Supporting Information

A one pot three-step process for the synthesis of an array of arylated benzimidazoribosyl nucleosides.

Jolanta Hałuszczak, Simon JF Macdonald† and Marie E. Migaud

School of Chemistry and Chemical Engineering, Queen’s University Belfast, Stranmillis Road, Belfast BT9 5AG, U.K., and †Respiratory CEDD, GlaxoSmithKline, Stevenage, SG1 2NY, U.K.

m.migaud@qub.ac.uk

Table of Contents:

General experimental methods ........................................................................................................................................... 2

Additional information ........................................................................................................................................................... 4

Rings numbering system ...................................................................................................................................................... 7

$^1$H NMR and $^{13}$C NMR spectra for novel compounds .................................................................................................. 8

Copies of HPLC spectra for novel compounds ................................................................................................................ 39
General experimental methods

Chemicals and solvents were obtained from Aldrich, ALLICHEM LLC, Chemical block Ltd., ACR Gelest Ltd. (UK), Priceton Bio, KairoKem and used without further purification.

NMR spectras were recorded on Bruker Avance 600 or Bruker DPX 400 in CDCl$_3$ or CD$_3$OD. $^1$H and $^{13}$C NMR shifts are given in ppm, and refered to tetramethylsilane ($^1$H, 0.0ppm), CDCl$_3$ ($^{13}$C, 77.0ppm), CD$_3$OD ($^{13}$C, 49.0ppm), respectively.

High resolution mass spectra were acquired as accurate mass centroided data using a Micromass Q-Tof 2 hybrid quadrupole time-of-flight mass spectrometer in positive ion mass spectra.

Microwave experiments were performed using two types of microwaves : Biotage Initiator 2.5 for single reactions and Antonpaar synthos 3000 used for the array of 20 reactions run simultaneously.

Flash column chromatography was performed either on CombiFlash Companion XL setup using prepacked RediSep Rf columns or using prepacked silica cartridges on equipment available from Biotage.

Three LC/MS systems were used:

- System I consisted of a Waters ZQ platform with an Agilent/HP 1100 auto sampler. The HPLC analysis was conducted on a Sunfire C18 column (30mm x 4.6mm i.d. 3.5µm packing diameter) at 30°C with a flow rate of 3 mL/min and an injection volume of 5 µL. UV detection was in the range 210-350 nm. The mobile phase consisted of 0.1% formic acid in water (solvent A) against 0.1% formic acid in acetonitrile (solvent B) with a gradient of 97% A for 0.1 min changing to 100% B over 4.2 min, maintained for 0.6 min and then reverting to 97% A over 0.1 min.

- System II consisted of a Waters ZQ platform with an Agilent/HP 1100 auto sampler. The HPLC analysis was conducted on a Sunfire C18 column (30mm x 4.6mm i.d. 3.5µm packing diameter) at 30°C with a flow rate of 3 mL/min and an injection volume of 5 µL. UV detection was in the range 210-350 nm. The mobile phase consisted of 0.1% trifluoroacetic acid in water (solvent A) against 0.1% trifluoroacetic acid in acetonitrile (solvent B) with a gradient of 97% solvent 1 for 0.1 min changing to 100% B over 4.2 min, maintained for 0.6 min and then reverting to 97% A over 0.1 min. (TFA)

- System III consisted of a Waters ZQ platform with an Agilent/HP 1100 auto sampler. The HPLC analysis was conducted on an XBridge C18 column (50mm x 4.6mm i.d. 3.5µm packing diameter) at 30°C with a flow rate of 3 ml/min and an injection volume of 5 µL. UV detection was in the range 210-350 nm. The mobile phase consisted of 10mM ammonium bicarbonate in water adjusted to pH 10 with ammonia solution (solvent A) against acetonitrile (solvent B) with a gradient of 99% A for 0.1 min changing to 97% B over 3.9 min, maintained for 1 min.

- System IV the UPLC analysis was conducted on an UPLC BEH C18 column (50mm x 2.1mm i.d. 1.7µm packing diameter) at 40°C with a flow rate of 1 ml/min and an injection volume of 5 µL. UV detection was in the range 210-350 nm. The mobile phase consisted of 0.1% formic acid in water (solvent A) against 0.1% formic acid in acetonitrile (solvent B) with a gradient of
97% A changing to 100% B over 1.5 min, maintained for 0.4 min and then reverting to 97% A over 0.1 min.

Mass-directed autopreparation was carried out using a Waters Micromass ZQ platform in one of the following conditions:

- **Method A**: Sunfire C18 column (150mmx30i.d. 5μm packing diameter) at ambient temperature with a flow rate of 40ml/min and an injection volume of 1ml. UV detection was in the range 210-350 nm. The mobile phase consisted of 0.1% formic acid in water (solvent 1) against 0.1% formic acid in acetonitrile (solvent 2) with a gradient of 95% solvent 1 for 1 min changing to 70% solvent 1 over 9 min, changing to 99% solvent 2 over 0.5min and maintained for 4.5 min.

- **Method B**: Sunfire C18 column (150mmx30i.d. 5μm packing diameter) at ambient temperature with a flow rate of 40ml/min and an injection volume of 1ml. UV detection was in the range 210-350 nm. The mobile phase consisted of 0.1% formic acid in water (solvent 1) against 0.1% formic acid in acetonitrile (solvent 2) with a gradient of 95% solvent 1 for 1 min changing to 70% solvent 1 over 19 min, changing to 99% solvent 2 over 0.5min and maintained for 4.5 min.

- **Method C**: XBridge C18 column (100mmx30i.d. 5μm packing diameter) at ambient temperature with a flow rate of 40ml/min and an injection volume of 1ml. UV detection was in the range 210-350 nm. The mobile phase consisted of 10mM ammonium bicarbonate in water (solvent 1) against acetonitrile (solvent 2) with a gradient of 95% solvent 1 for 1 min changing to 70% solvent 1 over 9 min, changing to 99% solvent 2 over 0.5min and maintained for 4.5 min.

- **Method D**: XBridge C18 column (100mmx30i.d. 5μm packing diameter) at ambient temperature with a flow rate of 40ml/min and an injection volume of 1ml. UV detection was in the range 210-350 nm. The mobile phase consisted of 10mM ammonium bicarbonate in water (solvent 1) against acetonitrile (solvent 2) with a gradient of 70% solvent 1 for 1 min changing to 15% solvent 1 over 19 min, changing to 99% solvent 2 over 0.5min and maintained for 4.5 min.

HPLC mass-directed autoprepared fractions were freeze-dried.

IR spectras were recorded on Perkin Elmer Spectrum One FT-IR spectrometer.
Additional information

Scheme of UV and fluorescence data (data collected in methanol)

Details of the purification method, yield and other remarks for compounds 11-34 can be found in the tables below.

<table>
<thead>
<tr>
<th>Compound no</th>
<th>R-Br structure</th>
<th>R structure</th>
<th>Purification method</th>
<th>% overall yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td><img src="Br.png" alt="Structure" /></td>
<td><img src="R.png" alt="Structure" /></td>
<td>Method B</td>
<td>45</td>
</tr>
<tr>
<td>18</td>
<td><img src="Br.png" alt="Structure" /></td>
<td><img src="R.png" alt="Structure" /></td>
<td>Method B</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Method</td>
<td>Value</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>--------------------</td>
<td>--------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Method B</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Method B</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Method A</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>Method A</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>Method A</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>Method A</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>Method A</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td><img src="image8" alt="Chemical Structure" /></td>
<td>Method A</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td><img src="image9" alt="Chemical Structure" /></td>
<td>Method A</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td><img src="image10" alt="Chemical Structure" /></td>
<td>Method A</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td><img src="image11" alt="Chemical Structure" /></td>
<td>Method A</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td><img src="image12" alt="Chemical Structure" /></td>
<td>Method A</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>30b</td>
<td><img src="image13" alt="Chemical Structure" /></td>
<td>Method A</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>
The yields were calculated based on a third of material purified.

The reaction was carried out again in the same conditions, different fraction was collected.

<table>
<thead>
<tr>
<th>Compound no</th>
<th>Purification method</th>
<th>% overall yield</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Method C</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Method C</td>
<td>50</td>
<td>Repeated reaction, different purification</td>
</tr>
<tr>
<td>13</td>
<td>Method C</td>
<td>-</td>
<td>Mixture of products 13 + 14 + unknown</td>
</tr>
<tr>
<td>14</td>
<td>Method A</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

* Mixture of products
Rings numbering system

Supplementary Material (ESI) for Organic & Biomolecular Chemistry
This journal is (c) The Royal Society of Chemistry 2011
\textbf{1H NMR and 13C NMR spectra for novel compounds.}

4-bromo-1-(2',3',5'-tri-O-benzoyl-\beta-D-ribofuranosyl)benzimidazole (4)
5-bromo-1-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (5)
6-bromo-1-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (6)
7-bromo-1-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (7)
6-(3’-pyridyl)-1-(2″,3″,5″-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (8).
6-phenyl-1-(2″,3″,5″-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (9).
6-(3’-pyridyl)-1-(β-D-ribofuranosyl)benzimidazole (11).
5-(3’-pyridyl)-1-(β-D-ribofuranosyl)benzimidazole (12)
7-(3’-pyridyl)-1-(β-D-ribofuranosyl)benzimidazole (13)
4-(3'-pyridyl)-1-(β-D-ribofuranosyl)benzimidazole (14)
5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (16).
5-(2’-methylphenyl)-1-(β-D-ribofuranosyl)benzimidazole (17).
5-(3'-methylphenyl)-1-(β-D-ribofuranosyl)benzimidazole (18).
5-(4’-methylphenyl)-1-(β-D-ribofuranosyl)benzimidazole(19).
5-(2',6'-dimethylphenyl)-1-(β-D-ribofuranosyl)benzimidazole (20).
5-(2’-carboxyphenyl)-1-(β-D-ribofuranosyl)benzimidazole (21).
5-(3'-carboxyphenyl)-1-(β-D-ribofuranosyl)benzimidazole (22).
5-(4'-carboxyphenyl)-1-(β-D-ribofuranosyl)benzimidazole (23).
5-(2’-methoxyphenyl)-1-(β-D-ribofuranosyl)benzimidazole (24).
5-(3’-methoxyphenyl)-1-(β-D-ribofuranosyl)benzimidazole (25).
5-(4’-methoxyphenyl)-1-(β-D-ribofuranosyl)benzimidazole (26).
5-(2’-pyridyl)-1-(β-D-ribofuranosyl)benzimidazole (27).
5-(4'-pyridyl)-1-(β-D-ribofuranosyl)benzimidazole (28).
5-(3'-pyrazolyl)-1-(β-D-ribofuranosyl)benzimidazole (29).
5-(1’-pyrazolyl)-1-(β-D-ribofuranosyl)benzimidazole (30).
5-(4'-isothiazolyl)-1-(β-D-ribofuranosyl)benzimidazole (31).
5-(2’-thiophenyl)-1-(β-D-ribofuranosyl)benzimidazole (32).
5-(3'-thiophenyl)-1-(β-D-ribofuranosyl)benzimidazole (33).
5-(2'-furanyl)-1-(β-D-ribofuranosyl)benzimidazole (34).
5-(3'-furanyl)-1-(β-D-ribofuranosyl)benzimidazole (35).
5-(3’-thiophenyl)-1-(β-D-ribofuranosyl)benzimidazole (33) and 3-(methyl)-5-(3’-thiophenyl)-1-(β-D-ribofuranosyl)benzimidazole (37).
Copies of HPLC spectra for novel compounds.

4-bromo-1-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (4).

5-bromo-1-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (5).

6-bromo-1-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (6).

7-bromo-1-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (7).

6-(3'-pyridyl)-1-(2'',3'',5''-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (8).
6-phenyl-1-(2'',3'',5''-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (9).

6-(3'-pyridyl)-1-(β-D-ribofuranosyl)benzimidazole (11).

5-(3'-pyridyl)-1-(β-D-ribofuranosyl)benzimidazole (12).

7-(3'-pyridyl)-1-(β-D-ribofuranosyl)benzimidazole (13)

4-(3'-pyridyl)-1-(β-D-ribofuranosyl)benzimidazole (14)
5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (16).

5-(2’-methylphenyl)-1-(β-D-ribofuranosyl)benzimidazole (17).

5-(3’-methylphenyl)-1-(β-D-ribofuranosyl)benzimidazole (18).

5-(4’-methylphenyl)-1-(β-D-ribofuranosyl)benzimidazole (19).

5-(2’,6’-dimethylphenyl)-1-(β-D-ribofuranosyl)benzimidazole (20).

5-(2’-carboxyphenyl)-1-(β-D-ribofuranosyl)benzimidazole (21).

5-(3’-carboxyphenyl)-1-(β-D-ribofuranosyl)benzimidazole (22).
5-(4’-carboxyphenyl)-1-(β-D-ribofuranosyl)benzimidazole (23).

5-(2’-methoxyphenyl)-1-(β-D-ribofuranosyl)benzimidazole (24).

5-(3’-methoxyphenyl)-1-(β-D-ribofuranosyl)benzimidazole (25).

5-(4’-methoxyphenyl)-1-(β-D-ribofuranosyl)benzimidazole (26).

5-(2’-pyridyl)-1-(β-D-ribofuranosyl)benzimidazole (27).
5-(4’-pyridyl)-1-(β-D-ribofuranosyl)benzimidazole (28).

5-(3’-pyrazolyl)-1-(β-D-ribofuranosyl)benzimidazole (29).

5-(1’-pyrazolyl)-1-(β-D-ribofuranosyl)benzimidazole (30).

5-(4’-isothiazolyl)-1-(β-D-ribofuranosyl)benzimidazole (31).

5-(2’-thiophenyl)-1-(β-D-ribofuranosyl)benzimidazole (32).

5-(3’-thiophenyl)-1-(β-D-ribofuranosyl)benzimidazole (33).
5-(2’-furanyl)-1-(\(\beta\)-D-ribofuranosyl)benzimidazole (34).

5-(3’-furanyl)-1-(\(\beta\)-D-ribofuranosyl)benzimidazole (35).