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Synthesis of isothiochroman 2,2-dioxide and 1,2-benzooxathiin 2,2-dioxide gyrase B inhibitors

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Abstract

The design, synthesis and in vitro biological evaluation of isothiochroman 2,2-dioxide and 1,2-benzooxathiin 2,2-dioxide analogues of coumarin inhibitors of gyrase B are described. Compared to coumarin derivatives, compounds of the 1,2-benzooxathiin 2,2-dioxide series display improved inhibitory potency in negative supercoiling of relaxed DNA gyrase.

Keywords: antibiotics; glycosidation; hydrogen bonding; structure–activity.

Over the past several years our efforts have been directed towards the design of effective, orally bioavailable coumarin antibiotics inhibitors of bacterial DNA gyrase.[1] Recently, we have disclosed a series of coumarin congeners bearing at the coumarin part of the molecule amide isosteres (**1**),[2a,b,e] carboxyl group,[2c] or basic amino groups.[2d] As in the complexes of these inhibitors with the 24 kDa N-terminal fragment of gyrase B protein, one of the key interactions is electrostatic/hydrogen bonding between the ester and carbonyl oxygens of the coumarin moiety and Arg-136,[3] we reasoned that the replacement of the coumarin carbonyl group with a more polar sulfone functionality would lead to stronger inhibition of DNA gyrase and improved antibacterial activity. Morever, the polar nature of the sulfone group would confer better aqueous solubility to the analogues. This led to the design of two series of DNA gyrase inhibitors wherein the coumarin was replaced with isothiochroman 2,2-dioxide and 1,2-benzooxathiin 2,2-dioxide derivatives.

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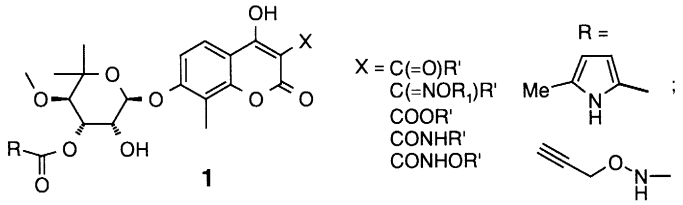
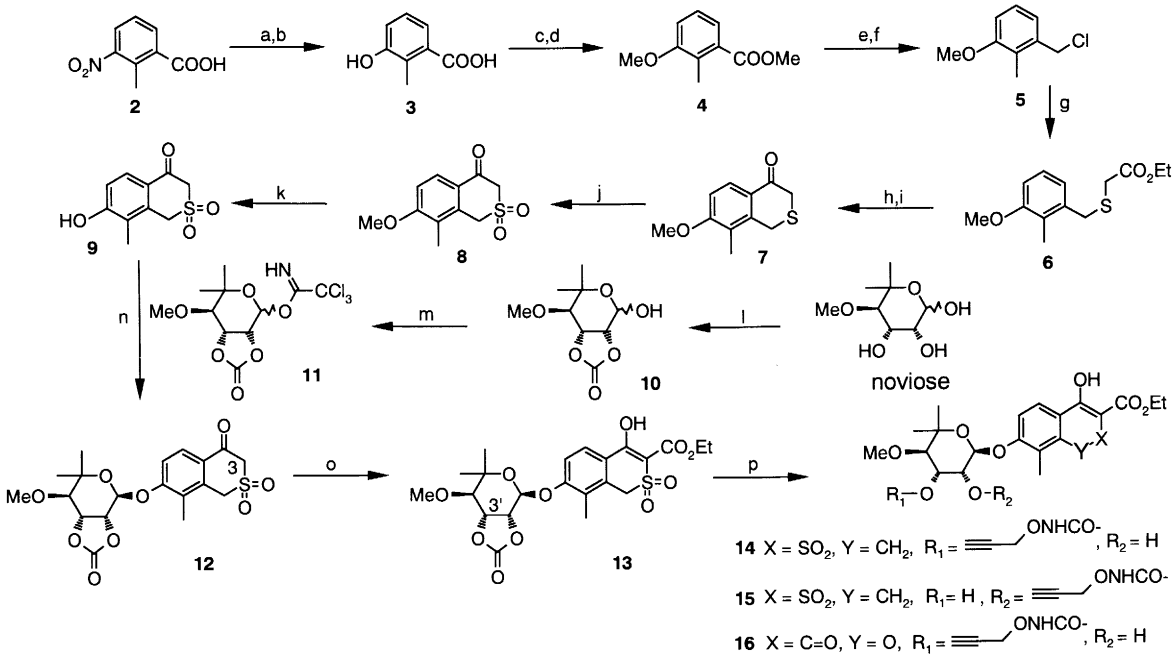
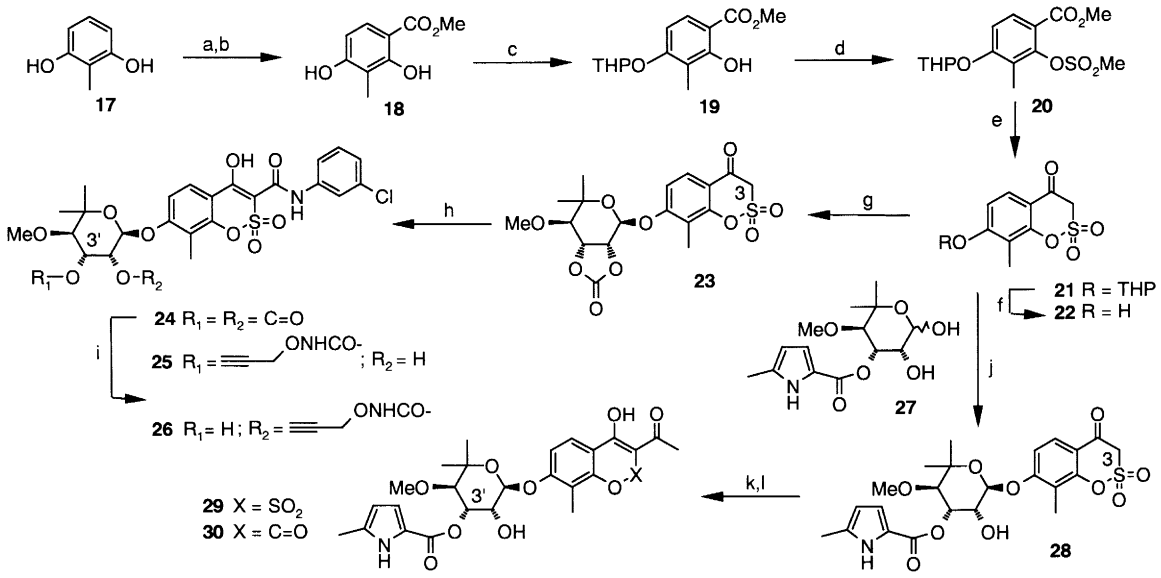


The synthesis of isothiochroman 2,2-dioxide inhibitors of gyrase B is depicted in Scheme 1. 3-Hydroxy-2-methylbenzoic acid (**3**) was prepared from 3-nitro-2-methylbenzoic acid (**2**) according to the literature.[4] The acid **3** was converted to methyl ester by HCl/MeOH at reflux in quantitative yield. Methylation of the free phenol under standard conditions (Me_2SO_4/K_2CO_3 in acetone) provided methyl ether **4**. Reduction of the ester group in **4** with $LiAlH_4$ in ether and subsequent conversion of the resulting benzyl alcohol with $CaCl_2$/HCl furnished benzyl chloride **5**. This was converted with ethyl thioacetate in the presence of NaH in DMF to *S*-alkyl derivative **6** which was hydrolysed to free acid. Cyclisation of the acid to isothiochroman **7** was effected with P_2O_5 in toluene in the presence of Celite. Oxidation of **7** with 3-chloroperoxybenzoic acid in CH_2Cl_2 gave the sulfone **8** which was demethylated with a mixture of HBr-acetic acid to provide the free phenol derivative **9** ready for glycosylation. Attempted glycosylation of the noviose carbonate **10**, prepared from noviose and 1,1′-carbonyldiimidazole in dichloroethane at reflux, with **9** under Mitsunobu's conditions provided a low yield (10%) of the desired α-anomer **12**. Searching for an alternative method of activation of the anomeric position of noviose carbonate **10**, we prepared the corresponding trichloroacetimidate **11** using trichloroacetonitrile in the presence of



Scheme 1. *Reagents and conditions*: (a) H_2, Pd–C/10%, EtOH, rt, 98%; (b) $NaNO_2$, aq. H_2SO_4, 0°C then reflux, 99%; (c) MeOH, HCl gas, reflux, quant.; (d) Me_2SO_4, K_2CO_3, acetone, rt, 72%; (e) $LiAlH_4$, Et_2O, rt, quant.; (f) $CaCl_2$, HCl, 94%; (g) $HSCH_2CO_2Et$, NaH, DMF, rt, 72%; (h) NaOH, MeOH, H_2O, rt, 86%; (i) P_2O_5, Celite, toluene, 90°C, 77%; (j) 3-$ClC_6H_4CO_3H$, CH_2Cl_2, 0°C, 60%; (k) HBr, AcOH, reflux, 90%; (l) 1,1′-carbonyldiimidazole, $ClCH_2CH_2Cl$, reflux, 70%; (m) NC–CCl_3, CH_2Cl_2, Cs_2CO_3 cat, rt, quant.; (n) BF_3–Et_2O, CH_2Cl_2, 84%; (o) $ClCO_2Et$, DMAP, CH_2Cl_2, rt, 60%; (p) $HC{\equiv}CCH_2ONH_2{}^-HCl$, $LiClO_4$, Py, rt, 33%



Scheme 2. *Reagents and conditions*: (a) DMF, $POCl_3$, $ClCH_2CH_2Cl$, rt, 73%; (b) MnO_2, KCN, AcOH, MeOH, rt, 68%; (c) DHP, cat TsOH, Et_2O, rt, 71%; (d) MsCl, Et_3N, Et_2O, rt, 90%; (e) NaH, DMF, 0°C, 82%; (f) 1 M HCl in MeOH, rt, 86%; (g) **11**, BF_3Et_2O, CH_2Cl_2, 50%; (h) 3-ClC_6H_4–NCO, DMAP, CH_2Cl_2, rt, 23%; (i) $HC{\equiv}CCH_2ONH_2$-HCl, $LiClO_4$, Py, rt, 64%; (j) PPh_3, $EtO_2CN{=}NCO_2Et$, CH_2Cl_2, rt, 15%; (k) Ac_2O, DMAP, CH_2Cl_2, rt; (l) KOMe, MeOH, 0°C, 37% (from **27**)

catalytic quantities of Cs_2CO_3 in CH_2Cl_2. The imidate **11** underwent smoothly glycosylation with **9** in the presence of BF_3–Et_2O in dichloromethane to afford 84% of desired α-glycoside **12**. As in the case of coumarin series[2a] isothiochroman 2,2-dioxide derivative **12** underwent C-acylation at C-3 with ethyl chloroformate in the presence of DMAP to provide **13**. Opening of the noviosyl carbonate part of **13** with *O*-propargylhydroxylamine in the presence of $LiClO_4$ in pyridine afforded a thermodynamic mixture of 3′- and 2′-*N*-propargyloxycarbamates **14** and **15** (4:1)[5] in 33% yield.

The synthetic approach to 1,2-benzooxathiin 2,2-dioxide inhibitors of gyrase B is summarised in Scheme 2. Vilsmeyer formylation[6] of 2-methylresorcinol **17** provided 2,4-dihydroxy-3-methylbenzaldehyde that was oxidised to the corresponding methyl ester **18** using Corey's procedure.[7] Regioselective tetrahydropyranylation of **18** afforded THP monoprotected derivative **19** in 74% yield. The phenol **19** was then converted under standard conditions into methanesulfonate **20** that was subjected to basic cyclisation with NaH in DMF to furnish 1,2-benzooxathiin 2,2-dioxide derivative **21**. Deprotection of THP in **21** with HCl/MeOH provided the intermediate **22** ready for glycosylation. Coupling of **22** with activated noviose carbonate **11** under BF_3–Et_2O catalysed conditions afforded α-glycoside **23** in 50% yield after chromatographic separation. Acylation at C-3 of 1,2-benzooxathiin 2,2-dioxide portion of **23** with 3-chlorophenylisocyanate in the presence of DMAP furnished the corresponding anilide **24**. This was subjected to lithium perchlorate catalysed opening of the noviosyl carbonate portion with *O*-propargylhydroxylamine in pyridine to provide, similarly to the isothiochroman 2,2-dioxide case, a mixture of regioisomeric 3′- and 2′-*N*-propargyloxycarbamates **25** and **26** in the ratio 4:1, respectively. The 1,2-benzooxathiin 2,2-dioxide analogue **29** bearing 3′-(5-methylpyrro-2-yl)ester at noviose was synthesised by Mitsunobu's coupling between pyrrole-noviose **27**[2a] and **22**. The introduction of an acetyl group at the 3-position of the 1,2-benzooxathiin 2,2-dioxide **28** by the established technique[2a] was accompanied by acetylation of 2′-OH of noviose. Hydrolysis of this 2′-acetate in MeOH with KOMe gave 1,2-benzooxathiin 2,2-dioxide analogue **29**.

The results of the inhibition of the supercoiling activity of *S. aureus* or *E. coli* DNA gyrase by

novobiocin, clorobiocin and isothiochroman 2,2-dioxide and 1,2-benzooxathiin 2,2-dioxide derivatives are shown in Table 1. Also in Table 1 are the corresponding results of the reference compounds incorporating the coumarin scaffold: **16**[2b] (Scheme 1) and **30**[2a] (Scheme 2). As predicted, substitution of the C=O carbonyl group of coumarin **30** by SO_2 **29** did result in a twofold increase of inhibitory potency in negative supercoiling of DNA gyrase. However, replacement of -O-CO- of coumarin moiety **16** by -CH_2-SO_2- in isothiochroman 2,2-dioxide **14** lowered the inhibitory activity by an order of magnitude. Taking into account the distances between the guanidinium group of Arg-136 and the ester oxygen and carbonyl group of coumarin ring as 3.2 and 2.6 Å, respectively,[3c] the principal hydrogen bonding interaction could be attributed to Arg-136 and the C=O of the coumarin moiety. Decrease in activity of isothiochroman 2,2-dioxide derivative **14** with respect to **16** could be explained by the CH_2 of **14** hindering the tight binding of the 8-Me group of coumarin to a hydrophobic pocket. Although the 1,2-benzooxathiin 2,2-dioxide series displayed increased in vitro inhibitory activity when compared to coumarin analogues, the series was completely devoid of antibacterial activity (MIC >40). Increased polarity caused by replacement of the coumarin carbonyl group by SO_2[8] completely abolished the intracellular uptake of the analogues. These results clearly demonstrate that the fine tuning of lipophylicity of gyrase B inhibitors is essential for their biological activity.

Table 1
In vitro activity of isothiochroman 2,2-dioxide and 1,2-benzooxathiin 2,2-dioxide inhibitors against *S. aureus* or *E. coli* DNA gyrase supercoiling (IC_{50}),[a,b] and selected in vitro antibacterial activity (MIC)[c]

Compound	Novobiocin	Clorobiocin	**14**	**16**	**25**	**29**	**30**
IC_{50}nov[a,b]/IC_{50}comp	1[a,b]	1.7[a]	0.33[b]	5.6[a]	1[b]	4.2[a]	2[a]
MIC(μg/mL) *S. aureus* 011HT3	≤0.04	≤0.04	>40	1.2	>40	>40	≤0.04

a) IC_{50} was determined for gyrase B of *E. coli* against novobiocin (0.25 μg/mL) as reference. For the details see ref. 2a; b) IC_{50} was determined for gyrase B of *S. aureus* against novobiocin (0.5 μg/mL) as reference. For the details see ref. 2e; c) MIC, Minimal Inhibitory Concentrations (μg/mL) were measured by using a twofold broth microdilution after 24 hours incubation.

In conclusion, we succeeded in replacing the coumarin scaffold by a 1,2-benzooxathiin 2,2-dioxide skeleton to give analogues that proved to be more potent in inhibiting negative supercoiling of DNA gyrase. At the same time, however, the highly polar nature of this class of analogues had negative effects on intracellular permeability and antibacterial activity.

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