Discovery of Novel Antibacterial Agents Active Against Methicillin-Resistant *Staphylococcus aureus* from Combinatorial Benzopyran Libraries

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KEYWORDS:

antibiotics · benzopyrans · combinatorial chemistry · stilbenes · structure – activity relationships

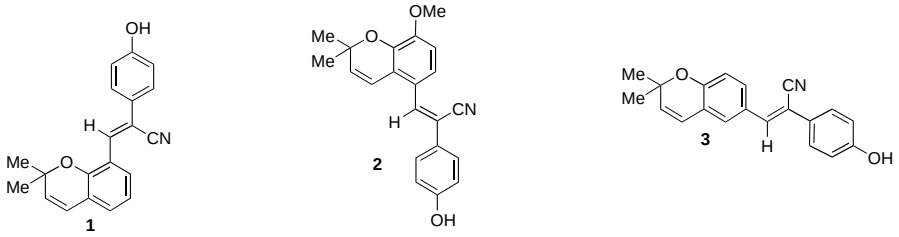
The increasingly rapid emergence of bacterial strains resistant to clinically approved antibiotics poses a significant challenge to the effective treatment of infectious diseases.[1] Particularly worrisome are the widespread occurrences of incidents with methicillin-resistant *Staphylococcus aureus* (MRSA), infections which require treatment with last-line antibiotics such as vancomycin.[2] This increasingly menacing problem has prompted renewed interest in the identification and development of new structural classes of antibacterial agents.[3]

In an effort to identify novel lead compounds for chemical biology studies and drug discovery purposes, we have been engaged in the design and solid-phase synthesis of large combinatorial libraries designed around "natural product derived" templates.[4–6] During high-throughput antibacterial screening of one of these libraries, a number of benzopyran-derived cyanostilbenes[7] **1** – **3** (Table 1) were identified as active (minimum inhibitory concentration (MIC) $< 50\ \mu g\,mL^{-1}$) against several MRSA strains.[8] Here we wish to detail the optimization of these lead compounds to a number of highly active antibiotics, some rivaling the in vitro potency of vancomycin.

The resynthesis of the aforementioned combinatorial leads and their subsequent screening in a panel of both methicillin-susceptible and methicillin-resistant Gram-positive strains (Table 1)[9] confirmed their activities and provided early structure – activity relationships (SAR). Most significantly, the orientation of the stilbene moiety on the benzopyran ring system was found to be important for biological activity as illustrated by the potency order **1** > **2** > **3** for these three compounds. Secondly, the presence of a free phenolic group on the terminal aromatic ring was determined to be essential for antibacterial activity since the original stilbene screening library[5] (> 1000 members) included a host of other compounds containing substituents in this position such as halogens, ethers, esters, sulfonates, nitro groups, and heterocycles, all of which proved to be inactive at the original screening concentration (MIC > 50 $\mu g\,mL^{-1}$). In light of these observations, we selected benzopyran **1** as the most promising lead compound and undertook a more systematic study of its structure – activity-relationships, the results of which are described below.

While the original combinatorial screening library was constructed in a split-and-pool fashion by using solid-phase syn-

Table 1. *Structures and antibacterial activities of lead compounds* ***1*** *–* ***3*** *identified from combinatorial libraries.*



	MIC [$\mu g\,mL^{-1}$]									
	SA[a] 6538	SA[b] 13709	SA[c] 29213	MRSA[d] 700698	MRSA[e] 33591	MRSA[f] 43300	MRSA[g] 700787	MRSA[h] 700788	MRSA[i] 700789	EF[j] 6057
1	4	4	3	4	3	12	6	3	6	4
2	12	12	12	12	25	12	12	12	12	12
3	12	25	25	25	25	25	12	25	12	> 50

[a] *Staphylococcus aureus*, subspecies *aureus* (ATCC 6538). [b] *S. aureus*, subspecies *aureus* (ATCC 13709). [c] *S. aureus*, subspecies *aureus* (ATCC 29213). [d] *S. aureus*, subspecies aureus (ATCC 700698), resistant to methicillin. This strain shows heterogeneous susceptibility to vancomycin. [e] *S. aureus*, subspecies *aureus* (ATCC 33591), resistant to methicillin. [f] *S. aureus*, subspecies *aureus* (ATCC 43300), resistant to methicillin. [g] *S. aureus*, subspecies aureus (ATCC 700787), resistant to methicillin and intermediate susceptibility to vancomycin. [h] *S. aureus*, subspecies *aureus* (ATCC 700787), resistant to methicillin and intermediate susceptibility to vancomycin. [i] *S. aureus*, subspecies *aureus* (ATCC 700787), resistant to methicillin and intermediate susceptibility to vancomycin. [j] *Enterococcus faecium* (ATCC 6057).

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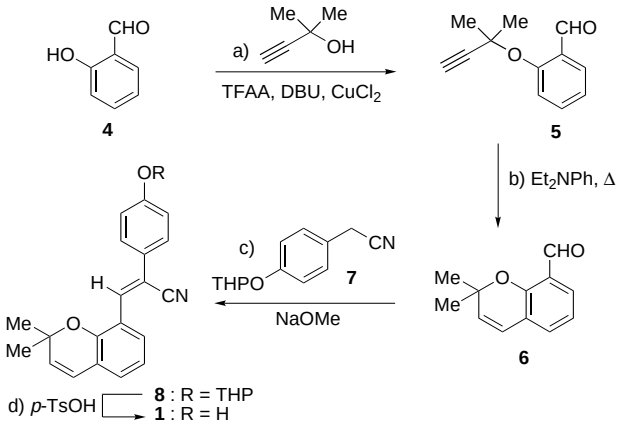
thesis,[5] resynthesis of the lead compounds and subsequent analogues was performed in solution and by parallel methods. Schemes 1 – 6 present representative syntheses of each type of compound. Thus, the initial lead compound, benzopyran **1**, was resynthesized as shown in Scheme 1 starting with salicylaldehyde (**4**). Alkylation under the Ding conditions[10] afforded

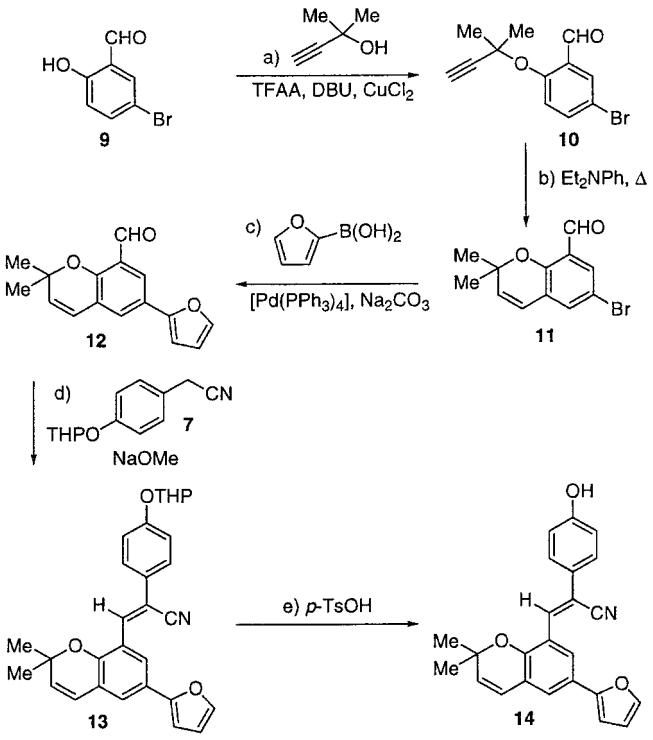


Scheme 1. *Synthesis of benzopyran-derived cyanostilbene **1**. a) 2-Methyl-3-butyn-2-ol (1.1 equiv), TFAA (1.1 equiv), DBU (2.3 equiv), $CuCl_2$ (0.01 equiv), CH_3CN, 0 °C, 12 h; b) Et_2NPh, 190 °C, 0.5 h, 42% (over two steps); c) 4-OTHP-phenylacetonitrile (**7**) (1.0 equiv), NaOMe (2.0 equiv), THF, 25 °C, 12 h, 90%; d) p-TsOH · H_2O (0.5 equiv), THF/MeOH (10:1, v/v), 25 °C, 1 h, 100%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene,* p-*TsOH · H_2O* = p-*toluenesulfonic acid monohydrate, TFAA = trifluoroacetic anhydride, THP = tetrahydropyanyl.*

propargyl ether **5** which was subjected to Claisen rearrangement by heating to 190 °C, resulting in the formation of benzopyran **6** in 42% overall yield. The aldehyde **6** was then condensed with THP-protected 4-hydroxybenzonitrile (**7**) in the presence of NaOMe to provide cyanostilbene **8** (90% yield).[11] Finally, the phenolic THP protecting group was removed quantitatively with *p*-TsOH · H_2O to afford benzopyran **1**. This reaction sequence was repeated with other substituted salicylaldehydes and phenyl acetonitriles to provide analogues **35** – **41** (Table 2) and **49** – **56** (Table 3).

Analogues containing aromatic and heteroaromatic substituents on the benzopyran ring system were prepared by a Suzuki coupling protocol[12] as outlined in Scheme 2 for representative compound **14**. Initially, 5-bromosalicylaldehyde (**9**) was alkylated by using the Ding conditions[10] to provide propargyl ether **10** which was closed to benzopyran **11** through Claisen rearrangement. Subsequently, the aryl bromide of **11** was coupled with 2-furanboronic acid in the presence of catalytic amounts of $[Pd(Ph_3P)_4]$ to afford furanyl benzopyran **12** in 80% yield. Aldehyde **12** was then condensed with THP-protected 4-hydroxybenzonitrile (**7**) in the presence of NaOMe to provide cyanostilbene **13** (65% yield) which was deprotected (*p*-TsOH · H_2O) to give benzopyran **14** in 97% yield. This palladium-catalyzed coupling sequence was repeated in parallel using other aryl and heterocyclic boronic acids to provide analogues **42** – **45** (Table 2).

As illustrated in Scheme 3, the representative carbohydrate conjugate **17** was prepared by glycosidation of phenol **1** with an L-rhamnose-derived trichloroacetimidate[13] to afford the pro-



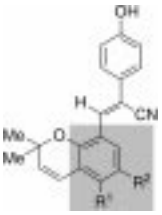
Scheme 2. *Synthesis of benzopyran-derived cyanostilbene **14**. a) 2-Methyl-3-butyn-2-ol (1.1 equiv), TFAA (1.1 equiv), DBU (2.3 equiv), $CuCl_2$ (0.01 equiv), CH_3CN, 0 °C, 12 h, 55%; b) Et_2NPh, 190 °C, 0.5 h, 74%; c) furanboronic acid (1.0 equiv), $[Pd(PPh_3)_4]$ (0.05 equiv), Na_2CO_3 (3.0 equiv), PhMe/H_2O/MeOH (10:3:1, v/v/v), 90 °C, 12 h, 80%; d) 4-OTHP-phenylacetonitrile (**7**) (1.0 equiv), NaOMe (2.0 equiv), THF, 25 °C, 12 h, 65%; e)* p-*TsOH · H_2O (0.5 equiv), THF/MeOH (10:1, v/v), 25 °C, 1 h, 97%.*

tected glycoside conjugate **16** (60% yield), which was then deprotected with NaOMe to provide compound **17** in 92% yield. The iteration of this sequence with other trichloroacetimidates provided analogues **57** – **62** (Table 3).

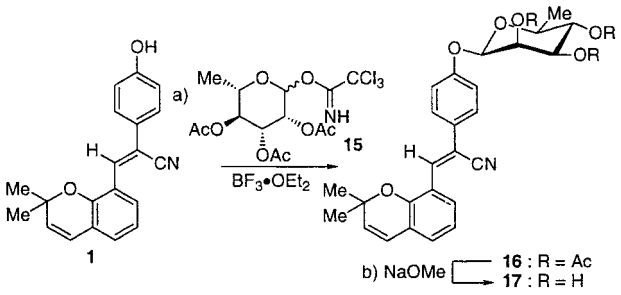
Compounds containing modifications of the pyran olefin moiety were prepared as shown in Schemes 4 and 5. Treatment of benzopyran **6** (Scheme 4) with NBS in aqueous DMSO[14] afforded bromohydrin **18** (90% yield), which was converted to epoxide **19** by exposure to NaH[15] (80% yield). The resulting epoxide was treated with ethanol in the presence of a catalytic amount of Amberlyst-15 to provide alcohol **20** in quantitative yield. This secondary alcohol was subsequently protected as a triethylsilyl ether by reaction with TESOTf and 2,6-lutidine to afford **21** in 95% yield. Condensation of aldehyde **21** with THP-protected 4-hydroxybenzonitrile (**7**) in the presence of NaOMe gave adduct **22** in 84% yield, which was globally deprotected by exposure to *p*-TsOH · H_2O to afford cyanostilbene **23** (92% yield). A similar reaction sequence was utilized to prepare diol **64** (Table 4).

Preparation of a saturated pyran analogue was achieved as shown in Scheme 5. After several unsuccessful attempts to selectively hydrogenate the olefin moiety of benzopyran **6** in the presence of the aromatic aldehyde, this aldehyde was reduced to the corresponding benzyl alcohol **24** in 90% yield by treatment with $NaBH_4$. Acetylation of the benzyl alcohol with acetic anhydride and iPr_2NEt gave ester **25** in 87% yield. The

Table 2. *Structure – activity relationships for the benzopyran aromatic ring system.*

	compd	R^1	R^2	MIC [μg mL^{-1}][a] SA 6538	SA 13709	SA 29213	MRSA 700698	MRSA 33591	MRSA 43300	MRSA 700787	MRSA 700788	MRSA 700789	EF 6057
	**1**	H	H	4	4	3	4	3	12	6	3	6	4
	35	OH	H	50	>50	>50	>50	>50	50	>50	>50	>50	>50
	36	Et_2N	H	12	4	8	>50	2	6	>50	>50	>50	1
	37	H	Me	3	6	4	3	4	4	4	4	4	3
	38	H	OMe	12	12	12	12	12	12	12	12	12	12
	39	H	Cl	12	12	3	25	50	16	3	3	3	25
	40	H	Br	1	1	3	1	3	3	3	3	3	2
	41	H	*t*Bu	1	1	3	1	2	3	6	4	6	1
	42	H	Ph	6	3	12	4	2	6	>50	>50	>50	4
	43	H	2-thienyl	3	6	6	8	4	12	>50	8	12	6
	44	H	3-thienyl	3	4	3	3	2	4	3	6	6	4
	14	H	2-furyl	3	2	2	2	2	2	2	2	2	2
	45	H	4-biphenyl	>50	>50	>50	>50	32	>50	>50	>50	>50	>50
	46 tetracycline			<0.5	<0.5	0.5	>50	>50	0.5	1	1	1	0.5
	47 vancomycin			1	1	1	3	2	1	3	3	4	1
	48 penicillin G			<0.5	<0.5	>50	50	>50	>50	50	>50	>50	0.5

[a] The bacterial strains tested were the same as those listed in Table 1.

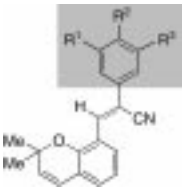


Scheme 3. *Synthesis of glycosidated cyanostilbene **17**. a) Trichloroacetimidate of* L*-rhamnose (**15**) (1.0 equiv), $BF_3 \cdot OEt_2$ (0.9 equiv), CH_2Cl_2, $-40 \rightarrow 0\,^{\circ}C$, 12 h, 60%; b) NaOMe (10.0 equiv), THF/MeOH (10:1, v/v), 25 °C, 12 h, 92%.*

benzopyran olefin was then successfully reduced with H_2 in the presence of 10% palladium on carbon to afford saturated benzopyran **26**, whose deprotection proceeded smoothly upon exposure to NaOMe to give **27** in 90% overall yield (two steps). The primary alcohol function of the latter compound (**27**) was then oxidized with Dess – Martin periodinane to give aldehyde **28** in 82% yield. Treatment of this aldehyde with THP-protected 4-hydroxybenzonitrile (**7**) and NaOMe once again provided the condensation product **29** in 77% yield, which was then deprotected with *p*-$TsOH \cdot H_2O$ to afford saturated cyanostilbene **30** in quantitative yield.

Finally, the synthesis of the unsubstituted stilbene analogue **34** began with the olefination of aldehyde **6** by exposure to the phosphorous ylide formed from methyltriphenylphosphonium

Table 3. *Structure – activity relationships for the terminal aromatic ring system.*

	compd	R^1	R^2	R^3	MIC [μg mL^{-1}][a] SA 6538	SA 13709	SA 29213	MRSA 700698	MRSA 33591	MRSA 43300	MRSA 700787	MRSA 700788	MRSA 700789	EF 6057
	**1**	H	OH	H	4	4	3	4	3	12	6	3	6	4
	49	H	OH	OMe	>50	>50	8	>50	8	>50	>50	>50	>50	>50
	50	H	H	H	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
	51	H	Br	H	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
	52	H	OMe	H	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
	53	OMe	H	H	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
	54	OMe	OMe	OMe	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
	55	H	-O-CH_2-O-		>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
	56	H	OMe	OMe	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
	57	H	O-(D)-glucose	H	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
	58	H	O-(L)-glucose	H	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
	59	H	O-(D)-arabinose	H	>50	>50	>50	>50	>50	>50	>50	>50	>50	50
	60	H	O-(L)-arabinose	H	50	50	50	>50	50	>50	>50	>50	>50	>50
	17	H	O-(L)-rhamnose	H	12	25	25	25	25	25	25	25	25	25
	61	H	O-(D)-xylose	H	50	25	25	50	50	50	50	50	50	50
	62	H	O-(D)-galactose	H	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50

[a] The bacterial strains tested were the same as those listed in Table 1.

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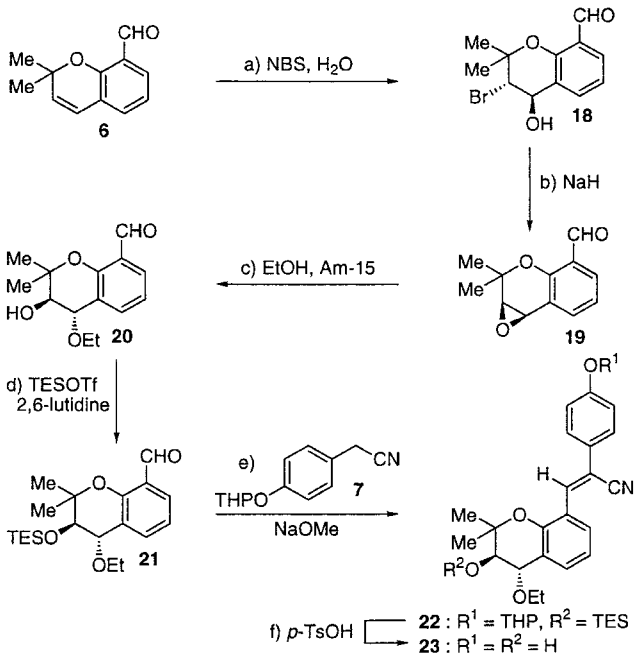
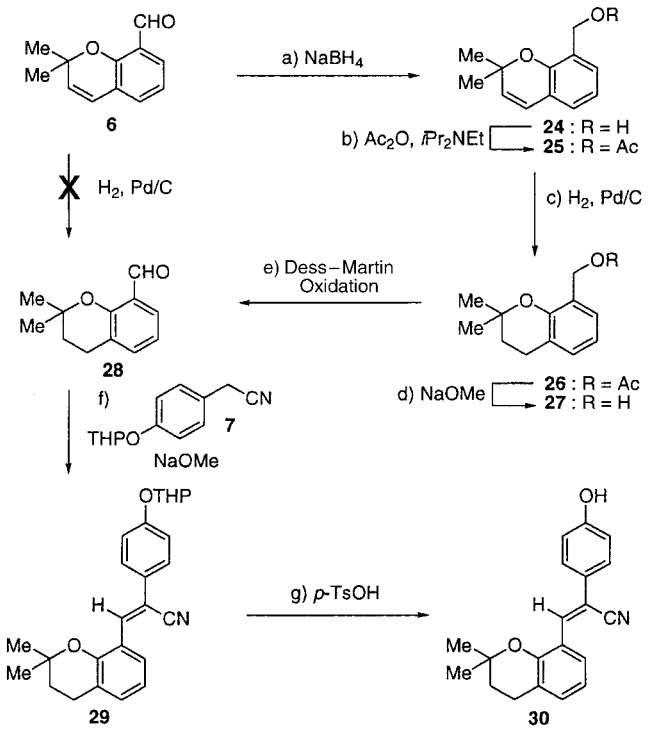


*Scheme 4. Synthesis of pyran-modified cyanostilbene **23** (relative configuration as indicated). a) NBS (1.1 equiv), DMSO/H_2O (10:1, v/v), 0 °C, 1 h, 90%; b) NaH (1.3 equiv) 25 °C, 2 h, 80%; c) Amberlyst-15 (Am-15, 0.1 equiv), EtOH, 25 °C, 0.5 h, 100%; d) TESOTf (2.0 equiv), 2,6-lutidine (2.5 equiv), CH_2Cl_2, 25 °C, 1 h, 95%; e) 4-OTHP-phenylacetonitrile (1.0 equiv), NaOMe (2.0 equiv), THF, 25 °C, 12 h, 84%; f) p-TsOH·H_2O (1.0 equiv), THF/MeOH (10:1, v/v), 25 °C, 1 h, 92%. NBS = N-bromosuccinimide, TESOTf = triethylsilyltrifluoromethanesulfonate.*

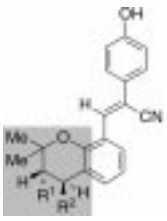


*Scheme 5. Synthesis of saturated benzopyran cyanostilbene **30**. a) $NaBH_4$ (1.2 equiv), MeOH, 0 °C, 1 h, 90%; b) Ac_2O (1.3 equiv), iPr_2NEt (1.4 equiv), 25 °C, 1 h, 87%; c) H_2 (1.0 atm), 10% Pd/C (10 wt%), EtOAc/hexane (1:1, v/v), 25 °C, 0.5 h, 100%; d) NaOMe (3.0 equiv), THF, 25 °C, 1 h, 90%; e) Dess–Martin periodinane (1.1 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, 25 °C, 82%; f) 4-OTHP-phenylacetonitrile (**7**) (1.0 equiv), NaOMe (2.0 equiv), THF, 25 °C, 12 h, 77%; g) p-TsOH·H_2O (0.5 equiv), THF/MeOH (10:1, v/v), 25 °C, 1 h, 100%.*

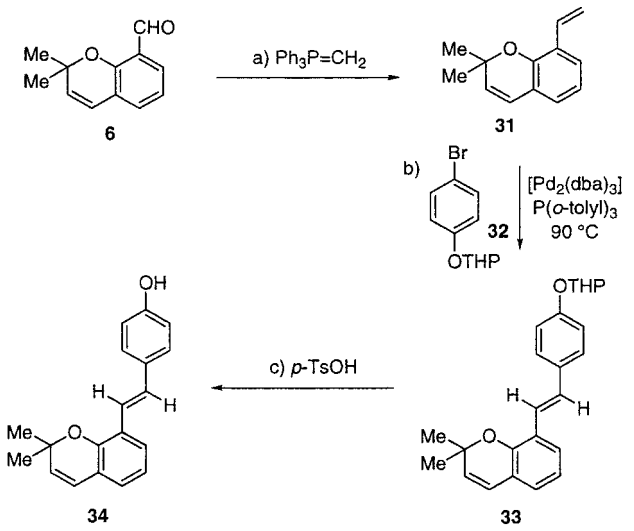
bromide to afford styrene **31** in 80% yield (Scheme 6). Styrene **31** was then engaged in a Heck reaction with 4-OTHP-bromophenol (**32**) in the presence of catalytic amounts of tri-*o*-tolylphosphane and tris(dibenzylideneacetone)dipalladium(0) to afford disubstituted styrene **33** in 12% yield. Styrene **33** was then deprotected with *p*-TsOH·H_2O in quantitative yield to afford benzopyran stilbene **34**.

The synthesized compound libraries were evaluated in a panel containing both methicillin-susceptible and methicillin-resistant strains of *Staphylococcus aureus* as illustrated in Tables 2–5. The first structural region of interest was the aryl ring of the benzopyran system. As shown in Table 2, a series of analogues (R^1, R^2 = OH, Et_2N, Me, OMe, Cl, Br, *t*Bu, aromatic, heterocyclic) were prepared and evaluated. Substituents which made the benzopyran system more polar resulted in compounds with decreased activity such as **35** and **36**. Interestingly, the introduction of more lipophilic groups (R^2 = Me, *t*Bu, Br; **37**, **40**, and **41**, respectively) resulted in slightly more potent compounds than the parent compound **1**. Among these, the bulkier substituents (e.g., R^2 = Br; **40** and R^2 = *t*Bu; **41**) proved to be better than the smaller substituent (R^2 = Me; **37**), leading to the following potency order: **37**, **38** > **34** > **1**. Attempts to further capitalize on this trend led to the synthesis of a series of aryl-substituted compounds (**42**—**45**). While the phenyl-substituted

***Table 4.** Structure–activity relationships for the pyran ring system.*

	compd	R^1	R^2	MIC [μg mL^{-1}][a] SA 6538	SA 13709	SA 29213	MRSA 700698	MRSA 33591	MRSA 43300	MRSA 700787	MRSA 700788	MRSA 700789	EF 6057
	**1**	–	–	4	4	3	4	3	12	6	3	6	4
	63	H	H	25	25	6	25	32	25	12	12	12	12
	64[b]	OH	OH	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50
	23[b]	OH	OEt	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50

[a] The bacterial strains tested were the same as those listed in Table 1. [b] Compounds **23** and **64** were screened as racemates.



Scheme 6. *Synthesis of benzopyran stilbene* ***34****. a) Methyltriphenylphosphonium bromide (1.1 equiv),* n*-butyllithium (1.1 equiv), THF, 0→25 °C, 12 h, 80%; b) 4-OTHP-bromobenzene (****32****) (1.1 equiv), [Pd$_2$(dba)$_3$] (0.1 equiv), P(o-tolyl)$_3$ (0.12 equiv), DMF, 90 °C, 12%; c)* p*-TsOH·H$_2$O (0.5 equiv), THF/MeOH (10:1, v/v), 25 °C, 1 h, 100%. [Pd$_2$(dba)$_3$] = tris(dibenzylideneacetone)dipalladium(0), P(o-tolyl)$_3$ = tri-*o*-tolylphosphane.*

compound **42** proved less active, the two thiophene-containing compounds, **43** and **44**, were found to be equipotent with the original lead compound **1**. Installation of a 2-furan moiety at the R^2 position (compound **14**) resulted in a compound nearly twice as active as the original lead **1**. Further increasing the steric bulk at this position through installation of a biphenyl substituent at R^2 (compound **45**) resulted in a complete loss of antibacterial activity. In summary, modifications of the benzopyran aryl ring system resulted in three compounds (**14**, **40**, and **41**) which were more potent than the original lead compound **1** and proved to be nearly equipotent with vancomycin against these strains. More importantly, and unlike both tetracycline and penicillin G, analogues **14**, **40**, and **41** retained their in vitro activity against all of the MRSA strains.

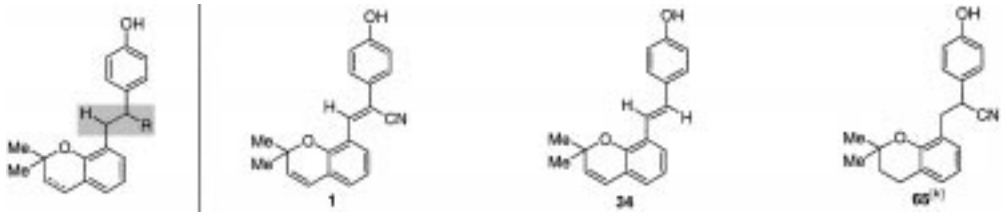
The second region of interest was the terminal aromatic ring of the stilbene system (Table 3). As eluded to above, initial screening data from the discovery library suggested the importance of the free phenolic group at this position. The importance of this hydroxy group was confirmed by the synthesis of the unsubstituted analogue **50**, the halogenated analogue **51**, and several ether analogues (**52** – **56**), all of which proved inactive. A second finding of interest was revealed when various carbohydrate moieties were appended onto phenol **1**, as illustrated by compounds **57** – **62**.[16] While all these compounds were less potent than the original lead compound **1**, the L-rhamnose- and D-xylose-containing analogues (**17** and **61**, respectively) did retain some antibacterial activity.

A third region for SAR studies was the pyran ring system as illustrated by the three analogues in Table 4. Reduction of the pyran olefin moiety of **1** to give the saturated counterpart **63** resulted in a two- to fourfold decrease in antibacterial activity. Introduction of more polar substituents at this position such as a *trans*-diol (compound **64**) or an α-hydroxyethyl ether group (compound **23**) resulted in complete loss of antibacterial activity, suggesting the importance of lipophilic groups at this position.

The final area of interest with regard to SAR was to discern the functional and/or structural role of the cyanostilbene unit of the scaffold (Table 5). Its importance was evaluated through the chemical synthesis and biological screening of compounds **34** and **65**. Benzopyran **34** is identical to the original lead compound **1** except it lacks a nitrile group on the stilbene olefin part. Interestingly, the antibacterial activities of **1** and **34** were indistinguishable, proving that the α,β-unsaturated nitrile moiety has no functional role in the activity of these compounds. This suggests that these compounds do not act through an electrophilic mechanism. More likely, the cyanostilbene unit serves a structural role, as supported by the fact that reduction of this olefin (**1**→**65**) results in a significant loss of antibacterial potency. With this evidence in hand, it seems appropriate that future compounds in this series be constructed to resemble the unsubstituted stilbene bridge (i.e. compound **34**) rather than a cyanostilbene bridge (i.e. compound **1**) in order to minimize any potential toxicity that might result from possible indiscriminate electrophilicity of the α,β-unsaturated nitrile functionality.

In summary, we have described the identification of a structurally novel benzopyran-based series of antibacterial

Table 5. *Structure – activity relationships for the cyanostilbene unit.*



	MIC [μg mL^{-1}][a]									
compd	SA 6538	SA 13709	SA 29213	MRSA 700698	MRSA 33591	MRSA 43300	MRSA 700787	MRSA 700788	MRSA 700789	EF 6057
1	4	4	3	4	3	12	6	3	6	4
34	4	4	4	4	6	4	8	4	8	8
65[b]	25	25	16	25	25	25	25	25	25	16

[a] The bacterial strains tested were the same as those listed in Table 1. [b] Compound **65** was screened as a racemate.

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agents that demonstrate significant activity against MRSA bacterial strains. Through analogue generation, we have determined the gross structural feature of this series necessary for activity and used that information to construct several compounds with in vitro potencies comparable to that of vancomycin against MRSA strains. Efforts to further improve the potency and pharmacological profiles of these compounds may lead to drug candidates for the treatment of infectious diseases.

Experimental Section

Characteristic analytical data of a selected compound:

Cyanostilbene 41: IR (film): $\tilde{\nu}_{max}$=3379, 2963, 2343, 1763, 1609, 1453, 1373, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.08$ (s, 1H), 7.80 (s, 1H), 7.55 (d, $J = 8.8$ Hz, 2H), 7.06 (s, 1H), 6.91 (d, $J = 8.8$ Hz, 2H), 6.33 (d, $J = 9.7$ Hz, 1H), 5.71 (s, 1H), 5.64 (d, $J = 9.7$ Hz, 1H), 1.45 (s, 6H), 1.34 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.5$, 149.4, 143.2, 135.6, 130.7, 127.7, 127.6, 127.5, 125.7, 124.6, 122.4, 121.5, 120.7, 118.7, 115.8, 110.2, 34.5, 31.3, 28.2; HR-MS (MALDI-FT-MS): *m/z*: calcd for $C_{24}H_{25}NO_2$ [$M+H^+$]: 360.1958, found: 360.1951.

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Cyberpills

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Despite several decades of developing improved therapies and prevention mechanisms, infectious pathogens remain a major cause of morbidity and mortality for humans worldwide.[1] A potential solution to this predicament is arising through the development of regimented treatment programs such as multi-drug therapies.[2] While effective in clinical studies, execution of these programs can be problematic for the patient.[3] Often this problem can only be solved by in-patient treatment or by associated training programs. Clearly, these treatments—and pharmaceutical therapy in general—would benefit from an information network that allows the patient and his physician to monitor the progress of a pharmaceutical therapy.[4]

Medical communication networks, online medicine, and electronic patient databanks[5] are now available through developments in the fields of e-medicine, telemedicine, and telepharmacy. These resources aid physicians by expediting their diagnostic workload (for example, a growing number of radiographic examinations can be accessed through online networks).[6] When approved by the patient, information from these systems can also be compiled into databanks, therein providing a powerful resource and research tool. Collection of this information is critical in learning how to control the evolution of drug resistance.

Currently, the administration of pharmaceuticals is rarely monitored, and when conducted, its process requires extensive clinical visits and laboratory analyses. The information transacted by these examinations, like radiographic methods,[6] could be adapted to remote networks through the development of noninvasive sensing systems. Methods exist that monitor

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