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New potential antibacterials: A synthetic route to *N*-aryloxazolidinone/3-aryltetrahydroisoquinoline hybrids

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Abstract—A synthetic route to a new structural type of potential antibacterials, with a hybrid 3-aryltetrahydroisoquinoline-6,7-diol/*N*-aryloxazolidinone structure, is reported. The synthesis involves the successive construction of the 3-aryltetrahydroisoquinoline and 4-substituted oxazolidinone moieties, the latter taking advantage of the functionalization at the *para* position of the aryl group.

N-Aryloxazolidinones are a novel and promising class of synthetic antibiotics that have recently emerged as important therapeutic agents, active against numerous multidrug-resistant Gram-positive organisms.[1] DuP 721 was the first drug candidate of this family,[2] whereas linezolid was the first member of this series introduced in the market[3] (Fig. 1). *N*-Aryloxazolidinones are currently the focus of intensive research, and continuous synthetic efforts[4] are necessary to develop more effective antibacterial agents, in particular after the appearance of linezolid-resistant strains.[5]

A recent report[6] on the antibacterial activity of a series of 3-aryl-1,2,3,4-tetrahydroisoquinoline-6,7-diol derivatives against both Gram-positive and Gram-negative organisms prompted us to design a novel type of linezolid analogs, which embody both the characteristic *N*-aryloxazolidinone core of this antibiotic and a 3-aryltetrahydroisoquinoline-6,7-diol fragment.

The synthetic route to the target hybrid **1**, which fulfills the Lipinski rule of five parameters,[7] is depicted in Scheme 1. It involves the successive construction of the 3-aryltetrahydroisoquinoline and 4-substituted oxazolidinone moieties, the latter taking advantage of the

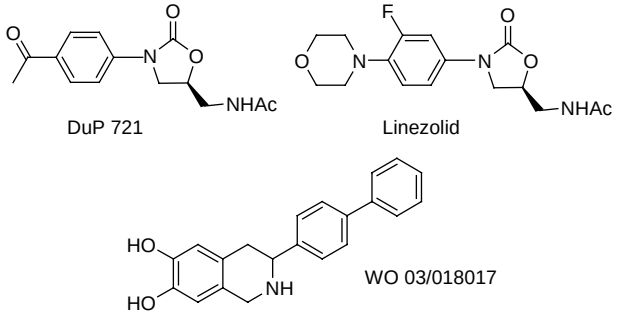

Figure 1.

functionalization at the *para* position of the aryl group. For the sake of simplicity, in the exploratory studies reported in this letter we used racemic 3-aryltetrahydroisoquinolines, although practical general methods for the asymmetric synthesis of these compounds are now available.[8]

Alkylation of methyl *p*-nitrophenylacetate[9] (**2a**) with 3,4-dimethoxybenzyl bromide[10] in the presence of LDA, followed by alkaline hydrolysis of the resulting ester **3a**, led to acid **4a**, which was then converted to carbamate **5a** by a modified Curtius rearrangement using diphenyl phosphorazidate in the presence of triethylamine and an excess of benzyl alcohol.[11]

The closure of the tetrahydroisoquinoline ring was satisfactorily accomplished by Pictet–Splenger reaction with

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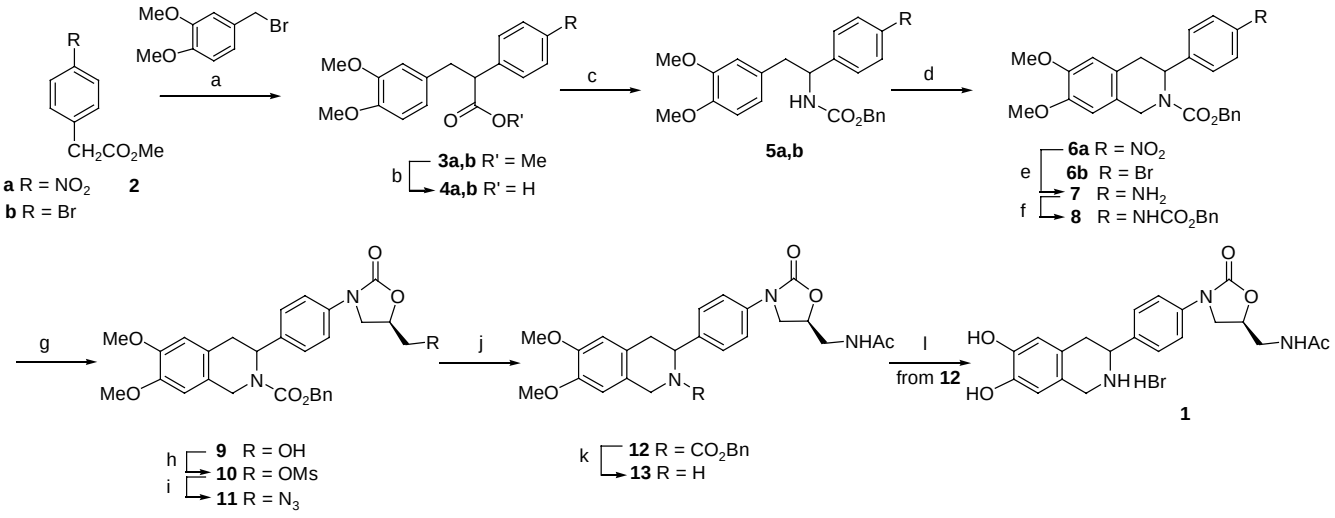
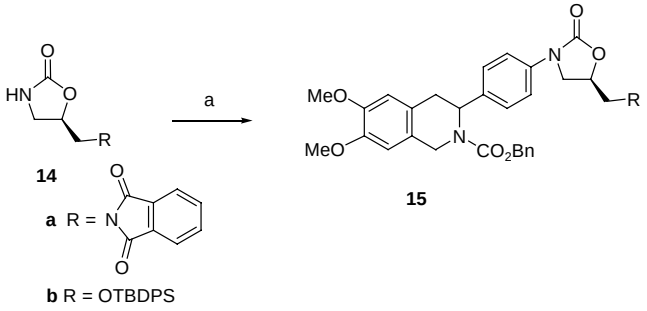


Scheme 1. Reagents and conditions: (a) LDA, THF, −78 °C to rt, 60% (**3a**), 89% (**3b**); (b) 2 M NaOH, MeOH, reflux, 85% (**4a**), 89% (**4b**); (c) DPPA, Et_3N, BnOH, THF, reflux, 60% (**5a**), 84% (**5b**); (d) HCOOH, HCHO, 70 °C, 68% (**6a**), 56% (**6b**); (e) Fe, EtOH, HCl, 0 °C to rt, 92%; (f) $ClCO_2Bn$, Na_2CO_3, acetone, 0 °C to rt, 67%; (g) (*R*)-glycidyl butyrate, *n*-BuLi, THF, −78 °C to rt, 55%; (h) MsCl, Et_3N, CH_2Cl_2, 0 °C, 90%; (i) NaN_3, DMF, 80 °C, 67%; (j) CH_3COSH, rt, 50%; (k) H_2, $Pd(OH)_2$, MeOH, rt, 70%; (l) BBr_3, CH_2Cl_2, −10 °C, 90%.

formaldehyde and formic acid. Reduction of the nitro group present in **6a** with Fe and HCl gave aniline **7**, which was then converted to carbamate **8** by treatment with benzyl chloroformate.

For the construction of the 5-substituted oxazolidinone ring we took advantage of the carbamate function present in **8** and used the previously reported regiospecific lithium-ion dependent alkylation-cyclization of aryl *N*-lithiocarbamates with (*R*)-glycidyl butyrate.[3,12,13] Thus, the aryl carbamate **8** was treated with *n*-BuLi, and the resulting lithiated intermediate was allowed to react with (*R*)-glycidyl butyrate to furnish, after in situ hydrolysis of the ester function, 5(*R*)-(hydroxymethyl)oxazolidinone **9**[14] in 55% overall yield as a mixture of two indistinguishable diastereoisomers.

An alternative route for assembling the oxazolidinone moiety, involving the Pd(0)-catalyzed cross coupling of 3-(*p*-bromophenyl)tetrahydroisoquinoline **6b** with oxazolidinones **14**,[15] was abandoned because the coupled products **15** were formed in poor (<10%, from **14a**) or negligible yields (from **14b**)[16] (Scheme 2). The required aryl bromide **6b** was prepared in satisfactory overall yield as in the above nitro series by alkylation of methyl *p*-bromophenylacetate[9] (**2b**) with 3,4-dimethoxybenzyl bromide, followed by alkaline hydrolysis, Curtius rearrangement of the resulting acid **4b**, and finally Pictet–Splenger cyclization from carbamate **5b**.



Scheme 2. Reagents and conditions: (a) **6b**, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, toluene, 100 °C.

The synthesis of the target oxazolidinone **1** from **9** only required functional group interconversions. Mesylation of the hydroxy group of **9**, followed by treatment of the resulting mesylate **10** with sodium azide, and then reductive acetylation of azide **11** using thiolacetic acid[17] provided acetamide **12** in good overall yield. Finally, removal of the carbamate function present in **12** by catalytic debenzylation gave tetrahydroisoquinoline **13**, whereas treatment of **12** with boron tribromide[18] brought about the cleavage of both the carbamate and methoxy groups leading to the target hybrid **1** as the hydrobromide.[19,20]

Acknowledgments

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14. Spectroscopic data for **9**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.00 (m, 1 H), 3.28 (m, 1 H), 3.68 (m, 1 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 3.88 (m, 3H), 4.16 (m, 1 H), 4.66 (m, 1 H), 4.81 (m, 1 H), 5.17 (s, 2 H), 6.62 (bs, 2 H), 7.13 (m, 2 H), 7.34 (m, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 32.8 (CH_2), 43.2 (CH_2), 46.3 (CH_2), 52.8 (CH), 55.9 (CH_3), 62.7 (CH_2), 67.4 (CH_2), 72.9 (CH), 108.9 (CH), 111.2 (CH), 118.0 (CH), 124.6 (C), 125.3 (C), 127.3 (CH), 127.8 (CH), 127.9 (CH), 128.4 (CH), 135.2 (C), 136.4 (C), 136.8 (C), 147.6 (C), 147.8 (C), 154.8 (C), 156.0 (C).
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19. Spectroscopic data for **1** (hydrobromide): ^{1}H NMR (200 MHz, CD_3OD): δ 1.99 (s, 3 H), 3.04 (m, 1 H),3.30 (m, 2 H), 3.61 (d, J = 5 Hz, 1 H), 3.90 (m, 1 H), 4.20 (m, 1 H), 4.36 (m, 1 H), 4.64 (m, 1 H), 4.84 (m, 1 H), 5.12 (m, 1 H), 6.60 (s, 2 H), 7.60 (d, J = 9 Hz, 2 H), 7.72 (d, J = 9 Hz, 2 H); ^{13}C NMR (50.3 MHz, CD_3OD): δ 20.3 (CH_3), 31.6 (CH_2), 41.2 (CH_2), 44.7 (CH_2), 45.8 (CH_2), 56.7 (CH), 71.3 (CH), 111.7 (CH), 114.0 (CH), 116.8 (C), 118.0 (CH), 121.6 (C), 127.2 (CH), 131.2 (C), 138.6 (C), 144.0 (C), 144.8 (C), 154.4 (C), 171.0 (C).
20. Biological data for **1** (hydrobromide): the in vitro antibacterial activity was tested against four different strains of methicillin-susceptible *Staphylococcus aureus*, including *S. aureus* ATCC 29213, giving in all cases MIC values higher than 64 μg/mL. Linezolid (MIC = 2 μg/mL) was used as the reference compound.