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SYNTHESIS, STRUCTURE AND ENZYMATIC EVALUATION OF NEW SPIRO OXATHIAZOLE SUGAR DERIVATIVES

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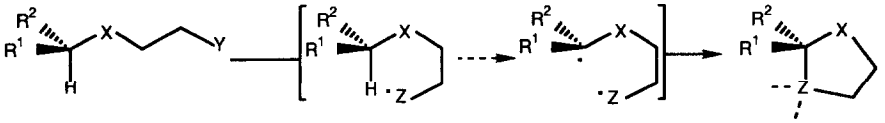
Abstract: On treatment with *N*-bromosuccinimide under irradiation in refluxing carbon tetrachloride, 2,3,4,6-tetra-O-acetyl-1-*S*-(*Z*)-benzhydroximoyl-1-thio-D-glucopyranose **1** and various analogs yielded new spiro anomeric oxathiazole derivatives in ~60% total yield. After deacetylation, the tested major 1(*S*) epimers were found good competitive inhibitors of emulsin β-D-glucosidase whereas a 1(*R*) counterpart had no effect on the enzyme.

In connection with the outstanding development of radical-mediated methodologies over the last decade, a number of new synthetic modifications involving the anomeric centre of oligosaccharides has been proposed. A large array of methods is now available for the generation of carbon-centered anomeric radicals[1] by either inter- or intramolecular processes. In this latter case, especially designed glycosides must be used to promote, under appropriate conditions, the formation of activated species or free-radical transients able to cleave homolytically anomeric carbon-hydrogen bonds. Pioneering studies have shown that such homolyses occur via six-membered cyclic transition states involving the activated species and the hydrogen atom to be abstracted, in either the intramolecular cyclization of hypohalides[2] or the Barton reaction[3]. Hence, only glycosides in which suitable functional groups are located at the γ carbon atom of the aglycon are good candidates for efficient generation of anomeric radicals via 1,5-shifts. Afterwards, a cascade of steps ensues which ends up in ring-closure by either C—C or C—O bond formation as illustrated by the high-yielding syntheses of new spiro derivatives from either 3'-oxoalkyl-β-D-glucopyranosides[4] or their 2'-hydroxyalkyl counterparts[5,6]. The recently described reductive cyclization of iodoepoxy-β-D-glucopyranosides[7] in the presence of tributyltin hydride used the same concept and showed again the high α-stereoselectivity of the ring-closures in sugar derivatives displaying the $^4C_1$-D chair conformation.

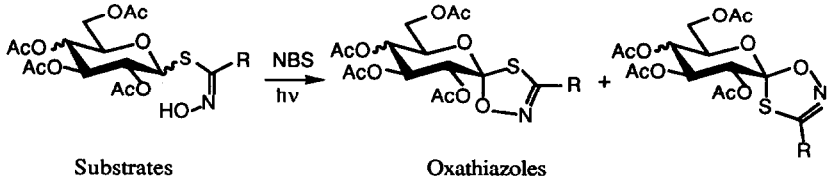


R^1, R^2 = H, alkyl, pyranose ring,...
X = C, O; Y = OH, C=O

Z = O,C

In light of these precedents, 2,3,4,6-tetra-O-acetyl-1-S-(Z)-benzhydroximoyl-1-thio-β-D-glucopyranose **1** and related compounds[8] could constitute, *a priori*, favourable candidates for the elaboration of a new spiro anomeric linkage. However, two drawbacks emerged from a critical analysis, namely the possible cleavage of the glycosidic bond following an electrophilic attack of the sulphur atom[9] and a relatively low reactivity of thioimidoxy radicals, as indicated for the related iminoxy radicals[10]. Nevertheless, regarding the first objection, halogen-mediated free-radical transformations only involve low concentrations of halogen in carbon tetrachloride so that the unwanted heterolysis of the thioglycosidic bond can be circumvented[11] in this non-dissociating solvent. Since sulphur atoms are known to efficiently activate neighbouring C—H bonds towards homolysis[12] and to stabilize the corresponding carbon-centered radical[13], treatment of the aforementioned favourably (Z)-configurated glycosyl thiohydroximates was attempted, under free-radical conditions, to explore a possible route to new spiro sugars. In addition, it was hoped that such compounds could reveal some biological activity since they correspond to modified glucosinolates, a class of natural compounds of widespread occurrence[14]. Following a preliminary communication[15], we herein describe our synthetic work together with the corresponding structural analysis and an enzymatic evaluation of representative spiro oxathiazole derivatives.

The studied compounds **1** - **9**[8] were treated with *N*-bromosuccinimide (NBS, 2 eq) in refluxing carbon tetrachloride for about 30 min, under visible light irradiation[15]. Structures and yields of the outcoming products are indicated below. The corresponding physical and analytical data are gathered in Table 3.

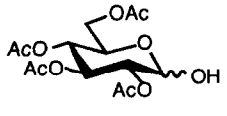


Substrates		Oxathiazoles			
	R	1(*S*)	yield %	1(*R*)	yield %
1β	C_6H_5	**11**	50 (15[a])	**12**	10(5[a])
1α	C_6H_5	**11**	44	**12**	-
2β	p-C_6H_4Br	**13**	45	**14**	6
3β	p-C_6H_4Cl	**15**	57	**16**	13
4β	p-C_6H_4F	**17**	30	**18**	16
5β	$C_{10}H_7$	**19**	40	**20**	12
6β	COOEt	**21**	37	**22**	-
7β	CN	**23**	7	**24**	3
8β	CH_3		-		-
9(β-D-galacto)	C_6H_5	**25**	50	**26**	10
10β	CH_2Br				

[a] - Yield recorded when using iodine and mercury oxide

Substrates carrying an aryl ring attached to the thiohydroximate function led to two epimeric spiro oxathiazole derivatives (total yield ~45 - 60%) via the anticipated intramolecular spirocyclization. This occurred with good selectivities as judged from the yields and the ratio of the 1(S) and 1(R) epimers, *ca.* 4/1. Comparison of the results obtained for each of the anomers of **1** showed that neither the rate nor the stereoselectivity of the transformation were significantly affected by the anomeric configuration in the substrates. Similarly, structural

changes affecting their lateral sites such as introduction of halogen substituents at the *para* position of the aromatic ring or, in **9**, inversion of the configuration of the C-4 pyranose carbon atom, seem to have no significant influence on the course of the reaction. The corresponding spiro oxathiazoles were also obtained in lower yields when the aryl ring in the substrates was replaced by carboethoxy or cyano groups[16]. In contrast, cyclization of the acetothiohydroximate **8** did not occur since the major outcoming product was identified as the opened monobromide **10** (35% yield[16]). In this case, bromination occurred at the "allylic" position, precluding cyclization to take place. Finally, side-reactions could be identified on the basis of the characterized minor by-products. Formation of 2,3,4,6-tetra-O-acetyl-D-glucopyranose **27** (~10% yield) can be explained by the heterolysis of the thioglycosidic bond, most probably as a result of an electrophilic attack at the sulphur atom and subsequent reaction of the liberated glycopyranosyl cation with trace amounts of water in the medium. Bis (2,3,4,6-tetra-O-acetyl-β-D-glucopyranose) disulfide **28**[17] (~20% yield) can result from the decomposition of thiohydroximates into their nitrile oxide and thiosugar precursors, followed by oxidative coupling of the latter.



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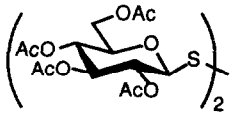

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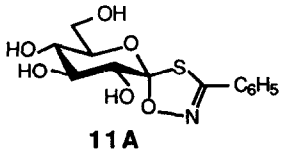


11A

The absence of anomeric and hydroximino protons in the ^1H NMR spectra of the products and, simultaneously, the presence in their ^{13}C NMR spectra of downfield signals corresponding to quaternary anomeric carbons near either 122 ppm (1(*S*)-epimers) or 127 ppm (1(*R*)-epimers) established the spiroannelation. Besides the C-1 signals, only the H-3 and H-5 resonances in the ^1H NMR spectra of the products showed significant changes which should reflect the absolute configuration of the spiro carbon. In peracetylated α-D-glucopyranosides, the H-3 and H-5 proton signals are deshielded (0.2 - 0.3 ppm), as compared to the corresponding nuclei in the β anomers, by the axially oriented oxygen atom in the glycosidic residue. However, since the deshieldings of these protons due to similarly located sulphur atoms in α-D-thioglucopyranosides are of comparable magnitude[18], this criterion was useless to assign the anomeric configuration in the cyclized products, so that we resorted to crystal structure determination. Although most of the prepared spiro oxathiazole derivatives crystallized from various solvent mixtures, they invariably formed thin and entangled needles unsuitable for X-ray crystal analysis. However, deacetylation of **11** occurred quantitatively under Zemplen conditions to yield the corresponding spiro oxathiazole **11A** as colourless prisms after crystallization from methanol (80% yield). The PLUTO drawing[19] obtained for **11A** clearly showed the equatorial and axial orientations of, respectively, the C-1—S and C-1—O bonds and the $^4C_1$-D chair conformation of the pyranose ring[20]. Since such spiro compounds should not be prone, under basic conditions, to anomerization — a process which can be excluded on the basis of the recorded optical rotations [+53° (**11**) and +56° (**11A**) as compared to +179° (**12**)] — the major cyclized product obtained regardless of the α or β anomeric configuration in the substrates also displays an equatorial C-1—S bond. This confirms that formation of the C-1—O bond occurred preferentially from the α side of the pyranose ring of both **1**α and **1**β as is consistent with the known preferential axial trapping of radicals at anomeric centres.

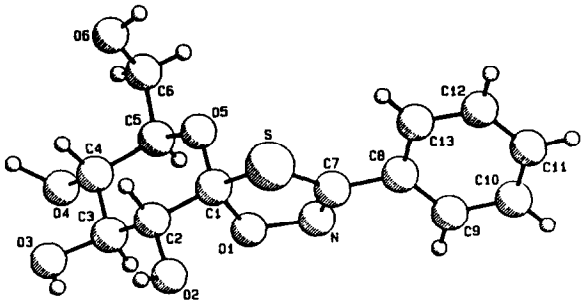


Fig. 1: PLUTO[19] drawing of **11A** showing the atom numbering scheme

Table 1: Bond distances in Angstroms

Bond	Distance	Bond	Distance	Bond	Distance
S - C1	1.817(4)	O5 - C5	1.454(4)	C7 - C8	1.473(5)
S - C7	1.741(3)	O6 - C6	1.417(5)	C8 - C9	1.402(5)
O1 - N	1.425(4)	N - C7	1.276(5)	C8 - C13	1.390(6)
O1 - C1	1.432(4)	C1 - C2	1.523(5)	C9 - C10	1.384(6)
O2 - C2	1.421(4)	C2 - C3	1.521(5)	C10 - C11	1.370(7)
O3 - C3	1.429(5)	C3 - C4	1.511(5)	C11 - C12	1.383(6)
O4 - C4	1.423(4)	C4 - C5	1.520(5)	C12 - C13	1.383(6)
O5 - C1	1.390(4)	C5 - C6	1.513(6)		

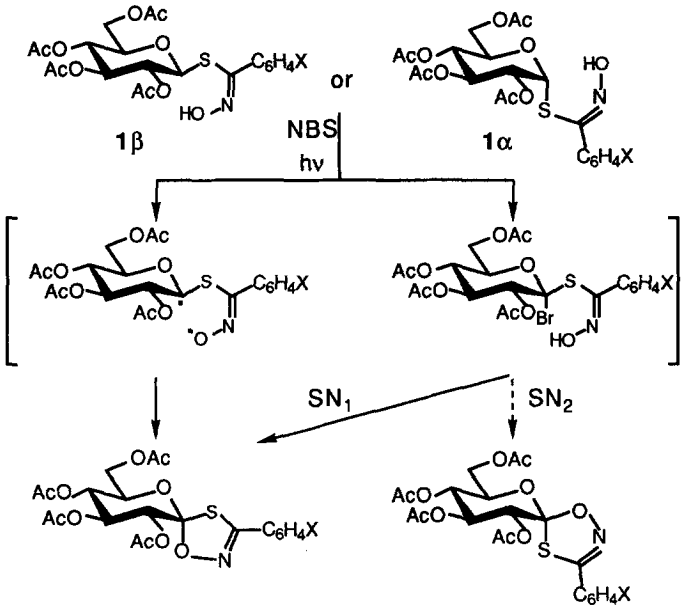
Table 2: Bond angles in Degrees

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C1	S	C7	88.1(2)	C1	C2	C3	109.4(3)	S	C7	C8	121.5(3)
N	O1	C1	112.9(3)	O3	C3	C2	111.0(3)	N	C7	C8	121.4(3)
C1	O5	C5	115.0(3)	O3	C3	C4	106.9(3)	C7	C8	C9	120.1(4)
O1	N	C7	110.4(3)	C2	C3	C4	109.1(3)	C7	C8	C13	120.4(3)
S	C1	O1	104.4(2)	O4	C4	C3	109.5(3)	C9	C8	C13	119.5(4)
S	C1	O5	106.6(2)	O4	C4	C5	108.0(3)	C8	C9	C10	119.8(4)
S	C1	C2	114.7(2)	C3	C4	C5	111.2(3)	C9	C10	C11	120.1(4)
O1	C1	O5	111.8(3)	O5	C5	C4	111.8(3)	C10	C11	C12	120.6(4)
O1	C1	C2	108.4(3)	O5	C5	C6	104.7(3)	C11	C12	C13	120.1(4)
O5	C1	C2	110.8(3)	C4	C5	C6	112.5(3)	C8	C13	C12	119.8(4)
O2	C2	C1	109.1(3)	O6	C6	C5	112.5(3)				
O2	C2	C3	111.4(3)	S	C7	N	117.2(3)				

Numbers in parentheses are estimated standard deviations in the least significant digits.

This unprecedented spirocyclization was also shown to take place slowly on stirring the reaction mixture for extended time without either heating or irradiation. Use of excess of iodine and mercury oxide[2,5,6] also brought about the formation of the cyclized products although with a lower selectivity. These observations were not surprising for free-radical transformations which could be rationalised taking into account two main pathways. On one hand, as postulated for the conversion of primary alcohols to tetrahydrofuran derivatives[2], exchange of the hydrogen atom of the hydroximate moiety could lead to oxygen-centered oximidoyl radicals favourably disposed to trigger the homolysis of the anomeric hydrogen atom. Then, in a similar fashion, the

restored hydroximate group could produce again the oxygen-centered species in a biradical prone to intramolecular cyclization. On the other hand, due to the favourable influence of the sulphur atom, homolysis of the C—H anomeric bond by either a bromine atom or a succinimidyl radical[21,22] could occur first, leading to an intermediate brominated at the anomeric position. Such bromo (O,S) acetals, although postulated in related transformations[11] remained elusive, leading to further transformations[11] most probably via the heterolysis of the C—Br bond. There are several examples in the literature which show that nucleophiles attack stabilized glucopyranosyl cations stereoselectively from the α side in either an inter[23,24,25] or intramolecular process[26]. This rationalises satisfactorily the anomeric configuration of the major stereoisomer, via a stereoselective SN_1 process. The minor one could also be generated by a SN_2 nucleophilic displacement of the bromine atom by the hydroximate group. It is noteworthy that both processes, namely attack of either a stabilized glucopyranosyl cation or a corresponding radical by nucleophiles/radicals should lead to the same observed major 1(*S*) stereoisomers.



It was then decided to examine whether these new spiro sugar derivatives could be of interest in enzymatic tests. Since deacetylation should occur in a straightforward manner, as proved by ^{13}C NMR spectroscopy and preparative runs in the case of **11**, products **12**, **13**, **15** and **17** were deacetylated (Zemplen conditions) to yield the corresponding non-isolated tetrahydroxy spirooxathiazoles **12A**, **13A**, **15A** and **17A** whose properties were investigated, after treatment of the methanolic solutions with ion-exchange resin. Catalytic activities of β-D-glucosidase from sweet almonds, in the presence of the aforementioned compounds were determined. They all caused an inhibition which was of the competitive type, except compound **12A** which had no effect on the enzyme activity, as shown below:

Compounds	K_i (mM)
11A	5.9
12A	-
13A	6.7
15A	4.5
17A	5.5

Taking the inhibitory efficacy of the glucono-1,5-lactone ($K_i = 4.8 \times 10^{-2}$ mM) as a reference, the compounds **11A**, **13A**, **15A** and **17A** are much less potent. These compounds, however, perform about equally well in all tests as compared to the substrate analog inhibitors. It has been shown that *p*-nitrophenyl-1-S-1-thio-β-D-glucopyranoside, *p*-nitrophenyl-1-S-1-thio-β-D-galactopyranoside and phenyl-1-S-1-thio-β-D-galactopyranoside inhibited the β-D-glucosidase from white clover with K_i values[27] equal to 3.8, 3.7 and 4.7 mM, respectively, which are similar to that measured with the studied compounds. Similar K_i (1.2 mM) was observed for the benzyl-1-S-1-thio-β-D-glucopyranoside with the emulsin β-D-glucosidase[28]. The β-D-glucosidase from pig kidney displayed a K_i value equal to 1.2 mM for *p*-aminophenyl-1-S-1-thio-β-D-galactopyranoside and 9.4×10^{-1} mM for *p*-aminophenyl-1-S-1-thio-β-D-glucopyranoside respectively[29]. *p*-Nitrophenyl-1-S-1-thio-β-D-galacto (and gluco) pyranoside are more potent inhibitors in this case than the tested compounds ($K_i = 8.9 \times 10^{-2}$ and 1.2×10^{-1} mM respectively)[29]. Since the hydrophobic aryl group of the substrates plays an important role in the binding[29, 30], the observed differences may be explained by structural features, in particular, those concerning the aglycon residue of the studied compounds. In this respect, it is of interest to precisely know the structure of compound **11A** in the solid state, for comparison purposes.

In conclusion, cyclization of both α and β anomers of 2,3,4,6-tetra-O-acetyl-1-S-(*Z*)-benhydroximoyl-1-thio-D-glucopyranose as well as β-configurated analogs has been carried out in the presence of NBS, under free-radical conditions to yield mixtures of epimeric spiro oxathiazoles. The (*S*) anomeric configuration of the major products was deduced from the crystal analysis of a deacetylated derivative and from comparison of NMR data and optical rotations (deshielded H-3 and H-5 resonances, shielded C-1 resonances, smaller optical rotations for the (*S*) epimers, as compared to their (*R*) counterparts). The preparation of these new spiro sugars attached to an oxathiazole ring by the anomeric carbon confirms the stability of the thioglycosidic bond in the presence of NBS in carbon tetrachloride. Enzyme assays showed that four deacetylated compounds obtained from the corresponding major spiro oxathiazoles were competitive inhibitors of β-D-glucosidase of sweet almonds whereas a 1(*R*) analog was found inactive.

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Experimental:

Spirocyclization : in the presence of N-bromosuccinimide: A mixture containing the substrate (1 mmol) and N-bromosuccinimide (1.2 mmol) in dry carbon tetrachloride (20 mL) was heated with a 150 W tungsten lamp. After 10 min, another portion of NBS (0.8 mmol) was added in order to achieve the complete transformation of the starting material within approximately 20-30 min. On silica gel 60 F_{254} plates (hexane-ethyl acetate 6:4 v/v), two faster moving compounds were visible under UV light. After cooling and removal of the solids by filtration, the organic phase was washed with a solution of sodium thiosulfate and then with water. After concentration under

diminished pressure, the reaction mixture was resolved by column chromatography on silica gel (hexane-ethyl acetate 7:3 v/v). *in the presence of iodine and yellow mercury oxide:* A mixture of **1** (400 mg, 0.83 mmol), yellow mercury oxide (1.07 g, 4.9 mmol) and iodine (1.68 g, 6.6 mmol) was heated with a 150 W tungsten lamp for 20 min to completely transform the substrate. After filtration through a bed of celite and washing three times the organic phase with a sodium thiosulfate solution then with water and drying ($MgSO_4$), the solvent was removed under diminished pressure. The residue was applied to a column of silica gel (petroleum ether-ethyl acetate 7:3 v/v) to yield pure **11** and **12** (15 and 5 % yield, respectively).

Deacetylation of **11**: Peracetylated spirooxathiazole **11** (145 mg, 0.3 mmol) dissolved in anhydrous methanol (12 mL) was stirred overnight at room temperature in the presence of a catalytic amount of sodium methoxide whereupon the reaction mixture gave a single spot on TLC plate (ethyl acetate-methanol, 1:1, v/v). After filtration

Table 3: Physical data for compounds **11** - **20**, **25**, **26** and **11A**

Compounds	mp (°C)[a]	$[\alpha]_D$[b]	UV[c]	Formula	Analysis				
		c	λ, εx10^{-2}		C	H	N	O	S
11	119-120	+53°	203.8, 177	$C_{21}H_{23}NO_{10}S$	52.39	4.82	2.91	33.23	6.66
		0.5	243.2, 123		52.06	4.72	2.78	33.39	6.25
12	112-113	+179°	203.4, 168	$C_{21}H_{23}NO_{10}S$	52.39	4.82	2.91	33.23	6.66
		0.8	243.0, 115		52.11	5.01	2.91	33.51	6.55
13	168	+52	205.8, 272	$C_{21}H_{22}BrNO_{10}S$	45.01	3.96	2.50	28.55	5.72
		1.2	254.6, 175		45.31	3.95	2.34	28.67	5.78
14	167-169	+177	207.0, 168	$C_{21}H_{22}BrNO_{10}S$	45.01	3.96	2.50	28.55	5.72
		0.4	255.8, 191		45.57	4.15	2.54	27.95	
15	160-161	+55°	205.8, 151	$C_{21}H_{22}ClNO_{10}S$	48.89	4.30	2.71	31.01	6.21
		1	252.0, 149		48.16	4.25	2.73	30.48	5.79
16	165-167	+192°	205.6, 173	$C_{21}H_{22}ClNO_{10}S$	48.89	4.30	2.71	31.01	6.21
		0.9	251.8, 184		48.03	4.35	2.80	30.33	
17	139-140	+56°	205.6, 189	$C_{21}H_{22}FNO_{10}S$	50.50	4.44	2.80	32.04	6.42
		0.6	243.4, 115		50.52	4.32	2.82		6.57
18	137-138	+165°	203.6, 158	$C_{21}H_{22}FNO_{10}S$	50.50	4.44	2.80	32.04	6.42
		0.75	244.0, 119		50.63	4.37	2.79		6.93
19	148-149	+44°		$C_{25}H_{25}NO_{10}S$	56.49	4.74	2.64	30.10	6.03
		0.5			56.52	4.96	2.62	29.79	5.61
20	gum	+99°		$C_{25}H_{25}NO_{10}S$	56.49	4.74	2.64	30.10	6.03
		1.1				4.71		30.01	
25	amorphous	+83°		$C_{21}H_{23}NO_{10}S$	52.39	4.82	2.91	33.23	6.66
		1.2			52.32	4.93	2.82	33.25	6.60
26	180-181	+221°		$C_{21}H_{23}NO_{10}S$	52.39	4.82	2.91	33.23	6.66
		0.5			52.33	4 83		32.27	
11A	180-183 dec.	+56°		$C_{13}H_{15}NO_6S$	49.83	4.82	4.47	30.64	10.23
	MeOH	*0.9* (MeOH)			49.56	4.78	4.52	30.92	9.97

[a] - Unless otherwise indicated, the products were crystallized from diethyl ether - petroleum ether; [b] - Unless otherwise indicated, the optical rotations of chloroform solutions were measured at ambient temperature; [c] - The products (~2mg) were dissolved in 100 mL 95% ethanol (λ in nm).

through a bed of silica gel and concentration under diminished pressure, the residue (109 mg) was crystallized from methanol-ethyl acetate to yield **11A** (85 mg, 90 % yield) as colourless crystals. Deacetylated substrates used for enzyme assays were obtained similarly, except that sodium ions were removed with a cation-exchange resin (Amberlite IR 120).

Enzyme assays: β-D-glucosidase activity was measured in 0.2 M citrate-phosphate buffer (pH = 5.2) at 37°C using *p*-nitrophenyl-β-D-glucopyranoside as the substrate. The total volume was 1 mL. The hydrolysis reaction, initiated by addition of the substrate, was allowed to proceed for 15 min and then terminated by addition of 2 mL of 0.5 M borate buffer (pH = 10). The concentration of *p*-nitrophenolate ion was measured spectrophotometrically at 400 nm, using a Beckman DU 65 spectrophotometer. For each tested compound, the measurements were done in three replicates at 6 inhibitor concentrations (0.5 - 5 K_i) and three different substrate concentrations (0.5, 1 and 2 Km). Data were determined using the GraFit Enzyme Kinetic Computer program.

Crystal data: $C_{13}H_{15}NO_6S$, M=313.3, orthorhombic, space group $P2_12_12_1$, a=6.4724(8), b=9.8569(7), c=21.650(2) Å, V=1381.2(4) $Å^3$, Z=4, D_c=1.507 $g.cm^{-3}$. Data were collected on a Nonius CAD4 diffractometer. Of 1619 unique reflections measured (2θ max=146°, μ(CuKα)=23 cm^{-1}), 1577 had $I > 3\sigma(I)$ and were used for all calculations with the Structure Diffraction Package[31]. The hydrogen atoms of the CH_2 and phenyl groups were fixed at idealized positions. The others were found from ΔF syntheses and their coordinates were refined. The final refinement gave R=0.038. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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Table 4: ^{1}H NMR data[a] for compounds **11** - **21**, **23** - **26** and **11A**

Compounds	H-2 *J2,3*	H-3 *J3,4*	H-4 *J4,5*	H-5 *J5,6*	H-6 *J5,6'*	H-6' *J6,6'*	$\underline{C}H_3C{=}O$	Aromatic protons
11	~5.63, m b	~5.63, m b	5.27, m *~10*	4.42, ddd *3.6*	4.34, dd *1.7*	4.07, dd *12.5*	2.09, 2.08, 2.06, 2.03	7.45, m, 3H; 7.67, m, 2H
11[c]	5.55, t *10.2*	5.67, d *8.5*	5.32, t *10.2*	4.44, ddd *4.2*	4.34, dd *2.4*	4.13, dd *12.5*	2.06, 2.05, 2.02, 2.01	7.73, m, 2H; 7.57, m, 3H
12	5.60, d *10.1*	5.10, dd *9.4*	5.27, t *9.6*	4.10, m *~3.5*	4.33, dd b	4.10, m *~12*	2.07, 2.06, 2.05, 2.04	7.45, m, 3H; 7.70, m, 2H
13	~5.61, m b	~5.61, m b	5.26, m b	4.41, m *3.8*	4.33, dd *2.1*	4.08, dd *12.6*	2.08, 2.08, 2.06, 2.03	7.53, d, 2H, 7.58, d, 2H *Jvic 8.7*
14	5.60, d *10.1*	5.10, t *9.9*	5.27, t *9.9*	~4.11, m *3.7*	4.33, dd *2.0*	~4.11, m *12.4*	2.07, 2.07, 2.05, 2.04	7.58, s, 4H
15	~5.61, m b	~5.61, m b	5.29, m b	4.41, m *3.7*	4.33, m *2.0*	4.08, dd *12.4*	2.09, 2.09, 2.06, 2.04	7.41, d, 2H; 7.60, d, 2H *Jvic 8.6*
16	5.61, d *10.1*	5.10, t *9.6*	5.27, t *9.9*	~4.10, m *4.1*	4..33, dd b	~4.10, m b	2.07, 2.07, 2.05, 2.04	7.42, d, 2H; 7.63, d, 2H *Jvic 8.7*
17	5.62, m b	5.62, m b	5.26, m b	4.41, m *3.8*	4.34, dd *2.0*	4.09, dd *12.6*	2.08, 2.08, 2.05, 2.03	7.13, t, 2H; 7.67, dd, 2H *Jvic ~8.8, JH,F 8.8 and 5.4*
18	5.60, d *10.1*	5.10, t *9.4*	5.27, t *9.4*	~4.10, m *4.1*	4.34, dd b	~4.10, m *13.0*	2.07, 2.07, 2.05, 2.04	7.14, t, 2H; 7.71, dd, 2H *Jvic ~8.8, JH,F 8.8 and 5.4*
19	5.67, m b	5.67, m b	5.29, m *10.3*	4.51, ddd *3.9*	4.38, dd *2.1*	4.14, dd *12.7*	2.13, 2.10, 2.07, 2.05	7.46 to 7.73, m, 4H; 7.88 - 8.00, m, 2H 8.63, d , 1H; *Jvic 8.7*
20	5.66, d *10.1*	5.13, t *9.5*	5.29, t *9.9*	~4.18, m *4.3*	4.37, dd *12.3*	~4.18, m b	2.12, 2.10, 2.06, 2.05	7.48 to 7.75, m, 4H; 7.88 to 8.01, m, 2H 8.51, d, 1H; *Jvic 8.7*
21	~5.60, m b	~5.60, b	5.24, m b	~4.38, m *3.9*	4.30, dd b	4.09, dd *12.9*	2.09, 2.09, 2.05, 2.02	4.33 to 4.44, m, 2H, $\underline{C}H_2CH_3$ 1.39, t, 3H, $CH_2\underline{C}H_3$; *Jvic 7.1*
23	~5.62, m b	~5.62, m b	5.23, m b	~4.20, m b	~4.20, m b	4.16, dd *12.7*	2.10, 2.10, 2.05, 2.02	
24	5.62, d *10.3*	5.03, t *9.6*	5.24, t *9.9*	4.05, m *4.3*	4.33, dd *2.4*	4.13, dd *12.6*	2.10, 2.08, 2.04, 2.03	
25	5.58, d *11.1*	5.50, dd *3.3*	5.58, d *0*	4.66, m *7.1*	4.19, dd *6.3*	4.08, dd *11.5*	2.20, 2.09, 2.01, 2.01	7.68, d, 2H, *Jvic 7.3* 7.40 - 7.50, m, 3H
26	5.80, d *11.2*	4.94, dd *3.5*	5.48, d *~0*	4.35, t *7.7*	4.22, dd *6.0*	4.11, dd *11.2*	2.19, 2.06, 2.01, 2.00	7.70, d, 2H, Jvic 6.0 7.40 - 7.50, m, 3H
11A[d]	3.88, d *9.5*	3.76, t *8.8*	3.52, dd *9.8*	3.90, ddd *2.5*	3.83, dd *4.2*	3.74, dd *13.0*		

[a] - Spectra recorded for deuteriochloroform solutions, unless otherwise indicated (δ ppm/TMS, J Hz); [b] - Not determined; [c] - In CD_3COCD_3 as the solvent; [d] - In CD_3OD as the solvent.

Table 5: ^{13}C NMR data[a] for compounds **11 - 20, 25, 26** and **11A**

Compounds	C-1	C-2	to		C-5	C-6	C=N	C=O	CH_3	Aromatic carbons
11	122.44	71.09	70.66	68.00	67.52	61.14	156.39	170.58, 169.68	20.72	131.71 (p), 127.04 (ipso)
								169.49, 169.42	20.57 (3C)	128.99 (2C), 128.01 (2C)
12	127.30	73.41	70.61	68.39	67.20	61.13	155.32	170.56, 169.95	20.65, 20.56	131.68 (p), 126.92 (ipso)
								169.19, 168.56	20.52	129.00 (2C), 127.96 (2C)
13	122.84	71.04	70.80	67.50	68.00	61.11	155.45	170.50, 169.63	20.54 (3C)	126.18, 126.03
								169.41, 169.37	20.68	132.26 (2C), 129.34 (2C)
14	127.36	73.35	70.71	67.14	68.37	61.07	154.47	170.54, 169.86	20.65, 20.55	126.28, 126.18
								169.16, 168.50	20.51, 20.48	132.27 (2C), 129.31 (2C)
15	122.82	71.02	70.79	67.49	67.98	61.12	155.32	170.47, 169.61	20.52 (3C)	137.79, 125.58
								169.40, 169.36	20.67	129.30 (2C), 129.20 (2C)
16	127.34	73.35	70.69	67.13	68.36	61.07	154.36	170.57, 169.88	20.66, 20.57	137.85, 125.82
								169.18, 168.52	20.52, 20.49	129.31 (2C), 129.16 (2C)
17	122.76	71.09	70.77	67.54	68.01	61.13	155.31	170.55, 169.67	20.55 (3C)	130.15 (2C, $J_{C,F}$ 8.8), 116.28 (2C, $J_{C,F}$ 22.3)
								169.47, 169.40	20.70	164.63 ($J_{C,F}$ 253.5), 123.35 ($J_{C,F}$ 3.5)
18	127.27	73.39	70.66	67.16	68.37	61.09	154.25	170.58, 169.89	20.66, 20.57	130.09 (2C, $J_{C,F}$ 8.7), 116.27 (2C, $J_{C,F}$ 22.3)
								169.18, 168.54	20.52 (2C)	164.64 ($J_{C,F}$ 253.7), 123.60 ($J_{C,F}$ 3.5)
19	121.78	71.17	70.72	67.68	68.04	61.31	155.88	170.60, 169.70	20.73, 20.59	132.15, 129.93, 128.65, 127.89, 126.77, 125.64
								169.46, 169.46	20.57 (2C)	124.87 (7 C-H); 133.82, 130.43, 123.50 (3C)
20	126.26	73.48	70.67	67.34	68.49	61.33	154.69	170.63, 169.92	20.70, 20.64	132.13, 129.55, 128.65, 127.88, 126.81, 125.66
								169.25, 168.65	20.53, 20.51	124.85 (7 C-H); 133.84, 130.44, 123.86 (3C)
25	123.18	69.94	68.93	67.43	65.58	60.85	156.15	170.22, 170.05	20.67, 20.53	131.64 (p), 127.17 (ipso)
								169.71, 169.60	20.62 (2C)	128.99 (2C), 127.96 (2C)
26	127.87	71.92	69.74	66.36	66.05	60.60	155.41	170.22, 170.17	20.70, 20.63	131.65 (p), 127.39 (ipso)
								169.85, 168.72	20.60, 20.50	128.98 (2C), 128.02 (2C)
11A[b]	128.75[c]	78.23	76.32	70.62	72.93	61.74	155.84			131.31 (p), 128.67[c] (ipso), 129.20 (2C), 127.98 (2C)

[a] - Spectra recorded for deuteriochloroform solutions, unless otherwise indicated (δ ppm/ TMS); [b] - C_5D_5N as the solvent; [c] - may be reversed.

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