-[2-(*tert*-Butyldimethylsilanyloxymethyl)phenyl]-*N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide (16a). A solution of **15a** (1 equiv), hydroxyacetaldehyde dimethyl acetal (1 equiv) and triphenylphosphine (1.2 equiv) in dried THF (5 mL/mmol of **15a**) was prepared under argon atmosphere. To this solution, DIAD (1.1 equiv) was added dropwise at −20 °C and temperature was then allowed to rise to 5 °C before heating to 30 °C. Stirring under argon atmosphere was maintained for 21 h after which the solvent was removed in vacuum and the residue purified by flash chromatography (gradient elution mixtures EtOAc/hexane 1/20→1/8) to afford **16a** (70% yield) as a pale yellow, low melting point solid (mp 83.5–84.5 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.68–7.57 (m, 3H), 7.48–7.34 (m, 3H), 7.16 (ddd, $J_1=J_2$=7.7 Hz, J_3=1.7 Hz, 1H), 6.98 (dd, J=8.0 Hz, J=1.3 Hz, 1H), 4.85 (d, $J_{gem\ OCH2}$= 14.3 Hz, 1H, OCH_2), 4.56 (d, 1H, OCH_2), 4.42 [dd, J_{CH-CH2}=5.8 Hz, J_{CH-CH2}=5.3 Hz, 1H, $CH(OCH_3)_2$], 3.92 (dd, $J_{gem\ NCH2}$=14.6 Hz, J_{CH-CH2}=5.8 Hz, 1H, NCH_2), 3.71 (dd, J_{CH-CH2}=5.3 Hz, 1H, NCH_2), 3.30 (s, 3H, OCH_3), 3.23 (s, 3H, OCH_3), 0.91 [s, 9H, $(CH_3)_3C$], 0.06 [s, 3H, $(CH_3)_2Si$], 0.05 [s, 3H, $(CH_3)_2Si$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 148.16 ($C_{2\ sulfonamide}$), 142.56, 135.11 (C_1, $C_{1\ sulfonamide}$), 133.80 ($C_{5\ sulfonamide}$), 132.19 ($C_{4\ sulfonamide}$), 131.74 (C_2), 131.08, 129.86, 129.26, 128.21, 127.44, 123.73 ($C_{3\ sulfonamide}$, $C_{6\ sulfonamide}$, C_3, C_4, C_5, C_6), 101.58 [$CH(OCH_3)_2$], 60.69 (OCH_2), 53.58, 52.72 [$(OCH_3)_2$], 53.13 (NCH_2), 25.99 [$(CH_3)_3C$], 18.41 [$(CH_3)_3C$], −5.32 [$(CH_3)_2Si$]. LSIMS *m/z* (relative intensity) 536 (2), 535 (14), 534 (31), 533 [$(M+Na)^+$, 100], 481 (3), 480 (7), 479 (22), 455 (2), 454 (6), 453 (18), 349 (1), 348 (3), 347 (8), 295 (4), 294 (12), 293 (50), 269 (1), 268 (2), 267 (8). HR LSIMS *m/z* calcd for $C_{23}H_{34}N_2O_7SSiNa$ $(M+Na)^+$: 533.1754, found: 533.1758.

4.1.7. *N*-[2-(*tert*-Butyldimethylsilanyloxymethyl)phenyl]-*N*-(2,2-dimethoxyethyl)-4-nitrobenzenesulfonamide (16b). Compound **16b** was obtained from **15b** following the procedure described for **15a**, as a white, low melting point solid (mp 92.0–93.0 °C) eluted with gradient elution mixtures EtOAc/hexane (1/50→1/20) by flash chromatography (80% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.32 (d, $J_{6-5\ sulfonamide}=J_{3-2\ sulfonamide}$=8.8 Hz, 2H, $H_{3,5\ sulfonamide}$), 7.83 (d, 2H, $H_{2,6\ sulfonamide}$), 7.69 (d, J= 7.7 Hz, 1H), 7.38 (t, J=7.5 Hz, 1H), 7.10 (t, J=7.4 Hz, 1H), 6.42 (d, J=7.5 Hz, 1H), 4.99 (d, $J_{gem\ OCH2}$=14.4 Hz, 1H, OCH_2), 4.93 (d, 1H, OCH_2), 4.36 [dd, J_{CH-CH2}=5.5, 5.7 Hz, 1H, $CH(OCH_3)_2$], 3.84 (dd, $J_{gem\ NCH2}$=14.0 Hz, J_{CH-CH2}=5.5 Hz, 1H, NCH_2), 3.41 (dd, J_{CH-CH2}=5.7 Hz, 1H, NCH_2), 3.32 (s, 3H, OCH_3), 3.15 (s, 3H, OCH_3), 0.96 [s, 9H, $(CH_3)_3C$], 0.14 [s, 3H, $(CH_3)_2Si$], 0.13 [s, 3H, $(CH_3)_2Si$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 150.26 ($C_{4\ sulfonamide}$), 143.97, 143.36 ($C_{1\ sulfonamide}$, C_1), 135.70 (C_2), 129.48 ($C_{2\ sulfonamide}$, $C_{6\ sulfonamide}$), 129.29, 128.48, 127.30, 127.10 (C_3, C_4, C_5, C_6), 124.03 ($C_{3\ sulfonamide}$,

$C_{5\ sulfonamide}$), 101.26 [*C*H(OCH$_3$)$_2$], 61.05 (O*C*H$_2$), 53.77, 52.50 [(O*C*H$_3$)$_2$], 52.79 (N*C*H$_2$), 26.04 [(*C*H$_3$)$_3$C], 18.46 [(CH$_3$)$_3$*C*], −5.25 [(*C*H$_3$)$_2$Si]. LSIMS *m/z* (relative intensity) 536 (3), 535 (15), 534 (34), 533 [(M+Na)$^+$, 100], 482 (1), 481 (3), 480 (5), 479 (15), 455 (4), 454 (9), 453 (33), 349 (2), 348 (3), 347 (7), 331 (3), 330 (9), 329 (30), 311 (40), 295 (4), 294 (13), 293 (52), 284 (21), 262 (14), 254 (6). HR LSIMS *m/z* calcd for $C_{23}H_{34}N_2O_7SSiNa$ (M+Na)$^+$: 533.1754, found: 533.1753.

4.1.8. *N*-(2,2-Dimethoxyethyl)-*N*-(2-hydroxymethylphenyl)-2-nitrobenzenesulfonamide (17a). To a stirred solution of **16a** (1 equiv) in THF (6 mL/mmol of **16a**) monohydrated TBAF (1 equiv) was added at rt. The reaction mixture was stirred for 1 h (until no starting material could be visualised on TLC). The solvent was then removed in vacuum, the residue solved in CH_2Cl_2 and washed with water. The organic layer, dried on Na_2SO_4, was evaporated and purified by flash chromatography (gradient elution mixtures EtOAc/hexane 1/10→1/1). **17a** was obtained as a yellow oil (83% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.71–7.59 (m, 3H), 7.47 (ddd, $J_1=J_2=7.6$ Hz, $J_3=$ 1.4 Hz, 1H), 7.41–7.35 (m, 2H), 7.14 (ddd, $J_1=J_2=7.7$ Hz, $J_3=1.6$ Hz, 1H), 6.74 (dd, $J=8.0$, 1.1 Hz, 1H), 4.89 (d, $J_{gem\ OCH2}=12.4$ Hz, 1H, OC*H*$_2$), 4.65 (d, 1H, OC*H*$_2$), 4.45 [dd, $J_{CH-CH2}=5.9$, 5.3 Hz, 1H, C*H*(OCH$_3$)$_2$], 4.29 (dd, $J_{gem\ NCH2}=14.5$ Hz, $J_{CH-CH2}=5.9$ Hz, 1H, NC*H*$_2$), 3.46 (dd, $J_{CH-CH2}=5.3$ Hz, 1H, NC*H*$_2$), 3.37 (s, 3H, OC*H*$_3$), 3.14 (s, 3H, OC*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 148.46 ($C_{2\ sulfonamide}$), 142.95, 136.78 (C_1, $C_{1\ sulfonamide}$), 134.11 ($C_{5\ sulfonamide}$), 132.52 ($C_{4\ sulfonamide}$), 130.86 (C_2), 131.94, 131.03, 129.81, 128.77, 128.38, 123.86 ($C_{3\ sulfonamide}$, $C_{6\ sulfonamide}$, C_3, C_4, C_5, C_6), 101.20 [*C*H(OCH$_3$)$_2$], 61.02 (O*C*H$_2$), 53.23, 52.22 [(O*C*H$_3$)$_2$], 53.13 (N*C*H$_2$). LSIMS *m/z* (relative intensity) 420 (20), 419 [(M+Na)$^+$, 100], 413 (11), 369 (6), 334 (8), 333 (37), 326 (11). HR LSIMS *m/z* calcd for $C_{17}H_{20}N_2O_7SNa$ (M+Na)$^+$: 419.0889, found: 419.0889.

4.1.9. *N*-(2,2-Dimethoxyethyl)-*N*-(2-hydroxymethylphenyl)-4-nitrobenzenesulfonamide (17b). Compound **17b** was prepared from **16b** following the procedure described for **17a** and obtained as a yellow solid (mp 139.5–140.7 °C) eluted by flash chromatography (gradient elution mixtures EtOAc/hexane 1/10→1/2) (90% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.34 (d, $J_{3-2\ sulfonamide}=J_{6-5\ sulfonamide}=8.9$ Hz, 2H, $H_{3,5\ sulfonamide}$), 7.81 (d, 2H, $H_{2,6\ sulfonamide}$), 7.64 (dd, $J=7.7$, 1.6 Hz, 1H), 7.39 (ddd, $J_1=J_2=7.6$ Hz, $J_3=$ 1.1 Hz, 1H), 7.16 (ddd, $J_1=J_2=7.7$ Hz, $J_3=1.6$ Hz, 1H), 6.36 (dd, $J=8.0$, 0.9 Hz, 1H), 4.94 (dd, $J_{gem\ OCH2}=$ 12.4 Hz, $J_{CH2\text{-}OH}=6.7$ Hz, 1H, OC*H*$_2$), 4.69 (dd, $J_{CH2\text{-}OH}=7.2$ Hz, 1H, OC*H*$_2$), 4.43 [dd, $J_{CH-CH2}=5.9$, 5.6 Hz, 1H, C*H*(OCH$_3$)$_2$], 4.01 (dd, $J_{gem\ NCH2}=14.0$ Hz, $J_{CH-CH2}=$ 5.9 Hz, 1H, NC*H*$_2$), 3.38 (s, 3H, OC*H*$_3$), 3.35 (dd, 1H, O*H*), 3.24 (dd, $J_{CH-CH2}=5.6$ Hz, 1H, NC*H*$_2$), 3.09 (s, 3H, OC*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 150.43 ($C_{4\ sulfonamide}$), 143.02, 142.99 ($C_{1\ sulfonamide}$, C_1), 136.95 (C_2), 132.10, 129.82, 128.77, 126.48 (C_3, C_4, C_5, C_6), 129.48 ($C_{2\ sulfonamide}$, $C_{6\ sulfonamide}$), 124.25 ($C_{3\ sulfonamide}$, $C_{5\ sulfonamide}$), 100.62 [*C*H(OCH$_3$)$_2$], 61.14 (O*C*H$_2$), 53.38, 51.75 [(O*C*H$_3$)$_2$], 52.22 (N*C*H$_2$). LSIMS *m/z* (relative intensity) 421 (9), 420 (24), 419 [(M+Na)$^+$, 100], 405 (9), 403 (6), 365 (7), 335 (4), 334 (6), 333 (27), 331 (6), 330 (23), 329 (88), 325 (10). HR LSIMS *m/z* calcd for $C_{17}H_{20}N_2O_7SNa$ (M+Na)$^+$: 419.0889, found: 419.0889.

4.1.10. *N*-(2-Chloromethylphenyl)-*N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide (18a). A solution of **17a** (1 equiv) and triphenylphosphine (1 equiv) in CCl_4 was suddenly heated to 110 °C and then stirred at this temperature for 30 min. After this time, the reaction mixture was allowed to cool at rt, the solvent was removed in vacuum and the residue solved in CH_2Cl_2. Purification by flash chromatography eluting with CH_2Cl_2 gave **18a** as a liquid (40% yield). After standing it solidified giving a white amorphous solid (mp 65.4–66.4 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.69–7.59 (m, 3H), 7.48–7.35 (m, 3H), 7.20 (ddd, $J_1=J_2=7.4$ Hz, $J_3=1.6$ Hz, 1H), 6.99 (dd, $J=$ 8.0, 1.2 Hz, 1H), 4.86 (d, $J_{gem\ CH2Cl}=12.6$ Hz, 1H, C*H*$_2$Cl), 4.59 (d, 1H, C*H*$_2$Cl), 4.47 [dd, $J_{CH-CH2}=5.8$, 5.2 Hz, 1H, C*H*(OCH$_3$)$_2$], 4.05 (dd, $J_{gem\ NCH2}=14.6$ Hz, $J_{CH-CH2}=$ 5.8 Hz, 1H, NC*H*$_2$), 3.69 (dd, $J_{CH-CH2}=5.2$ Hz, 1H, NC*H*$_2$), 3.34 (s, 3H, OC*H*$_3$), 3.28 (s, 3H, OC*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 148.18 ($C_{2\ sulfonamide}$), 139.04, 136.39 (C_1, $C_{1\ sulfonamide}$), 134.05 ($C_{5\ sulfonamide}$), 132.28 ($C_{4\ sulfonamide}$), 131.40 (C_2), 131.20, 131.04, 129.64, 128.96, 123.99 ($C_{3\ sulfonamide}$, $C_{6\ sulfonamide}$, C_3, C_4, C_5, C_6), 101.76 [*C*H(OCH$_3$)$_2$], 53.71 (N*C*H$_2$), 53.66, 53.28 [(O*C*H$_3$)$_2$], 41.56 (*C*H$_2$Cl). LSIMS *m/z* (relative intensity) 441 (3), 440 (7), 439 (40), 438 (21), 437 [(M+Na)$^+$, 100], 413 (6), 385 (8), 384 (3), 383 (20). HR LSIMS *m/z* calcd for $C_{17}H_{19}ClN_2O_6SNa$ (M+Na)$^+$: 437.0550, found: 437.0557.

4.1.11. *N*-(2-Chloromethylphenyl)-*N*-(2,2-dimethoxyethyl)-4-nitrobenzenesulfonamide (18b). The same procedure that led to **18a** was applied to **17b** to afford **18b** as a liquid in quantitative yield (purification by flash chromatography, elution with CH_2Cl_2) which solidified on standing as a white solid (mp 100.0–101.0 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.33 (d, $J_{3-2\ sulfonamide}=J_{6-5\ sulfonamide}=8.8$ Hz, 2H, $H_{3,5\ sulfonamide}$), 7.80 (d, 2H, $H_{2,6\ sulfonamide}$), 7.73 (dd, $J=7.8$, 1.3 Hz, 1H), 7.41 (ddd, $J_1=J_2=7.7$ Hz, $J_3=1.1$ Hz, 1H), 7.18 (ddd, $J_1=J_2=$ 7.7 Hz, $J_3=1.5$ Hz, 1H), 6.46 (dd, $J=8.0$, 1.0 Hz, 1H), 5.04 (d, $J_{gem\ CH2Cl}=12.8$ Hz, 1H, C*H*$_2$Cl), 4.73 (d, 1H, C*H*$_2$Cl), 4.43 [dd, $J_{CH-CH2}=5.3$, 5.8 Hz, 1H, C*H*(OCH$_3$)$_2$], 3.93 (dd, $J_{gem\ NCH2}=14.1$ Hz, $J_{CH-CH2}=5.3$ Hz, 1H, NC*H*$_2$), 3.42 (dd, $J_{CH-CH2}=5.8$ Hz, 1H, NC*H*$_2$), 3.36 (s, 3H, OC*H*$_3$), 3.19 (s, 3H, OC*H*$_3$). LSIMS *m/z* (relative intensity) 440 (5), 439 (37), 438 (20), 437 [(M+Na)$^+$, 100], 435 (7), 433 (5), 427 (7), 426 (6), 425 (10), 424 (6), 423 (9), 422 (5), 421 (7), 419 (6), 413 (35), 412 (11), 411 (16), 410 (9), 409 (14), 408 (6), 407 (9). HR LSIMS *m/z* calcd for $C_{17}H_{19}ClN_2O_6SNa$ (M+Na)$^+$: 437.0550, found: 437.0548.

4.1.12. *N*-[2-(*tert*-Butyldimethylsilanyloxymethyl)phenyl]bis(4-nitrobenzenesulfonyl)imide (19). Compound **19** is obtained as sole product when the initial amine **12** is treated with 4-nitrobenzenesulfonyl chloride (1.1 equiv) and TEA (1.5 equiv) in CH_2Cl_2 (3 mL/mmol of **12**) as described for the preparation of **15a**. After 5 h stirring at rt, the reaction mixture was washed with water and the final organic layer dried (Na_2SO_4) and evaporated under vacuum. Purification by flash chromatography (gradient elution mixtures EtOAc/hexane 1/50→1/10) afforded **19** as a

white solid (mp 178.9–179.9 °C) in quantitative yield. When the same reaction was carried out using only 1 equiv of 4-nitrobenzenesulfonyl chloride (1 equiv **12**, 1.36 equiv NEt_3), stirring at rt for 1 h it leads to a mixture of **19** (53% yield) and **15b** (23% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.42 (2d, $J_{3-2\ \text{sulfonylimide}}=J_{6-5\ \text{sulfonylimide}}=8.9$ Hz, 4H, $H_{3,5\ \text{sulfonylimide}}$), 8.17 (2d, 4H, $H_{2,6\ \text{sulfonylimide}}$), 7.67 (dd, $J=7.8$, 1.1 Hz, 1H), 7.55 (ddd, $J_1=J_2=7.6$ Hz, $J_3=$ 1.1 Hz, 1H), 7.27 (ddd, $J_1=J_2=7.6$ Hz, $J_3=1.6$ Hz, 1H), 6.83 (dd, $J=8.0$, 1.1 Hz, 1H), 4.32 (s, 2H, OCH_2), 0.87 [s, 9H, $(CH_3)_3C$], −0.02 [s, 6H, $(CH_3)_2Si$]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 151.10 ($C_{4\ \text{sulfonylimide}}$), 144.27 ($C_{1\ \text{sulfonylimide}}$), 143.23 ($C_1$), 131.54, 129.07, 127.89 (C_3, C_4, C_5, C_6), 130.49, 124.42 ($C_{2\ \text{sulfonylimide}}$, $C_{3\ \text{sulfonylimide}}$, $C_{5\ \text{sulfonylimide}}$, $C_{6\ \text{sulfonylimide}}$), 129.92 ($C_2$), 60.59 ($OCH_2$), 25.86 [$(CH_3)_3C$], 18.36 [$(CH_3)_3C$], −5.40 [$(CH_3)_2Si$]. LSIMS (relative intensity) 632 (16), 631 (23), 630 [$(M+Na)^+$, 50], 617 (7), 616 (19), 615 (16), 614 (11), 608 (10), 606 (8), 552 (18), 551 (33), 550 (100), 536 (3), 535 (7), 534 (15), 477 (4), 476 (23), 467 (12), 445 (8), 443 (6), 421 (9), 386 (14), 385 (21), 364 (20), 351 (5), 350 (7), 349 (43), 327 (24), 291 (39), 290 (26), 279 (67). HR LSIMS *m/z* calcd for $C_{25}H_{29}N_3O_9S_2SiNa$ $(M+Na)^+$: 630.1012, found: 630.1010.

4.1.13. (*RS*)-3-Methoxy-1-(2-nitrobenzenesulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine (9a). *Method A*. $BF_3\cdot OEt_2$ (2 equiv) was added dropwise to a stirred solution of **17a** (1 equiv) in dried ether (5 mL/mmol of **17a**) at rt under argon. The mixture was kept in a dark place maintaining inert atmosphere, until no initial material was visualised on TLC (4–7 days). Solvent was then evaporated under vacuum and the residue dissolved in CH_2Cl_2 and washed with distilled water. The organic layer was dried (Na_2SO_4), evaporated and chromatographed on silica flash by elution with CH_2Cl_2, to give **9a** as a white solid (mp 128.7–129.3 °C), in quantitative yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.92 (dd, $J=7.9$, 1.3 Hz, 1H), 7.75–7.59 (m, 3H), 7.32–7.17 (m, 3H), 7.07 (d, $J=7.7$ Hz, 1H), 4.86 (d, $J_{gem\ 5-5}=13.7$ Hz, 1H, H_5), 4.74 (dd, 1H, H_3), 4.42 (d, 1H, H_5), 3.90 (bs, 1H, H_2), 3.75 (bs, 1H, H_2), 3.39 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 148.02 ($C_{2\ \text{sulfonamide}}$), 139.34, 138.28 ($C_{9a}$, $C_{1\ \text{sulfonamide}}$), 134.25 ($C_{5a}$), 133.86, 132.08, 131.42, 129.63, 128.81, 128.54, 128.28, 124.24 ($C_{3\ \text{sulfonamide}}$, $C_{4\ \text{sulfonamide}}$, $C_{5\ \text{sulfonamide}}$, $C_{6\ \text{sulfonamide}}$, C_6, C_7, C_8, C_9), 101.00 (bs, C_3), 64.00 (bs, C_5), 55.58 (OCH_3), 54.36 (C_2). LSIMS *m/z* (relative intensity) 389 (25), 388 (13), 387 [$(M+Na^+$, 100], 386 (6), 385 (44), 371 (10), 369 (13), 367 (11), 349 (5), 345 (12), 329 (10), 327 (44), 311 (21), 301 (12). HR LSIMS *m/z* calcd for $C_{16}H_{16}N_2O_6SNa$ $(M+Na)^+$: 387.0627, found: 387.0626. Anal. for $C_{16}H_{16}N_2O_6S$: calcd C 52.75; H 4.40; N 7.69. Found: C 52.69; H 4.51; N 7.73.

Method B. Compound **17a** (1 equiv) was dissolved in toluene (30 mL/mmol of **17a**) under argon atmosphere. A catalytic amount of *p*-toluenesulfonic acid (0.03 equiv) was added at rt and the mixture was then heated to 110 °C for 2 h. After cooling, neutralisation with an excess of K_2CO_3 under argon atmosphere was followed by filtration washing with ether. The filtrate was again neutralised with an excess of K_2CO_3 and after a second filtration the solvent was removed under vacuum. Flash chromatography (gradient elution mixtures EtOAc/hexane 1/10→1/2) gave **9a** in quantitative yield.

4.1.14. (*RS*)-3-Methoxy-1-(4-nitrobenzenesulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine (9b). *Method A*. The procedure described for the preparation of **9a** (method A), was applied to **17b** to obtain **9b** as a white solid (mp 171.8–172.6 °C, purification by flash chromatography with CH_2Cl_2 (67% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.24 (d, $J_{3-2\ \text{sulfonamide}}=J_{6-5\ \text{sulfonamide}}=8.9$ Hz, 2H, $H_{3,5\ \text{sulfonamide}}$), 7.79 (d, 2H, $H_{2,6\ \text{sulfonamide}}$), 7.67 (d, $J=$ 7.8 Hz, 1H), 7.37 (ddd, $J_1=J_2=7.7$ Hz, $J_3=1.7$ Hz, 1H), 7.30 (ddd, $J_1=J_2=7.4$ Hz, $J_3=1.4$ Hz, 1H), 7.18 (dd, $J=$ 7.4, 1.7 Hz, 1H), 4.67 (dd, 1H, H_3), 4.25 (d, $J_{gem\ 5-5}=$ 13.7 Hz, 1H, H_5), 4.17 (bdd, 1H, H_2), 3.99 (d, 1H, H_5), 3.68 (bdd, $J_{gem\ 2-2}=13.4$ Hz, 1H, H_2), 3.29 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 149.94 ($C_{4\ \text{sulfonamide}}$), 145.95, 138.94, 136.87 ($C_{1\ \text{sulfonamide}}$, C_{9a}, C_{5a}), 129.36, 129.13, 129.00, 128.49 (C_6, C_7, C_8, C_9), 129.00, 123.54 ($C_{2\ \text{sulfonamide}}$, $C_{3\ \text{sulfonamide}}$, $C_{5\ \text{sulfonamide}}$, $C_{6\ \text{sulfonamide}}$), 99.36 (bs, C_3), 62.75 (bs, C_5), 54.79 (OCH_3), 53.73 (C_2). LSIMS *m/z* (relative intensity) 389 (10), 388 (6), 387 [$(M+$ Na)+, 100], 386 (10), 385 (66), 383 (5). HR LSIMS *m/z* calcd for $C_{16}H_{16}N_2O_6SNa$ $(M+Na)^+$: 387.0627, found: 387.0627. Anal. for $C_{16}H_{16}N_2O_6S$: calcd C 52.75; H 4.40; N 7.69. Found: C 52.70; H 4.39; N 8.03.

Method B. The procedure described for the preparation of **9a** was applied to **17b** to obtain **9b** in quantitative yield (purification by flash chromatography with gradient elution mixtures EtOAc/hexane from 1/20→1/9).

4.1.15. (*RS*)-3-Methoxy-1,2,3,5-tetrahydro-4,1-benzoxazepine (9c). To a solution of **9a** or **9b** (1 equiv) in DMF (5 mL/mmol of **9a** or **9b**) at rt, was added K_2CO_3 (3 equiv) followed by PhSH (1.1 equiv). Stirring was maintained for 1 h after which the reaction was treated by addition of EtOAc and distilled water. The aqueous layer was extracted three times with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. Purification by flash chromatography (gradient elution mixtures EtOAc/hexane 1/50→1/15) yielded the free amine **9c** in 98% from **9a** and 90% yield from **9b** (white solid, mp 89.5–90.5 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.10–7.02 (m, 2H), 6.79 (ddd, $J_1=J_2=7.4$ Hz, $J_3=1.0$ Hz, 1H), 6.67 (dd, $J=7.8$, 0.8 Hz, 1H), 5.20 (d, $J_{gem\ 5-5}=14.3$ Hz, 1H, H_5), 4.78 (dd, $J_{3-2}=7.2$, 3.5 Hz, 1H, H_3), 4.33 (d, 1H, H_5), 3.48 (s, 3H, OCH_3), 3.41 (dd, $J_{gem\ 2-2}=14.0$ Hz, $J_{3-2}=$ 7.2 Hz, 1H, H_2), 3.25 (dd, $J_{3-2}=3.5$ Hz, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 148.48 (C_{9a}), 128.88, 128.23, 119.94, 117.64 (C_6, C_7, C_8, C_9), 126.84 (C_{5a}), 102.28 (C_3), 63.99 (C_5), 55.28 (OCH_3), 50.38 (C_2). Anal. for $C_{10}H_{13}NO_2$: calcd C 67.02; H 7.31; N 7.82. Found: C 67.09; H 7.13; N 7.98.

4.1.16. (*RS*)-1-Butyryl-3-methoxy-1,2,3,5-tetrahydro-4,1-benzoxazepine (9d). A solution of **9c** (1 equiv) in dried CH_2Cl_2 (3 mL/mmol of **9c**) was prepared under argon and then cooled to 0 °C. First TEA (3 equiv) and then butyryl chloride (2 equiv), were added in dropwise fashion. The mixture was then allowed to warm at rt and stirred for 17 h. After dilution with CH_2Cl_2, the organic layer was washed with water, dried (Na_2SO_4) and concentrated under

vacuum. Purification by flash chromatography with gradient elution using mixtures EtOAc/hexane (1/20→1/5), afforded the final amide **9d** as a colourless liquid (69% yield). In $CDCl_3$ at rt two isomers are observed: isomer A (60%) (numbers without primes), isomer B (40%) (numbers with primes): ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.39–7.10 (m, 4H, 4H′), 5.15 (d, J_{gem}=13.0 Hz, 1H′), 5.05 (d, J_{gem}=14.0 Hz, 1H′), 4.82 (d, $J_{gem\ 2\text{–}2}$=13.6 Hz, 1H, H_2), 4.76–4.67 (m, 2H, 1H′), 4.49 (d, $J_{gem\ 5\text{–}5}$=14.1 Hz, 1H, H_5), 4.15 (d, J_{gem}=13.0 Hz, 1H′), 3.49 (s, 3H, OCH_3), 3.43 (s, 3H, OCH'_3), 2.85 (d, J_{gem}=14.0 Hz, 1H′), 2.70 (dd, $J_{3\text{–}2}$=8.8 Hz, 1H, H_2), 2.26 (m, 2H, COCH_2, COCH'_2), 2.06 (m, 2H, COCH_2, COCH'_2), 1.58 (m, 4H, CH_3CH_2, $CH_3CH'_2$), 0.83 (t, $J_{CH2\text{–}CH3}$=$J_{CH2'\text{–}CH3'}$=7.4 Hz, 6H, CH_3, CH'_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 173.01 (*C*O), 143.60, 142.00, 136.70, 136.27 ($C_{9a'}$, C_{9a}, $C_{5a'}$, C_{5a}), 129.81–127.24 (C_6, $C_{6'}$, C_7, $C_{7'}$, C_8, $C_{8'}$, C_9, $C_{9'}$), 102.67 (C_3), 99.03 ($C_{3'}$), 66.05 (C_5), 61.58 ($C_{5'}$), 56.28 (O*C*H$_3$), 55.09 (O*C*H′$_3$), 50.71 (C_2), 48.94 ($C_{2'}$), 36.07 (CO*C*H$_2$, CO*C*H′$_2$), 19.83 (CH_3CH_2, $CH_3CH'_2$), 13.85 (*C*H$_3$, *C*H′$_3$). LSIMS *m/z* (relative intensity) 274 (13), 273 (17), 272 [(M+Na)$^+$, 66], 266 (16), 265 (50), 264 (25), 263 (34), 260 (19), 251 (11), 250 [(M+H)$^+$, 47], 249 (20), 248 (23), 247 (30), 246 (14), 245 (9), 244 (17), 243 (27), 237 (42), 236 (19), 235 (21), 234 (15), 233 (29), 232 (18), 231 (35), 230 (21), 229 (30), 228 (17), 227 (38), 226 (16), 225 (8), 222 (37), 221 (100), 220 (27), 219 (49), 218 (53). HR LSIMS *m/z* calcd for $C_{14}H_{19}NO_3Na$ (M+Na)$^+$: 272.1263, found: 272.1260. Anal. for $C_{14}H_{19}NO_3$: calcd C 67.45; H 7.68; N 5.62. Found: C 67.56; H 7.43; N 5.60.

4.1.17. (*RS*)-3-Methoxy-1-trifluoroacetyl-1,2,3,5-tetrahydro-4,1-benzoxazepine (9e). Reaction of **9c** with TFAA according to the procedure described for the preparation of **9d**. After 18 h stirring at rt, the reaction mixture was diluted with CH_2Cl_2 and the organic layer washed with water, dried (Na_2SO_4) and concentrated under vacuum. Purification was performed by flash chromatography (gradient elution mixtures EtOAc/hexane 1/50→1/16), to yield the final product **9e** as a white solid, mp 76.0–77.0 °C (79% yield). In $CDCl_3$ at rt two isomers are observed: isomer A (45%) (numbers without primes), isomer B (55%) (numbers with primes): ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.39–7.18 (m, 4H′, 4H), 5.21 (d, $J_{gem\ 5'\text{–}5'}$=13.2 Hz, 1H, $H_{5'}$), 4.91 (dd, $J_{gem\ 2'\text{–}2'}$=13.8 Hz, $J_{3'\text{–}2'}$=1.4 Hz, 1H, $H_{2'}$), 4.75–4.68 (m, 1H′, 3H), 4.56 (d, $J_{gem\ 5\text{–}5}$=14.0 Hz, 1H, H_5), 4.18 (d, 1H, $H_{5'}$), 3.51 (s, 3H, OCH_3), 3.44 (s, 3H, OCH'_3), 3.06 (d, 1H, $H_{2'}$), 2.85 (dd, $J_{gem\ 2\text{–}2}$=13.0 Hz, $J_{3\text{–}2}$=8.2 Hz, 1H, H_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 156.74 (q, $J_{CO\text{–}F}$=36.0 Hz, *C*O), 156.65 (q, $J_{CO'\text{–}F}$=36.0 Hz, *C*O′), 140.40 ($C_{9a'}$), 138.85 (C_{9a}), 136.55 ($C_{5a'}$), 136.42 (C_{5a}), 129.77–126.75 ($C_{6'}$, C_6, $C_{7'}$, C_7, $C_{8'}$, C_8, $C_{9'}$, C_9), 116.44 (q, $J_{C'\text{–}F}$=287.0 Hz, *C*F′$_3$), 116.25 (q, $J_{C\text{–}F}$=287.0 Hz, *C*F$_3$), 102.24 (C_3), 98.56 ($C_{3'}$), 66.32 (C_5), 61.30 ($C_{5'}$), 56.44 (O*C*H$_3$), 55.24 (O*C*H′$_3$), 52.90 (C_2), 51.27 ($C_{2'}$). LSIMS *m/z* (relative intensity) 331 (7), 330 (26), 329 (100), 308 (8), 307 (35), 299 (12), 299 (12), 298 [(M+Na)$^+$, 51], 289 (21), 277 (9), 276 [(M+H)$^+$, 34], 274 (15), 273 (15), 259 (13), 257 (11), 245 (22), 244 (61), 243 (13), 239 (9), 217 (14), 216 (18), 215 (29). HR LSIMS *m/z* calcd for $C_{12}H_{12}NO_3F_3Na$ (M+Na)$^+$: 298.0670, found: 298.0673. Anal. for $C_{12}H_{12}FNO_3$: calcd C 52.37; H 4.39; N 5.09. Found: C 52.41; H 4.22; N 5.21.

4.1.18. (*RS*)-1-Benzoyl-3-methoxy-1,2,3,5-tetrahydro-4,1-benzoxazepine (9f). A solution of **9c** (1 equiv) in dried CH_2Cl_2 (3 mL/mmol **9c**) was prepared under argon and cooled to 0 °C. At this temperature, TEA (3 equiv) and then benzoyl chloride (2 equiv) were added dropwise. The mixture was stirred between 0 and 5 °C for 3 h and afterwards diluted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and concentrated under vacuum. The final product carrying the benzoyl moiety was purified by flash chromatography (gradient elution mixtures EtOAc/hexane 1/20→1/4) as a white solid, mp 104.5–105.0 °C (quantitative yield). $CDCl_3$, rt: Isomer A (86%) (numbers without primes), isomer B (14%) (numbers with primes): ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.10 (d, 2H′), 7.59 (t, 1H′), 7.47 (t, 2H′), 7.38–7.04 (m, 7H, 4H′), 6.93 (t, 1H), 6.61 (d, 1H), 5.39–5.06 (bs), 4.87 (bs, 1H, 1H′), 4.70–4.33 (bs), 3.51 (s, 6H, OCH_3, OCH'_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.11 (*C*O), 135.59, 133.55, 130.18, 130.01, 129.17, 128.65, 128.49, 128.07, 127.86, 126.68, 126.34 ($C_{aromatic}$), 101.54 (C_3), 64.60 (C_5), 55.74 (O*C*H$_3$), 50.47 (C_2). DMSO-d_6, 80°C: Isomer A (90%) (numbers without primes), isomer B (10%) (numbers with primes): ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.91 (m, 2H′), 7.56 (dddd, J_1=J_2=7.4 Hz, J_3=J_4=1.4 Hz, 1H′), 7.45–7.38 (m, 3H′), 7.32 (dd, J=7.5, 1.4 Hz, 2H), 7.30–7.17 (m, 4H, 3H′), 7.09 (ddd, J_1=J_2=7.5 Hz, J_3=1.2 Hz, 1H), 6.97 (ddd, J_1=J_2=7.6 Hz, J_3=1.5 Hz, 1H), 6.69 (d, J=7.6 Hz, 1H), 5.07 (d, J_{gem}=13.9 Hz, 2H, $H_{5,5'}$), 4.77 (dd, J=5.0, 2.9 Hz, 2H, $H_{3,3'}$), 4.56 (d, J_{gem}=13.9 Hz, 2H, $H_{5,5'}$), 3.90 (bs), 3.40 (s, 6H, OCH_3, OCH'_3), 3.29 (m). LSIMS *m/z* (relative intensity) 285 (15), 284 [(M+H)$^+$, 100], 283 (M$^+$, 30), 282 (12). HR LSIMS *m/z* calcd for $C_{17}H_{18}NO_3$ (M+H)$^+$: 284.1287, found: 284.1282. Anal. for $C_{17}H_{17}NO_3$: calcd C 72.07; H 6.05; N 4.94. Found: C 71.92; H 6.00; N 4.99.

4.1.19. *N*-[2-(*tert*-Butyldimethylsilanyloxymethyl)phenyl]-*N*-isopropyl-4-nitrobenzenesulfonamide (20). Compound **20** was obtained from **15b** with the same procedure described for the preparation of **16b**, but using an excess of hydroxyacetaldehyde dimethyl acetal (4.3 equiv). Flash chromatography purification with a gradient elution mixture EtOAc/hexane (1/50→1/20) afforded **20** (38% yield) as a white solid (mp 178.0–179.0 °C) and **16b** (31% yield). *Compound* **20**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.33 (d, $J_{6\text{–}5\ sulfonamide}$=$J_{3\text{–}2\ sulfonamide}$ 8.8 Hz, 2H, $H_{3,5\ sulfonamide}$), 7.89 (d, 2H, $H_{2,6\ sulfonamide}$), 7.73 (d, J=7.2 Hz, 1H), 7.44 (ddd, J_1=J_2=7.6 Hz, J_3=0.8 Hz, 1H), 7.16 (ddd, J_1=J_2=7.7 Hz, J_3=1.5 Hz, 1H), 6.58 (dd, J=7.9, 0.8 Hz, 1H), 4.90 (d, $J_{gem\ CH2}$=15.0 Hz, 1H, CH_2), 4.85 (d, 1H, CH_2), 4.61 [m, 1H, C*H*(CH$_3$)$_2$], 1.13 [d, $J_{CH\text{–}CH3}$=6.7 Hz, 3H, CH(CH_3)$_2$], 1.00 [d, $J_{CH\text{–}CH3}$=6.8 Hz, 3H, CH(CH_3)$_2$], 0.96 [s, 9H, (*C*H$_3$)$_3$C], 0.14 [2s, 6H, (*C*H$_3$)$_2$Si]. LSIMS *m/z* (relative intensity) 490 (4), 489 (15), 488 (36), 487 [(M+Na)$^+$, 100], 468 (1), 467 (5), 466 (12), 465 [M+H)$^+$, 39], 410 (3), 409 (11), 408 (25), 407 (87), 393 (2), 392 (3), 391 (7), 336 (1), 335 (5), 334 (13), 333 (65), 331 (2), 330 (3), 329 (15), 282 (1), 281 (2), 280 (4), 279 (18). HR LSIMS *m/z* calcd for $C_{22}H_{32}N_2O_5SSiNa$ (M+Na)$^+$: 487.1699, found: 487.1702.

4.1.20. 2-(2,2-Dimethoxyethylaminomethyl)phenol (21). A solution of 2-hydroxybenzaldehyde (1 equiv) in EtOH

(0.2 mL/mmol of 2-hydroxybenzaldehyde) was prepared under argon atmosphere. Aminoacetaldehyde dimethyl acetal (1 equiv) was added at rt and the mixture was heated at reflux. Stirring continued for 5 h until the initial aldehyde disappeared on TLC. The mixture was then allowed to return to rt and the solvent eliminated under vacuum. The resulting residue was dissolved in anhydrous methanol under argon atmosphere and added dropwise on a mixture of $NaBH_4$ (2.5 equiv) and anhydrous methanol (1 mL/mmol of $NaBH_4$) at rt. After stirring 30 min at rt, the mixture was heated at 65 °C for 2 h. Water was then added and when bubbling ceased, methanol was eliminated under vacuum. The basic pH aqueous layer was extracted with CH_2Cl_2 and the organic layer dried ($MgSO_4$) and concentrated. Purification was performed by flash chromatography and the final product (**21**) eluted with EtOAc/hexane (3/10) as a yellow oil in quantitative yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.16 (ddd, $J_1=J_2=7.7$ Hz, $J_3=1.6$ Hz, 1H), 6.98 (dd, $J=7.4$, 1.2 Hz, 1H), 6.83 (dd, $J=8.1$, 0.9 Hz, 1H), 6.77 (ddd, $J_1=J_2=7.4$ Hz, $J_3=1.1$ Hz, 1H), 4.48 [t, $J_{CH-CH2}=5.4$ Hz, 1H, C*H*$(OCH_3)_2$], 4.00 (s, 2H, PhC*H*$_2$), 3.38 [s, 6H, $(OCH_3)_2$], 2.78 (d, 2H, CHC*H*$_2$N). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 158.19 (C_1), 128.87, 128.46, 119.14, 116.47 (C_3, C_4, C_5, C_6), 122.35 (C_2), 103.20 [*C*H$(OCH_3)_2$], 54.33 [$(OCH_3)_2$], 52.59, 49.73 (Ph*C*H$_2$, CH*C*H$_2$NH). LSIMS *m/z* (relative intensity) 234 [$(M+Na)^+$, 61], 233 (8), 213 (9), 212 [$(M+H)^+$, 100], 211 (M^+, 58), 210 (5). HR LSIMS *m/z* calcd for $C_{11}H_{17}NO_3Na$ $(M+Na)^+$: 234.1106, found: 234.1107.

4.1.21. *N*-(2,2-Dimethoxyethyl)-2,2,2-trifluoro-*N*-(2-hydroxybenzyl)acetamide (22). A solution of **21** (1 equiv) and 1-(trifluoroacetyl)benzotriazole[10] (2.5 equiv) in THF (2 mL/mmol of **21**) is stirred for 3 h at rt. The solvent was then evaporated under vacuum and the residue purified by flash chromatography [gradient elution mixtures with EtOAc/hexane (1/15 → 1/13) mixtures], to give **22** as a yellow oil in 72% yield. $CDCl_3$, rt: isomer A (89%) (numbers without primes), isomer B (11%) (numbers with primes): ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.80 (bs, 1H, OH), 7.30–7.15 (m, 2H, 1H′), 7.05 (dd, 1H′), 6.95–6.80 (m, 2H, 2H′), 4.76 (s, 4H, PhC*H*$_2$, PhC*H*′$_2$), 4.60 [t, 1H, C*H*′$(OCH_3)_2$], 4.50 [t, $J_{CH-CH2}=5.1$ Hz, 1H, C*H*$(OCH_3)_2$], 3.53 (2d, 4H, CHC*H*$_2$N, CHC*H*′$_2$N), 3.46, 3.43 [2s, 12H, $(OCH_3)_2$, $(OCH'_3)_2$]. ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 155.65 (C_2), 132.14, 130.80, 120.19, 117.71 (C_3, C_4, C_5, C_6), 129.76, 129.24, 121.33, 116.62 ($C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$), 114.92 (C_1), 104.43 [*C*H$(OCH_3)_2$], 102.67 [*C*H′$(OCH_3)_2$], 55.44 [$(OCH_3)_2$, $(OCH'_3)_2$], 48.25, 47.36 (Ph*C*H$_2$, CH*C*H$_2$N), 47.08, 46.44 (Ph*C*H′$_2$, CH*C*H′$_2$N). LSIMS *m/z* (relative intensity) 331 (15), 330 [$(M+Na)^+$, 100], 329 (12), 281 (8), 277 (11), 276 (76), 275 (22), 244 (6). HR LSIMS *m/z* calcd for $C_{13}H_{16}NO_4F_3Na$ $(M+Na)^+$: 330.0929, found: 330.0927.

4.1.22. (*RS*)-2-Methoxy-*N*-trifluoroacetyl-2,3,4,5-tetrahydro-1,4-benzoxazepine (10). A solution of **22** (1 equiv) in dried Et_2O (4 mL/mmol) was prepared under argon. $BF_3\cdot OEt_2$ (2 equiv) was then added dropwise at rt. The resulting mixture was kept away from light, under argon, until no initial product could be visualized on TLC (5 d). Et_2O was then added and the solution washed with water. The final organic phase was dried (Na_2SO_4), concentrated and purified by flash chromatography. The cyclic product **10** was eluted (with gradient elution mixtures EtOAc/hexane 1/50 → 1/25) as a colourless oil (49% yield). $CDCl_3$, rt: Isomer A (63%) (numbers without primes), isomer B (37%) (number with primes): ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.33–7.09 (m, 4H, 4H′), 4.91 (d, $J_{gem\ 5-5}=14.4$ Hz, 1H, H_5), 4.79 (dd, $J_{3'-2'}=2.2$, 7.1 Hz, 1H, $H_{2'}$), 4.73 (d, 1H, $H_{5'}$), 4.73 (dd, $J_{3-2}=2.3$, 7.8 Hz, 1H, H_2), 4.57 (d, $J_{gem\ 5'-5'}=15.5$ Hz, 1H, $H_{5'}$), 4.40 (dd, $J_{gem\ 3'-3'}=13.9$ Hz, $J_{3'-2'}=2.2$ Hz, 1H, $H_{3'}$), 4.35 (d, 1H, H_5), 4.04 (dd, $J_{gem\ 3-3}=15.1$ Hz, $J_{3-2}=2.3$ Hz, 1H, H_3), 3.61 (s, 3H, O*C*H_3), 3.59 (s, 3H, O*C*H'_3), 3.56–3.48 (m, 2H, $H_{3,3'}$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 156.06 (2q, $J_{CO-F}=J_{CO'-F}=36.0$ Hz, *C*O, *C*O′), 153.53 ($C_{9a'}$), 153.33 (C_{9a}), 130.25–122.34 ($C_{aromatic}$), 116.46 (q, $J_{C'-F}=286.3$ Hz, *C*F′$_3$), 116.31 (q, $J_{C-F}=286.0$ Hz, *C*F_3), 102.93 (C_2), 102.39 ($C_{2'}$), 56.63 (O*C*H′$_3$), 56.53 (O*C*H_3), 51.51, 49.85 (C_3, C_5), 51.19, 50.42 ($C_{3'}$, $C_{5'}$). LSIMS *m/z* (relative intensity) 300 (2), 299 (14), 298 [$(M+Na)^+$, 100], 290 (7), 289 (17), 277 (7), 276 [$(M+H)^+$, 60], 275 (M^+, 34). HR LSIMS *m/z* calcd for $C_{12}H_{12}NO_3F_3Na$ $(M+Na)^+$: 298.0667, found: 298.0666. Anal. for $C_{12}H_{12}F_3NO_3$: calcd C 52.37; H 4.39; N 5.09. Found: C 52.30; H 4.46; N 5.01.

4.2. Biological activity

4.2.1. Cell culture. The human breast cancer MCF-7 cell line, used for treatment with the drugs, was kindly provided by Dr. N. Olea of the Sánchez Mora Tumour Biology Institute, University Hospital of Granada. MCF-7 cells were grown at 37 °C in an atmosphere containing 5% CO_2, with Dubelcco's modified Eagle Medium (DMEM) (Gibco, Grand Island, NY) supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Gibco), 2% L-glutamine, 2.7% sodium bicarbonate, 1% Hepes buffer, 40 mg/L gentamicin and 500 mg/L ampicillin.

4.2.2. Drugs and drug treatments. After the synthesis and purification of the final compounds stock solutions were prepared. The drugs were dissolved in DMSO or water and stored at −20 °C. For each experiment, the stock solutions were further diluted in medium to obtain the desired concentrations. The final solvent concentration in cell culture was ≤0.5% v/v of DMSO, a concentration without effect on cell replication.[28] Parallel cultures of MCF-7 cells in medium with DMSO were used as controls.

4.2.3. Cytotoxicity assays in vitro. The effect of anticancer drugs on cell viability was assessed using the sulforhodamine-B (SRB) colorimetric assay. Aliquots of MCF-7 cells suspension (30×10^3 cells/well) were seeded onto 24-well plates and incubated for 24 h. The cells were then treated with different concentrations of drugs in the culture medium. Three days later, the wells were aspirated, fresh medium was added, and cells were maintained for 3 additional days. Thereafter, cells were processed as described previously,[29] using a Titertek Multiscan apparatus (Flow, Irvine, California) at 492 nm. We evaluated the linearity of the SRB assay with the cell number for each MCF-7 cell stock before each cell growth experiment. The IC_{50} values were calculated from semilogarithmic dose–response curves by linear interpolation. All of the

experiments were plated in triplicate wells and were carried out at least twice.

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