Synthesis and Structure-Activity Relationship of Xenocoumacin 1 and Analogues as Inhibitors of Ribosomal Protein Synthesis

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Ribosomal protein synthesis is an important target in antibacterial drug discovery. Numerous natural products have served as starting points for the development of antibiotics. We report here the total synthesis of xenocoumacin 1, a natural product that binds to 16S ribosomal RNA at a highly conserved region, as well as analogues thereof. Preliminary structure–activity relationship studies were aimed at understanding and modulating the selectivity between eukaryotic and prokaryotic ribosomes. Modifications were mainly tolerated in the aromatic region. Whole-cell activity against Gram-negative bacteria is limited by efflux and penetration, as demonstrated in genetically modified strains of *E. coli*. Analogues with high selectivity for eukaryotic ribosomes were identified, but it was not possible to obtain inhibitors selective for bacterial protein synthesis. Achieving high selectivity (albeit not the desired one) was thus possible despite the high homology between eukaryotic and prokaryotic ribosomes in the binding region.

Introduction

The need for novel antibacterial drugs is undisputed in the scientific community,[1–3] and numerous initiatives aim to foster research in this important domain.[4,5] In particular, hard-to-kill Gram-negative pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* accumulate resistance at high rates, and some species are also naturally unaffected by many antibiotic classes. Although the majority of commercially used antibacterials act via inhibition of i) cell-wall biosynthesis, ii) protein synthesis or iii) DNA metabolism, mining bacterial genomes to identify conserved essential functions has failed to provide useful novel targets.[2] Addressing old targets with novel chemical matter acting by a different mode[6] could be one way to identify inhibitors without cross-resistance. Inhibition of protein synthesis is one of the most important modes of action of antibiotics we currently have at our disposal.[7] A large variety of structural classes, including tetracyclines, aminoglycosides, macrolides, lincosamides, oxazolidinones as well as fusidic acid inhibit ribosomal protein synthesis at different stages of the process by binding at various sites of the 70S bacterial ribosome. Recently, several groups have been able to elucidate the binding sites of a number of natural products in complete ribosomal complex X-ray crystallography.[8–10] One of those natural inhibitors is amicoumacin A (**1**),[11] a close analogue of xenocoumacin 1 (**2**), which binds to the E-site of the ribosome. As this region does not overlap the binding sites of any of the clinically used antibiotics, it is reasonable to assume that the coumacin analogues might overcome pre-existing resistance to other antibiotics targeting protein synthesis. Compounds **1**[12] and **2**,[13] with reported antibacterial activity in whole-cell screens, were both discovered more than 25 years ago. Several total syntheses of amicoumacin-related natural products were published,[14] as well as the lack of selectivity for bacterial over eukaryotic ribosomes.[15]

A recent analysis of interactions of small molecules with RNA has shown that π-stacking as well as H-bonds are the most important type of bonding interactions, but in contrast to interactions in protein–inhibitor complexes, interactions with RNA are much less understood.[16] X-ray structures of **1** with the ribosomes of *Thermus thermophilus* (PDB ID: 4W2F) and *Saccharomyces cerevisiae* (PDB ID: 5I4L) were solved.[17] The binding of **1** to the bacterial ribosome is shown in Figure 1.

Main features of the interactions are the π-stacking of the aromatic coumacin moiety with G693, the H-bond network of the aminodiol linker bridging between rRNA and mRNA and the intercalation of the isobutyl moiety between residues C795 and C796. Unfortunately, in the *S. cerevisiae* structure mRNA is not visible (or absent) and the aminodiol moiety of amicoumacin adopts a slightly different conformation. Due to these differences and the relatively high flexibility of RNA, an approach using docking was rated too speculative. We resorted to a traditional medicinal chemistry approach for our structure–activity relationship studies for which in turn a robust synthetic access to derivatives of **2** was essential.

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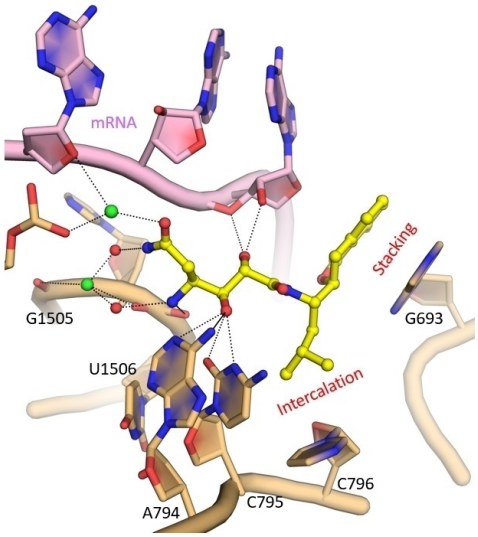


Figure 1. Representation of the X-ray crystal structure 4W2F showing the binding mode of amicoumacin A (**1**; adapted from ref. [11]).

Results and Discussion

We chose **2** as starting point for our investigations to attempt to improve potency and increase the selectivity window. Based on the binding mode and the knowledge on synthetic accessibility of **1** we devised the strategy depicted in Figure 2.

We were mainly interested in three regions of the molecule: the π-stacking aromatic moiety, the RNA-intercalating residue, which in the natural product originates from a lysine amino acid, and the right hand side chain (RHS) differing between **1** and **2**. Changes in the aminodiol moiety in the linker were of secondary interest because of its engagement in a neatly defined H-bond network which is clearly visible in the X-ray structure.

In a first step we devised the synthesis of the RHS of xenocoumacin as described in Scheme 1 and based on the published synthesis of **1**.[14] Starting form orthogonally protected (*S*)-ornithine (**4**) we set up the diol moiety as previously described.[18] The first step consisted of a coupling with Meldrum's acid (**3**), followed by cyclisation under concomitant decarboxylation. The double bond in **6** was installed via a three-step sequence (reduction, mesylation, elimination). Dihydroxylation of **6** proceeded stereoselectively and was followed by protection as a cyclic acetal (**7**). Hydrogenation of the Cbz group and introduction of the guanidine group using *N,N'*-bis-Boc-1-guanylpyrazole was performed in a one-pot procedure. Mild hydrolysis of the Boc-protected lactam ring with LiOH finally gave carboxylic acid **8** in good yields.

With the RHS ready for coupling, we turned our interest to the aromatic moiety (Figure 3). Our aim was to not only synthesise the methoxy isochromanone moiety **9** necessary for the synthesis of the natural product (and well precedented in the literature[14]), but to also investigate the replacement of the hydroxy group by hydrogen (**10**) and the corresponding isochromenones (**11**–**13**).

The synthesis of isochromenones by Sonogashira coupling of an acetylene followed by cyclisation is well documented in the literature.[19,20] The synthesis of the unsubstituted isochromenone **13** was achieved as depicted in Scheme 2.

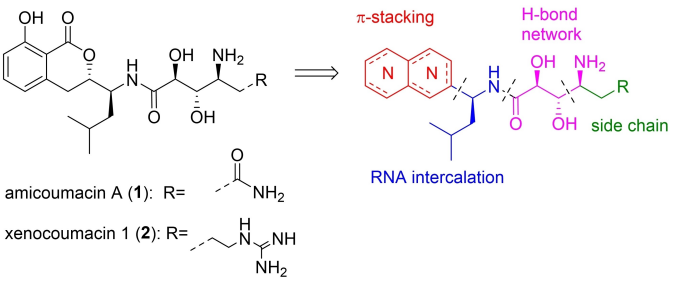
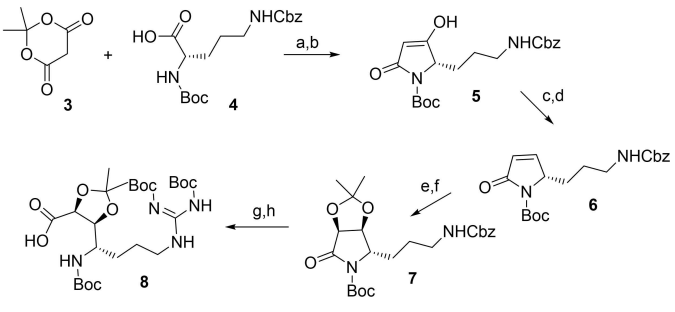


Figure 2. Strategy envisaged for SAR studies of **2**: Modifications in four parts of the molecule (colour coded) can be accessed by formation of the bonds indicated with a dashed line.



Scheme 1. Synthesis of the RHS of xenocoumacin. a) DCC, DMAP, CH_2Cl_2, RT, 4 h; b) MeOH, reflux, 1 h, 58% over 2 steps; c) $NaBH_4$, HOAc, CH_2Cl_2, 0 °C, 80%; d) MsCl, NEt_3, CH_2Cl_2, 0 °C–RT, then DBU, RT, 1 h, 86%; e) OsO_4, NMO, MeCN/water/acetone, RT, 1 h, 80%; f) acetone, CSA, 2,2-dimethoxypropane, RT, 1 h, 77%; g) Pd/C, H_2, *N,N'*-bis-Boc-1-guanylpyrazole, EA, RT; h) LiOH, THF/H_2O, RT, 15 min, 85% over 2 steps.

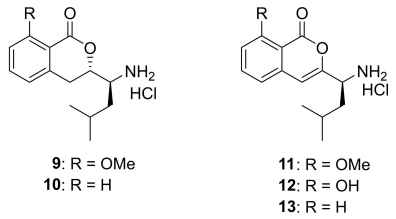
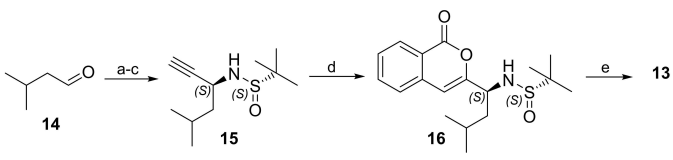


Figure 3. conservative modifications of coumacin left hand side (LHS).



Scheme 2. Synthesis of unsubstituted isochromenone **13**. a) (*S*)-(−)-2-Methyl-2-propanesulfinamide, $Ti(OEt)_4$, THF, RT, 2 h, 84%; b) TMS acetylene, *i*PrMgCl, THF, −78 °C, 65%; c) TBAF, THF, RT, 85%; d) 2-iodobenzoic acid, *trans*-4-hydroxy-(L)-proline, CuI, K_2CO_3, DMSO, 75 °C, 1 h, 33%; e) HCl, MeOH/THF, RT, 99%.

3-Methylbutanal **14** was condensed with (*S*)-2-methylpropane-2-sulfinamide[21] and treated with the anion of trimethylsilylacetylene (generated in situ by treatment with *i*PrMgCl) to give in good yield and with good diastereoselectivity the required intermediate which after cleavage of the trimethylsilyl group with tetrabutylammonium fluoride (TBAF) led to acetylene **15**. Copper catalysed coupling of **15** with 2-iodobenzoic acid gave the desired enantiomer of isochromenone **16** in modest yields, along with some phthalide by-product. Deprotection with HCl in MeOH yielded the desired unsubstituted isochromenone **13**.

All our attempts to synthesise the analogous methoxy derivative **11** via the same route failed, as cyclisation of the Sonogashira coupling product only led to the 5-membered phthalide derivative via formal 5-exo-dig process (data not shown). This methoxylated analogue **11** had to be accessed via a different route.[17] To obtain hydroxy analogue **12** (Scheme 3) we had to modify the sequence and use acetal protected salicylic acid derivative **17** for the Sonogashira coupling which, after hydrolysis of the acetal, was cyclised under Pd catalysed conditions.[22]

The employed sulfinimide-based chemistry proved versatile for the exploration of the intercalating moiety (Scheme 4, top), as well as for the variation of the aromatic moiety in general (Scheme 4, bottom) when using the opposite enantiomer of the chiral auxiliary. Yields of this unoptimised sequence were rather low but led rapidly to the desired enantiopure building blocks.

A range of additional side-chain analogues of **8** were synthesised varying the stereochemistry of the aminodiol part as well as the terminal moiety.[17] With side chains and aromatic moieties in hand, we proceeded to the final coupling followed by deprotection with BBr_3 to access hydroxychromanones or with TFA or HCl to obtain the methoxy as well as the corresponding unsubstituted analogues thereof (Scheme 5).

All new compounds were tested in vitro for their ability to inhibit bacterial (*Escherichia coli*) or eukaryotic (rabbit reticulocyte) protein synthesis (in vitro transcription translation assay (IVTT)).[17] The results are summarised in Table 1.

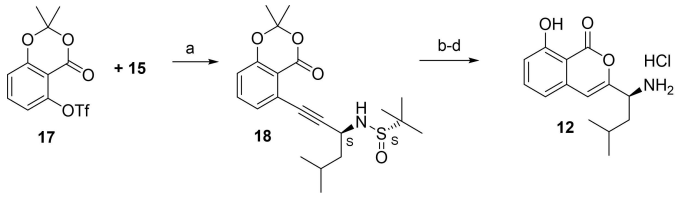
Novel xenocoumacin analogues were identified that inhibit protein synthesis in vitro at concentrations between 10 nM and >100 μM and showed very different potencies against eukaryotic or bacterial ribosomes. Surprisingly, despite virtually identical RNA sequence at the binding sites, the ribosome of eukaryotic systems is much less susceptible to structural changes of the inhibitors. While even small modifications drastically affected the inhibition of the ribosome of *E. coli*, the compounds still remained potent inhibitors of eukaryotic protein synthesis.

Conservative modifications on the aromatic portion of **2**, such as presence or absence of hydroxy or methoxy group, presence or absence of double bond does not have a profound effect on the activity (cf. compounds **2, 19**–**23**) in vitro. Bigger losses of potency were observed for the *R,R* analogue **24** with a ~100-fold higher IC_{50} value in the micromolar range.

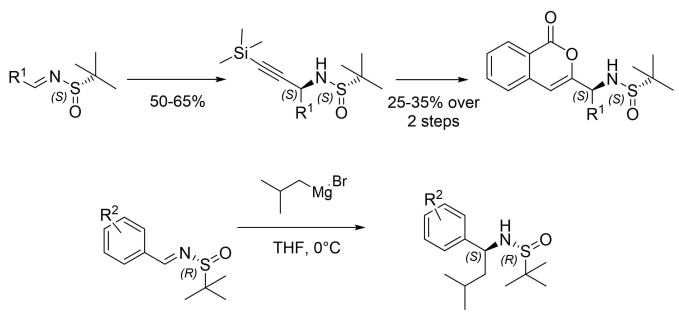
We chose the unsubstituted isochromenone (R=H) intermediate **13** as suitable simplified aromatic moiety for most of our investigations.

Modifications of the isobutyl group (intercalating moiety, compounds **25**–**30**) led to much bigger loss of activity in the *E. coli* IVTT assay (1.27→100 μM), whereas in the reticulocyte assay sub-micromolar activities were generally still measured.

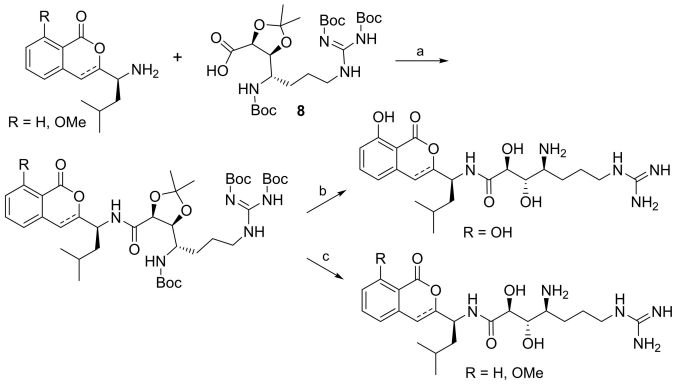
Variations in the linker region affected activity less than expected. In the X-ray structure of **1**, the two hydroxy groups and the amine are tightly bound in a H-bond network and were therefore expected to be essential for inhibitory activity. The two analogues with one inverted hydroxy group (**31** and **32**, absolute configuration of diol not assigned) as compared to **23** still retained some activity and showed IC_{50}'s in the double-digit micromolar range (about 100-fold less potent) in the bacterial assay and are about 15 to 150 times more active in the reticulocyte IVTT assay. The same range of activity was observed



Scheme 3. Synthesis of hydroxyisochromenone **12**. a) CuI, Pd(dppf), NEt_3, overnight, 70%; b) LiOH, THF/H_2O, RT, 2.5 h, 100%; c) $PdCl_2(MeCN)_2$, NEt_3, THF, 50 °C, 1 h, 43%; d) HCl/MeOH, 30 min, 70%.



Scheme 4. Synthetic access to various aromatic and intercalating moieties.



Scheme 5. Coupling and final deprotection. a) ((Benzotriazol-1-yloxy)tris (dimethylamino)phosphonium hexafluorophosphate or HBTU, NEt_3, DMF/CH_2Cl_2, 0 °C–RT, overnight, 56–93%; b) BBr_3 in CH_2Cl_2, −78 °C, 1 h, 11–55%; c) aq. TFA, or HCl in MeOH, 50 °C, overnight, 19–56%.

Table 1. Summary of IVTT of xenocoumacin 1 analogues.

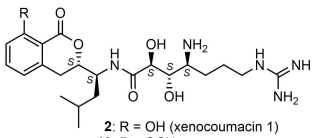
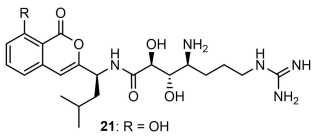
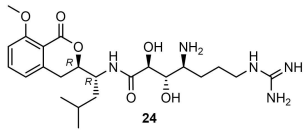
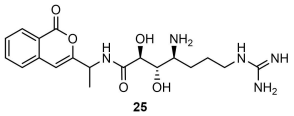
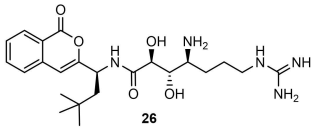
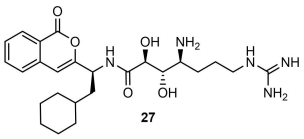
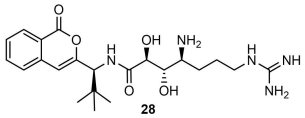
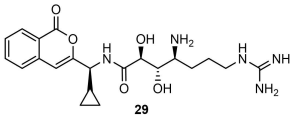
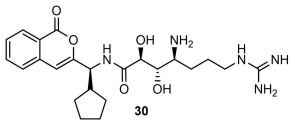
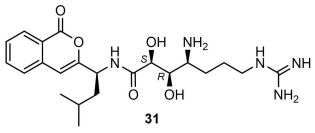
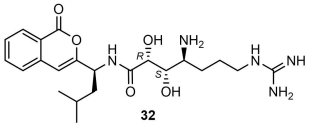
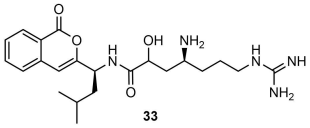
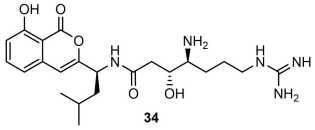
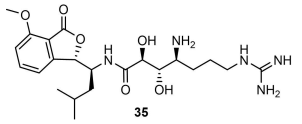
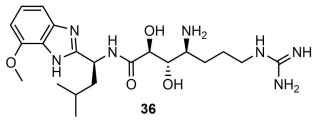
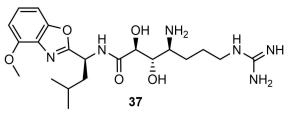
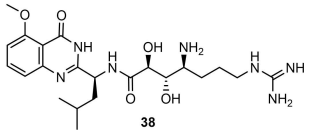
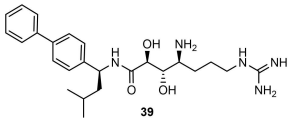
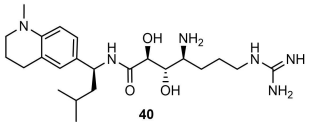
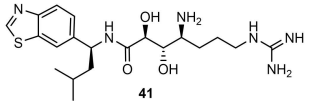
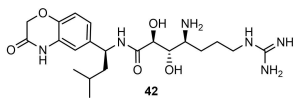
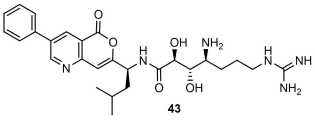
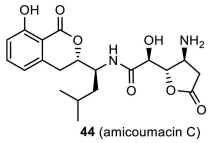
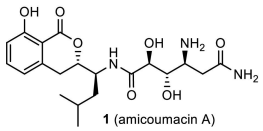
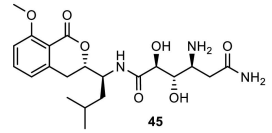
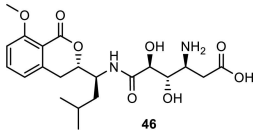
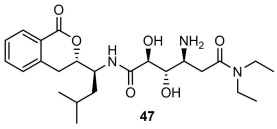
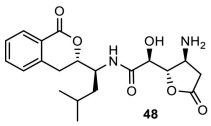
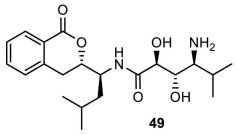
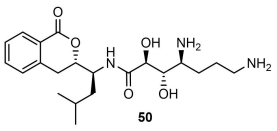
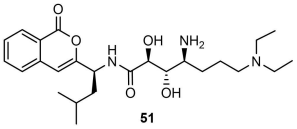
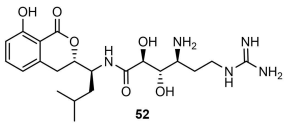
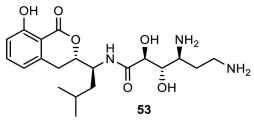
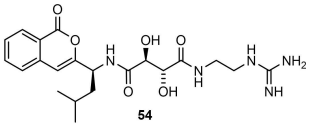
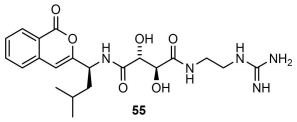
Structure / compound no.	IVTT [μM] *E. coli*[a]	reticulocytes	Structure / compound no.	IVTT [μM] *E. coli*[a]	reticulocytes
 **2**: R = OH (xenocoumacin 1) **19**: R = OCH_3 **20**: R = H	0.029 0.076 0.073	0.014 0.018 0.014	 **21**: R = OH **22**: R = OCH_3 **23**: R = H	0.076 0.200 0.200	0.017 0.030 0.013
 **24**	6.8	1.50	 **25**	>100	19.10
 **26**	1.27	0.025	 **27**	>100	0.48
 **28**	83	0.28	 **29**	>100	0.14
 **30**	7.2	0.021	 **31**	16.4	1.10
 **32**	18.2	0.13	 **33**	27.8	0.64
 **34**	2.00	0.029	 **35**	>100	0.26
 **36**	6.10	0.014	 **37**	2.90	0.035
 **38**	4.46	0.055	 **39**	72.0	0.068
 **40**	71.0	0.20	 **41**	15.2	0.027
 **42**	3.90	0.011	 **43**	3.0	0.039
 **44** (amicoumacin C)	1.7	0.53	 **1** (amicoumacin A)	0.10	0.047

Table 1. continued

Structure / compound no.	IVTT [μM] *E. coli*[a]	reticulocytes	Structure / compound no.	IVTT [μM] *E. coli*[a]	reticulocytes
 **45**	0.58	0.18	 **46**	34.4	18.0
 **47**	>100	48.7	 **48**	36.4	9.7
 **49**	16.7	0.76	 **50**	3.3	0.042
 **51**	>100	38.1	 **52**	1.60	0.029
 **53**	1.70	0.026	 **54**	>100	>100
 **55**	>100	>100			

[a] IC_{50} are means of several independent experiments.[17]

when one or the other hydroxy group in the linker were completely removed (compounds **33** (mixture of 2 isomers) and **34**).

More dramatic changes in the π-stacking region (compounds **35**–**43**) led to compounds with micromolar affinities in *E. coli* IVTT and roughly 100-fold better activity in the reticulocyte IVTT assay.

Modifications in the RHS also mostly led to loss of activity. The activity of amicoumacin (**1**) and the methoxylated analogue **45** showed the expected sub-micromolar activity in both assays, whereas the three degradation products thereof (lactones **44** and **48**, acid **46**) showed much weaker activity. The presence of the phenol, however, seems to be of importance in this series. Compound **44** only loses a factor of 10 as compared to **1**, while **48** loses dramatically more (additional 20-fold compared to **44**).

The presence of a substituted amide in **47** does not lead to improvement of activity compared to **48**. Neither does the substitution with a non-basic group (**49**). The addition of an additional primary amine in compound **50** does improve the activity against *E. coli* ribosomes tenfold, but **50** is still much less active than compound **20**, where the basicity is added through a guanidinium group. Similarly, replacement of that basic group by a tertiary amine in compound **51** leads to a drastic reduction of the activity when compared to **23**.

Surprisingly, shortening the carbon linker from three to two atoms led to compounds **52** and **53** which showed 100-fold lower activity against *E. coli*, but kept good affinity in the reticulocyte assay compared to the corresponding longer homologues **2** and **50**, respectively.

Finally, the basic amine present in the linker of **23** was replaced by an amide functionality (compounds **54** and **55**, absolute stereochemistry not determined) which however was detrimental for activity in both assays.

In addition, compounds were tested in a panel of Gram-positive and Gram-negative bacteria.[17] The panel consisted of wild-type reference strains of *Staphylococcus aureus, S. pneumoniae, Enterococcus faecalis, Moraxella catarrhalis, Haemophilus influenzae, E. coli*, and *P. aeruginosa*, as well as multi drug-resistant (MDR) clinical isolates of *Enterococcus faecium, A. baumannii*, and *K. pneumoniae*. Antibacterial activity was only observed against *S. aureus*, *S. pneumoniae*, *M. catarrhalis* and *H. influenzae* (minimal inhibitory concentrations (MIC) of 0.063–16 μg/mL, Table 2 and the Supporting Information) but were inactive on all other species (data not shown). Activity in the IVTT assay of *E. coli* correlated well with antibacterial activity on *M. catarrhalis*: $IC_{50} < 10$ μM translated to MIC < 8 μg/mL on this strain.

It has been hypothesised that microbial natural products with antibiotic activity have evolved their ability to reach their

Table 2. cellular activities of selected xenocoumacin analogues.[a]

Cpd	Microbiology panel (MIC [mg L^{-1}])				Permeability panel *E. coli* (MIC [mg L^{-1}])					Cytotoxicity (IC_{50} [μM])
	S aureus wt	*S pneum.* wt	*M catar.* A894	*H infl.* A921	MG1655 (wt)	2031 (ΔtolC)	2052 (ΔacrAB)	2081 (ΔrfaC)	2085 Δ(tolCrfaC)	CHO–K1 48 h
1	2	0.5	0.25	2	>16	0.5	1	16	1	1.2
2	1	1	≤0.063	2	16	0.5	0.5	8	0.25	0.3
19	4	16	0.25	8	>32	8	16	32	2	3.6
20	2	2	0.125	2	32	2	2	8	0.5	0.7
21	16	8	≤0.063	2	16	2	8	16	0.5	0.6
22	≥16	>32	0.25	8	>32	≥16	≥16	>32	8	2.4
23	>32	32	0.25	2	>16	4	8	>16	2	0.7
45	16	16	4	32	>32	16	>8	>16	4	26

[a] MIC (minimal inhibitory concentration), *S aureus* wt (ATCC29213), *S pneumoniae* wt (ATCC49619). MIC and IC_{50} are means of several independent experiments.[17]

intracellular targets.[23] Therefore, selected compounds (Table 2) were also tested on a set of genetically modified *E. coli* strains lacking either the main efflux pumps (Δ*tolC* or Δ*acrAB*) or with a modified lipopolysaccharide (LPS) layer (Δ*rfaC*). The results allowed to estimate the extent to which compounds are affected by efflux or have penetration issues.

The analysis revealed that **2** and its analogues are substrates for efflux pumps and, to a lesser extent, are prevented to penetrate through the outer membrane LPS layer. Intracellular concentrations are thus not high enough to exert reasonable antibacterial activity especially against Gram-negative bacteria.[17] A few compounds were also evaluated for cytotoxicity in eukaryotic cells (CHO cells) showing significant toxicity after 48 h. Generally, cytotoxicity tracked in parallel to protein synthesis inhibition measured with rabbit reticulocytes and thus confirmed on-target activity of these protein synthesis inhibitors.

Conclusion

We report here the first total synthesis of xenocoumacin 1 and several structurally diverse analogues which were tested for inhibition of prokaryotic and eukaryotic ribosomal protein synthesis. Although the binding site lies in a conserved region of the ribosome, surprising differences are observed between eukaryotic and prokaryotic systems. Some of the novel analogues were potent and selective inhibitors of eukaryotic protein synthesis with much reduced activity on bacterial systems. The reasons for this difference are not obvious from a structural point of view. Further investigations would be needed to formulate a hypothesis on the origin of these differences. Whole cell activity of xenocoumacin analogues was furthermore limited by efflux in many bacterial species. Due to all these findings we turned away from the coumacin natural products as starting point for novel antibiotics.

Experimental Section

Experimental Details (experimental methods, detailed description of the synthesis of all novel compounds as well as their characterization (PDF), and a summary table of biological data (IC_{50}, MIC, cytotoxicity) (PDF)) are available in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: antibiotics · natural products · protein synthesis inhibition · RNA recognition · structure-activity relationships

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FULL PAPERS

Different ribosome = different properties: Xenocoumacin 1 is an inhibitor of bacterial and eukaryotic ribosomal protein synthesis. For this first total synthesis, a convergent approach allowed the rapid assembly of structurally diverse analogues for SAR investigations. Despite the high homology between prokaryotic and eukaryotic ribosomes, the compounds showed surprising differences in potency and selectivity assessed in enzymatic and whole-cell assays.