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Synthesis and antibacterial evaluation of novel mono- and bis(2*H*-chromen-2-imine) hybrids linked to heteroarene units

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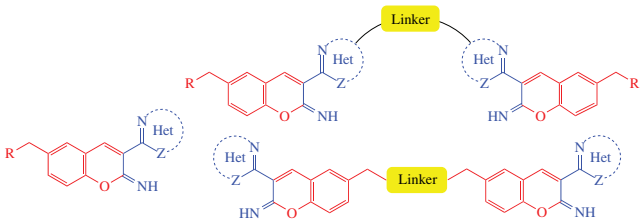
Novel mono- and bis(2*H*-chromen-2-imine) hybrids linked to different heteroarene units were prepared by cyclocondensation of 2-hydroxybenzaldehydes with 2-heteroarylacetonitriles. Their *in vitro* antibacterial activities against different strains of Gram-positive and negative bacteria were assessed. Piperazine-linked bis(3-heteroaryl-2*H*-chromen-2-imines) exhibited the best antibacterial efficacies against *E. coli*, *S. aureus* and *S. mutans* strains with MIC values of 1.4–20.8 μM.



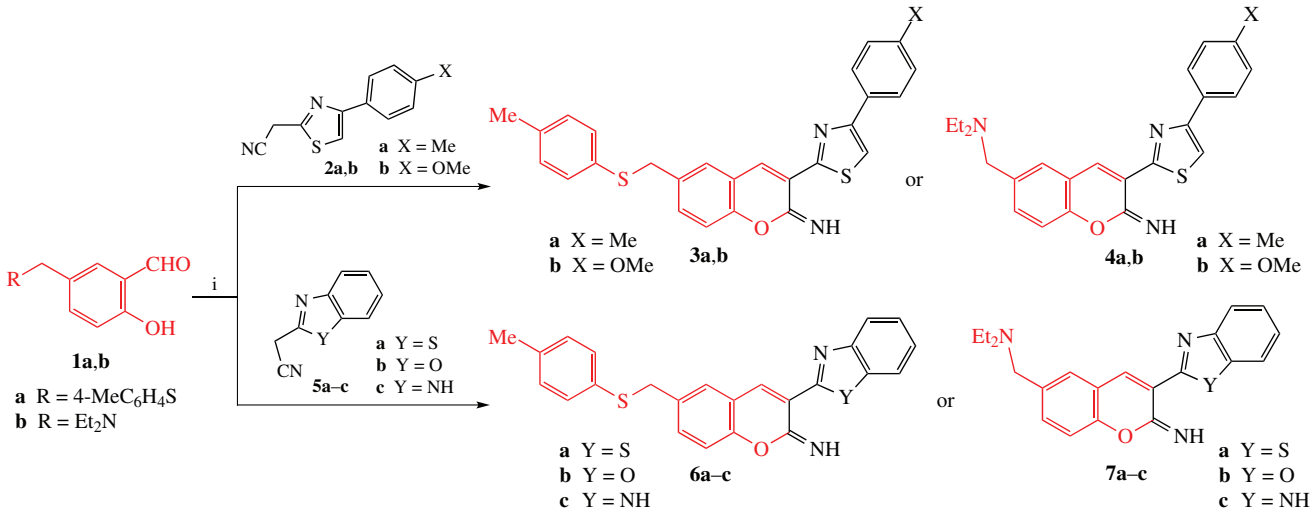
Keywords: 2*H*-chromen-2-imines, benzo[*f*]chromen-3-imines, nitriles, salicylic aldehydes, hybrid molecules, heterocyclization, Knoevenagel reaction, antibacterial activity.

Chromenes represent a notable class of both natural and synthetic heterocycles that demonstrate outstanding contributions in the inhibition and cure of different diseases.[1] Chromene derivatives display a wide range of bioactivities including antioxidant, antimicrobial, anti-inflammatory, analgesic and antitumor ones.[2–5] In addition, derivatives bearing chromene moieties can act as anticoagulants, anti-Alzheimer's, and anti-Parkinson's agents.[6–9]

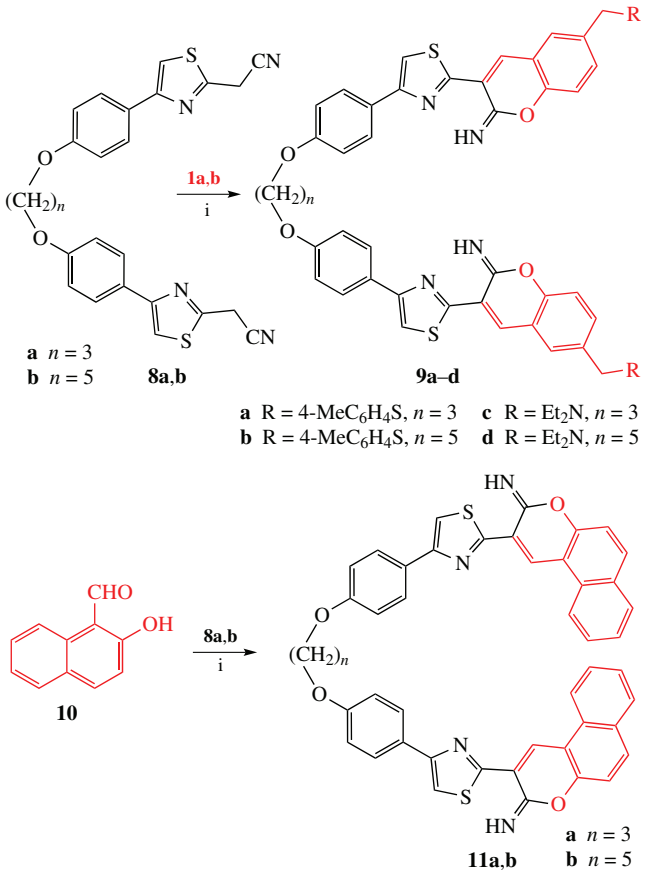
Several publications reported the fascinating biological activities of chromene derivatives linked to (benzo)thiazole moieties including antimicrobial, anticancer, potential adenosine receptor ligands, and aldose reductase inhibitors.[10–13] Chromene hybrids linked to benzoxazole and benzimidazole moieties possess a wide spectrum of significant biological activities including antitumor, anti-hepatitis C virus, antibacterial, anti-inflammatory and anthelmintic ones.[14–17] Numerous publications reported the preparation of chromenes with diverse related heterocyclic moieties.[18–21]

For the synthesis of new chromene derivatives, a generally recognized heterocyclization between 2-hydroxybenzaldehydes and 2-heteroarylacetonitriles leading to chromen-2-imines was employed.[22–29] By applying this method to new combinations of reactants, we obtained in this study some new chromene hybrids incorporating heterocycle diversity such as thiazole, benzothiazole, benzimidazole, and benzoxazole.

The reactivities of 2-hydroxybenzaldehydes **1a**,**b**[30–32] were investigated through their treatment with different 2-heteroarylacetonitrile derivatives (Scheme 1). Treatment of compounds **1a** or **1b** with acetonitriles **2a**,**b** in refluxing dioxane in the presence of catalytic amount of diethylamine (DEA) afforded 2*H*-chromen-2-imines **3a**,**b** or **4a**,**b**, respectively.[20] Similarly, benzo-fused heteroarylacetonitrile derivatives **5a–c**



Scheme 1 *Reagents and conditions*: i, Et_2NH, dioxane, reflux, 3 h.

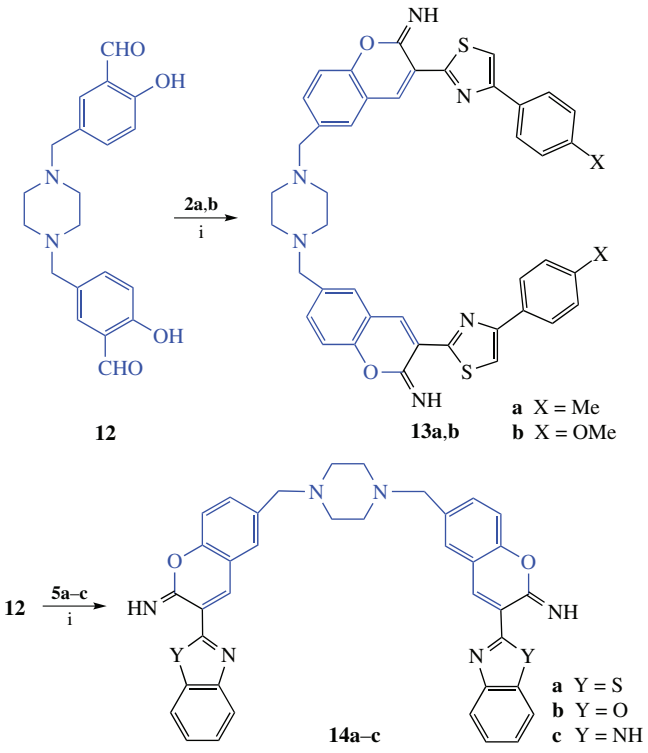


Scheme 2 *Reagents and conditions*: i, Et_2NH, dioxane, reflux, 5 h.

were transformed into chromenimine hybrids **6a–c** and **7a–c** (see Scheme 1).

Next, hydroxy aldehydes **1a**,**b** were employed as synthons for the construction of a second series of novel hybrids from alkylene-linked bis-nitriles **8a**,**b**[33,34] (Scheme 2). As a result, the corresponding bis-hybrids **9a–d** were obtained. In the same manner, compounds **8a**,**b** were condensed with 2-hydroxy-naphthaldehyde **10** to afford hybrids **11a**,**b**.

Using a similar approach, a third series of piperazine-linked bis(chromen-2-imines) were prepared based on bis(2-hydroxy-benzaldehyde) **12**[35,36] (Scheme 3). Structures of all new hybrids were established from spectral data and elemental analyses (for details, see Online Supplementary Materials).



Scheme 3 *Reagents and conditions*: i, Et_3N, dioxane, reflux, 5 h.

The *in vitro* antibacterial activities of the new hybrids were assessed against three different strains of Gram-positive bacteria [*Staphylococcus aureus* (ATCC:6538), *Streptococcus mutans,* (ATCC:25175), and *Enterococcus faecalis* (ATCC:29212)], in addition to three different strains of Gram-negative bacteria [*Escherichia coli* (ATCC:9637), *Pseudomonas aeruginosa* (ATCC:27953), and *Klebsiella pneumonia* (ATCC:10031)]. The microbroth serial dilution method[35,37] was used to assess the values of MIC for new hybrids using Ciprofloxacin as a standard drug with MIC of 2.7 μM against all the tested strains. The values of MIC of new hybrids are given in Table 1.

Regarding the *E. coli*, *S. aureus* and *S. mutans* bacterial strains, bis(3-heteroaryl-2*H*-chromen-2-imines), which are linked to piperazine core **13** and **14,** exhibited the best antibacterial efficacies. Therefore, hybrid **14c** demonstrated more effective activities than the standard Ciprofloxacin with MIC of 1.4 μM against all the tested strains. Hybrids **13a**,**b** and **14a**,**b** showed MIC values in the range of 2.9 to 20.8 μM. Furthermore, chromenimine hybrids **3b**, **4a**, **4b**, **6b**, **6c**, **7b** and **7c** exhibited decreased efficacies against these strains with MIC values in the range of 39.2 to 179.9 μM. In addition, bis-chromenimine hybrids **9** and **11** showed least antibacterial efficacies with MIC values more than 250 μM. Regarding the *E. faecalis*, *P. aeruginosa* and *K. pneumonia* bacterial strains, all the tested hybrids revealed reduced antibacterial efficacies in general. Therefore, hybrids **13** and **14** showed MIC values in the range of 98.7 to more than 250 μM. All other hybrids showed decreased antibacterial efficacies with MIC values more than 250 μM.

Table 1 MIC values of new hybrid compounds **3**, **4**, **6**, **7**, **9**, **11**, **13** and **14**.

Compound	Minimum inhibitory concentration/μM					
	S. aureus	*S. mutans*	*E. faecalis*	*E. coli*	*P. aeruginosa*	*K. pneumonia*
3a	>250	>250	>250	>250	>250	>250
3b	132.6	132.6	>250	132.6	>250	>250
4a	154.8	154.8	>250	154.8	>250	>250
4b	73.3	73.3	>250	73.3	>250	>250
6a	>250	>250	>250	>250	>250	>250
6b	78.3	78.3	>250	78.3	>250	>250
6c	39.2	39.2	>250	39.2	>250	>250
7a	>250	>250	>250	>250	>250	>250
7b	179.9	179.9	>250	179.9	>250	>250
7c	90.0	90.0	>250	90.0	>250	>250
9a	>250	>250	>250	>250	>250	>250
9b	>250	>250	>250	>250	>250	>250
9c	>250	>250	>250	>250	>250	>250
9d	>250	>250	>250	>250	>250	>250
11a	>250	>250	>250	>250	>250	>250
11b	>250	>250	>250	>250	>250	>250
13a	20.8	20.8	167.9	20.8	>250	>250
13b	10.0	10.0	160.4	20.0	>250	>250
14a	5.8	5.8	>250	5.8	>250	>250
14b	2.9	5.9	196.8	2.9	196.8	>250
14c	1.4	1.4	98.7	1.4	98.7	197.5
Ciprofloxacin	2.7	2.7	2.7	2.7	2.7	2.7

To sum up, efficient procedure for the preparation of mono- and bis(2*H*-chromen-2-imine) hybrids linked to different heteroarene units was developed based on cyclocondensation of 2-hydroxybenzaldehydes with 2-heteroarylacetonitriles. In general, the tested hybrids demonstrated enhanced antibacterial efficacies against *E. coli*, *S. aureus* and *S. mutans* strains compared to *E. faecalis*, *P. aeruginosa* and *K. pneumonia* strains. Hybrids possessing piperazine linker exhibited the best antibacterial efficacies against all tested strains.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.11.024.

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