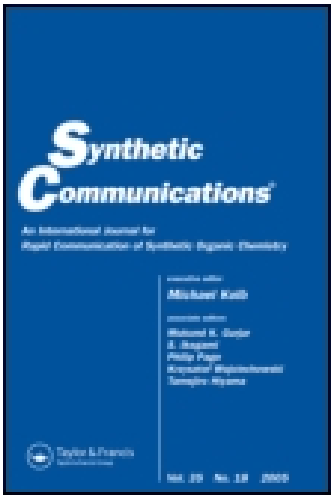


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Benzimidazole-Derived ATP Analogues as Potential Glutamine Synthetase Inhibitors

Babalwa S. B. Gxoyiya [a] , Perry T. Kaye [a] & Colin Kenyon [b]
[a] Department of Chemistry and Centre for Chemico- and Biomedicinal Research , Rhodes University , Grahamstown, South Africa
[b] CSIR BIO/CHEMTEK , Modderfontein, South Africa
Published online: 05 Aug 2010.

To cite this article: Babalwa S. B. Gxoyiya , Perry T. Kaye & Colin Kenyon (2010) Benzimidazole-Derived ATP Analogues as Potential Glutamine Synthetase Inhibitors, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:17, 2578-2587, DOI: 10.1080/00397910903289263

To link to this article: http://dx.doi.org/10.1080/00397910903289263

*Synthetic Communications*®, 40: 2578–2587, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903289263

Taylor & Francis
Taylor & Francis Group



# BENZIMIDAZOLE-DERIVED ATP ANALOGUES AS POTENTIAL GLUTAMINE SYNTHETASE INHIBITORS

**Babalwa S. B. Gxoyiya,[1] Perry T. Kaye,[1] and Colin Kenyon[2]**
[1]*Department of Chemistry and Centre for Chemico- and Biomedicinal Research, Rhodes University, Grahamstown, South Africa*
[2]*CSIR BIO/CHEMTEK, Modderfontein, South Africa*

***A series of mono- and dihydroxyalkyl- and -alkyloxybenzimidazoles and their phosphorylated derivatives have been prepared as adenosine triphoshate analogues for investigation as potential* M. Tb. *glutamine synthetase inhibitors.***

***Keywords***: ATP analogues; benzimidazole derivatives; glutamine synthetase inhibitors; phosphorylation

From being a well-controlled disease, tuberculosis (TB) has, once again, assumed epidemic proportions, a situation exacerbated by the emergence of multiple drug-resistant (MDR)[1] and, very recently, extreme drug-resistant (XDR) TB.[2] Chemotherapeutic intervention began with the discovery by Waksman and coworkers[3] that streptomycin effectively inhibited *Mycobacterium tuberculosis* (*M. Tb.*). This was followed, in 1952, by the discovery of the two critically important drugs, isoniazid (INH)[4–6] and pyrazinamide (PZA).[7] Other drugs that have proved to be effective anti-TB agents include rifampicin,[8] pyrazinamide,[9] cycloserine,[10] and the fluoroquinolone antibiotics.[11]

However, given the emergence of drug-resistant TB, there is clearly a need to develop new drugs that inhibit different targets and shorten the duration of therapy. Such targets include the *M. Tb.* type 1 glutamine synthetase (GSI), which is a dodecamer, unlike the octameric, human GSII.[12] L-Methionine-(*S,R*)-sulfoximine (MetSox)[13] has been found to inhibit both GSI and GSII, but the inhibitory effect is greater with GSI.[14] Since GS enzymes are adenosine triphoshate (ATP) dependent, research in our group has focused on the development of novel ATP analogues as potential GSI inhibitors and, hence, as potential anti-TB agents. Attention has been given to replacement of the three structural motifs present in ATP **1** (viz., the heterocyclic moiety, the linking group, and the triphosphate group), and in this communication, we report the preparation of a series of benzimidazole derivatives, such as **2**, which incorporate the replacement motifs in parentheses in Fig. 1.

Received May 19, 2009.
Address correspondence to Perry T. Kaye, Department of Chemistry and Centre for Chemico- and Biomedicinal Research, Rhodes University, Grahamstown 6140, South Africa. E-mail: P.Kaye@ru.ac.za

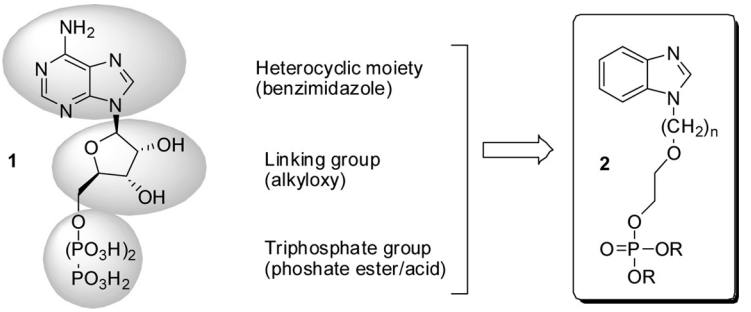
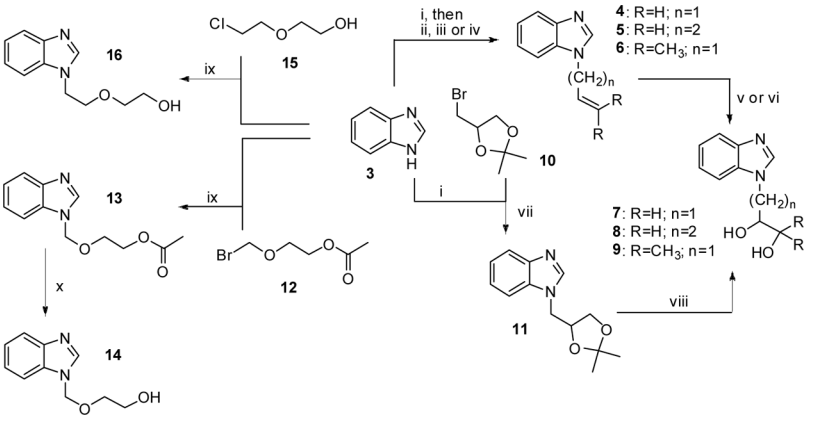



**Figure 1.** General design features of ATP analogues.



Benzimidazole-based drugs, such as albendazole (albenza), mebendazole, and thiabendazole, have enjoyed widespread application as microtubule inhibitors in the treatment of parasitic-related diseases.[15] While benzimidazole **3** lacks the 4-amino substituent present in ATP and thus cannot undergo normal Watson–Crick hydrogen bonding, this does not preclude the possibility that benzimidazole derivatives may fit well into the GS receptor cavity and bind sufficiently strongly to inhibit the normal functions of the enzyme.

*N*-Alkylation of benzimidazole **3** was first explored using the alkenyl bromides, allyl bromide, 4-bromobutene, and 4-bromo-2-methylbut-2-ene. Prior deprotonation was effected with sodium hydride, following the procedure described by Tan et al.[16] (Scheme 1). Flash chromatography of the crude material, in each case, afforded the corresponding *N*-alkenylbenzimidazoles, *N*-allylbenzimidazole **4**, *N*-(but-3-enyl) benzimidazole **5**, and *N*-(3-methylbut-2-enyl)benzimidazole **6** in moderate to excellent yields (43–96%). Two different methods were then investigated to achieve perhydroxylation of the *N*-alkenylbenzimidazoles **4–6**, namely, oxidation with $KMnO_4$[17]

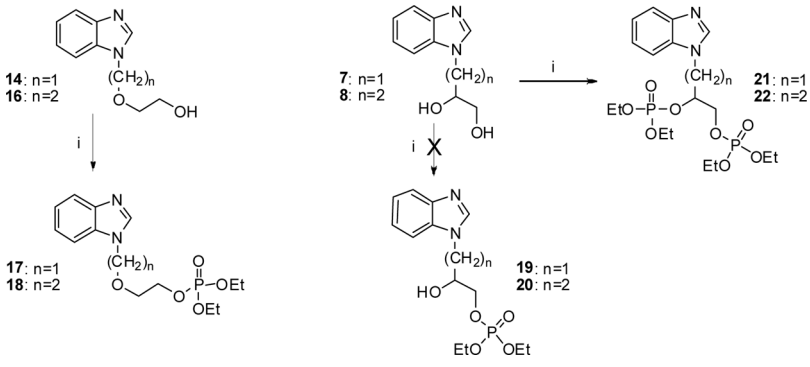



**Scheme 1.** Access to hydroxyl derivatives. Reagents and reaction conditions: (i) NaH, THF, 0 °C, 15 min; (ii) allyl bromide, 30 min reflux; (iii) 4-bromobutene, 4 h reflux; (iv) 4-bromo-2-methyl-2-butene, 40 min reflux; (v) *t*-BuOH, $KMnO_4$, $H_2O$, 0 °C then NaOH, rt; (vi) CTAP, *t*-BuOH, $H_2O$, 20 °C then $CHCl_3$, NaOH; (vii) 18 h reflux; (viii) 75% AcOH, 1 h reflux; (ix) NaH, THF, heat; and (x) $LiAlH_4$, heat.

and with cetyltrimethylammonium permanganate (CTAP), which was prepared from $KMnO_4$ and cetyltrimethylammonium bromide.[18] The reaction of compound **4** with $KMnO_4$ was conducted in water at 0 °C, and radial chromatography of the crude product afforded the desired *N*-(2,3-dihydroxypropyl)benzimidazole **7** as a colorless oil in only 15% yield. Attention was therefore turned to the use of CTAP.[18] The *N*-alkenylbenzimidazoles **4–6** were thus treated with CTAP in *t*-BuOH for several hours at 20 °C, and, following workup and radial chromatography, the pure dihydroxy derivatives **7–9** were isolated in yields that ranged from poor to good (26–77%). In an attempt to improve the yield of diol **7**, benzimidazole **3** was deprotonated as before and then treated with the bromoketal **10**. Flash chromatography, following workup, afforded the pure 1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1*H*-benzimidazole **11** in 38% yield. Subsequent hydrolysis with aqueous acetic acid gave the diol **7** in 97% yield, resulting in a somewhat improved overall yield of 37% for the two steps (**3** + **10** → **11** → **7**).

Access to the hydroxyalkyloxy derivative **16** was provided by heating benzimidazole **3** with 2-choloroethoxyethanol **15** in the presence of sodium hydride, following Tan's methodology.[16] Benzimidazole **3** was reacted similarly with (2-bromomethoxy)ethyl acetate **12**, but repeated chromatography was necessary to separate the acetate **13** from the hydrolyzed product **14**, concomitant formation of which was attributed to the presence of excess sodium hydride and consequent base-catalyzed hydrolysis of the acetyl group during work-up. The alkylation of benzimidazole **3** with (2-bromomethoxy)ethyl acetate **12** was therefore repeated, but the crude product was subjected, without further purification, to reduction with lithium aluminum hydride (LAH) in diethyl ether to afford the alcohol **14** in 21% yield after flash chromatography.

The monohydroxy derivatives **14** and **16** were phosphorylated following the method reported by Kanayama et al.[19] Thus, compounds **14** and **16** were each treated with molar equivalents of butyllithium and diethyl chlorophosphate at 0 °C (Scheme 2) to afford, after flash chromatography, the monophosphates **17** and **18** as oils in 23% and 35% yield, respectively. It was hoped that similar treatment of the diols **7** and **8** would afford the terminal monophosphates **19** and **20**. However, the diphosphates **21** and **22** were isolated instead, in very poor yield. The $^1$H NMR




**Scheme 2.** Access to phosphate esters. Reagents: (i) BuLi, THF, and $(EtO)_2POCl$.

spectrum of the diphosphate **21** clearly shows the presence of multiplets at ca. 1.2 and 4.1 ppm, corresponding to the methyl and methylene groups of the two phosphate ester moieties. The $^{31}P$ NMR spectrum reveals two distinct signals at $-0.63$ and $-0.77$ ppm due to the chemically nonequivalent phosphorus nuclei, whereas the $^{13}C$ and DEPT135 (distortionless enhancement by polarization transfer) spectra exhibit splitting of the methyl and methylene carbons by the phosphorus nuclei.

While reaction conditions remain to be optimized in some cases, synthetic routes to a range of benzimidazole derivatives have been established, thus providing a series of novel ATP analogues for biochemical assay as possible glutamine synthetase inhibitors. Depending on the results of such assays, attention could be given to the preparation of the corresponding phosphate mono-ester phosphonic acid analogues.



## EXPERIMENTAL

Low-resolution mass spectra were obtained on a Finnegan Mat GCQ spectrometer, whereas high-resolution mass spectra were recorded by the University of Witwatersrand mass spectrometry unit. NMR spectra were recorded on a Bruker 400 MHz Avance spectrometer and were referenced using solvent signals ($\delta_H$: 7.26 ppm for residual $CHCl_3$; $\delta_C$: 77.0 ppm for $CDCl_3$). Melting points were determined using a Reichert hot-stage apparatus and are uncorrected. 1-Allylbenzimidazole **4**,[16] 1-(but-3-enyl)benzimidazole **5**,[16] 1-(3-methylbut-2-enyl)benzimidazole **6**,[20] the bromoketal **10**,[21] 2-(bromomethoxy)ethyl acetate **12**,[22] and CTAP[18] were prepared following literature methods. The general procedures are illustrated by the following examples.

### 1-(2,3-Dihydroxypropyl)benzimidazole 7[23]

**Method A.**[16] A solution of CTAP (2.8166 g, 6.98 mmol) in *t*-BuOH (28 ml) and $H_2O$ (7 ml) was added dropwise to a stirred solution of *N*-allylbenzimidazole **4** (1.1016 g, 6.97 mmol) in BuOH (5.6 ml), and the mixture was stirred for 9 h at 20 °C. The mixture was diluted with $CHCl_3$ (70 ml) and 5% NaOH (22 ml) and then stirred for 30 min. The layers were separated, and the aqueous phase was extracted with $CHCl_3$ ($3 \times 70$ ml). The organic layers were combined, dried over anhydrous $MgSO_4$, and evaporated in vacuo. The residual oil was purified by flash chromatography [on silica gel; elution with EtOAc-$CH_2Cl_2$ (3:2)] to afford, as a colorless oil, 1-(2,3-dihydroxypropyl)-benzimidazole **7** (0.6089 g, 44.1%) (found: $M^+$, 192.09095; $C_{10}H_{12}N_2O_2$ requires *M*, 192.08988); $\delta_H$ (300 MHz; DMSO-$d_6$) 3.30 and 3.40 [(1H, td, $J = 5.7$ and 11.4 Hz) and (1H, td, $J = 5.2$ and 10.7 Hz) HOC$H_2$], 3.77–3.84 (1H, m, C*H*OH), 4.13 and 4.35 [(1H, dd, $J = 7.6$ and 14.4) and (1H, dd, $J = 3.2$ and 14.4 Hz) NC$H_2$], 4.83 (1H, t, $J = 5.6$ Hz, $CH_2OH$), 5.06 (1H, d, $J = 5.2$ Hz, CHO*H*), 7.18 (1H, t, $J = 7.1$ Hz, 6-H), 7.24 (1H, t, $J = 7.1$ Hz, 5-H), 7.58 (1H, d, $J = 8.0$ Hz, 4-H), 7.64 (1H, d, $J = 8.0$ Hz, 7-H) and 8.13 (1H, s, 2-H); $\delta_C$ (100 MHz, DMSO-$d_6$) 47.4 ($NCH_2$), 63.1 ($CH_2OH$), 70.0 (CHOH), 110,5 (C-4), 119.1 (C-7), 121.1 (C-6), 121.9 (C-5), 134.3 (C-3a), 143.2 (C-7a) and 144.6 (C-2); *m/z* 192 ($M^+$, 11.6%) and 131 (100%).

**Method B.**[17] To a vigorously stirred mixture of 1-allylbenzimidazole **4** (0.509 g, 3.22 mmol), in a solution of NaOH (0.0543 g, 1.36 mmol) in $H_2O$ (0.3 ml) and *t*-BuOH (11 ml) cooled to $-5$ °C by the addition of ice (5 g), a cooled solution

of $KMnO_4$ (0.340 g, 2.15 mmol) in $H_2O$ (11 ml) was added dropwise at a rate such that the temperature did not exceed 15 °C. Celite (0.1–0.2 g) was then added, and the mixture was heated almost to boiling. The hot mixture was filtered by suction and washed several times with $H_2O$-*t*-BuOH [1:1 (5 ml)]. The filtrate was distilled off until 6 ml of solution remained. The hot solution was weighed, and solid $K_2CO_3$ (1 g/g of solution) was dissolved in small portions until an oil separated. The oil was allowed to solidify, and the rest of the $K_2CO$ was added. The solid was filtered off and redissolved in hot EtOAc, with the insoluble residue being removed by gravity filtration. The EtOAc was evaporated in vacuo, and the residual oil was purified by radial chromatography [on silica; elution with EtOH–$CHCl_3$ (2:3)] to afford, as a colorless oil, 1-(2,3-dihydroxypropyl)benzimidazole **7** (0.092 g, 15%).

**Method C.** A solution of 1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]benzimidazole **11** (0.205 g, 0.884 mmol) in 75% (v/v) acetic acid (20 ml) was boiled under reflux for 1 h, and the solvent was removed in vacuo to afford, as a golden oil, 1-(2,3-dihydroxypropyl)benzimidazole **7** (0.165 g, 97.0%).

### 3-(Benzimidazol-1-yl)propane-1,2-diol bis(diethyl phosphate) 21

BuLi (1.6 M in hexane; 0.46 ml, 0.732 mmol) was added to a solution of 1-(2,3-dihydroxypropyl)benzimidazole **7** (0.140 g, 0.728 mmol) in dry tetrahydrofuran (THF, 7 ml) cooled to 0 °C under argon, and the reaction mixture was stirred for 0.5 h at 0 °C. Diethyl chlorophosphate (27 µl, 0.727 mmol) in dry THF (1 ml) was added, and the reaction mixture was stirred for a further 3 h at 0 °C. The reaction was quenched with saturated aqueous $NH_4Cl$ (0.4 ml), and the solvent was evaporated in vacuo. The residual solid was redissolved in EtOAc and washed with brine (2 ml). The organic layer was dried with anhydrous $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by radial chromatography [on silica; elution with ethanol-$CHCl_3$-hexane (1:1.5:2.5)] to afford, as a pale yellow oil, 3-(benzimidazol-1-yl)propane-1,2-diol bis(diethyl phosphate) **21** (6.8 mg, 2.0%) (found: $M^+$, 464.14687; $C_{18}H_{30}N_2O_8P_2$ requires *M*, 464.14774); $\delta_H$ (400 MHz; $CDCl_3$) 1.13 and 1.23 (6H, 2 × t, $J = 7.0$ Hz, $POCH_2CH_3$), 1.30–1.36 (6H, m, $POCH_2CH_3$), 3.84 (2H, q, $J = 6.9$ Hz, $OCH_2CH_3$) 4.05–4.19 (8H, m, $CH_2OP$ and 3 × $OCH_2CH_3$), 4.44–4.58 (2H, m, $CH_2CHOP$), 4.77–4.85 (1H, m, $CH_2CHOP$), 7.29 (2H, m, 5- and 6-H), 7.47 (1H, d, $J = 7.5$ Hz, 4-H), 7.79 (1H, d, $J = 7.7$ Hz, 7-H) and 7.96 (1H, s, 2-H); $\delta_C$ (100 MHz; $CDCl_3$) 15.8–16.2 ($POCH_2CH_3$), 45.4 (d, $J = 5.5$ Hz, $NCH_2CHOP$), 62.6 (d, $J = 5.4$, $CHCH_2OP$), 64.2–64.4 and 65.4 (C, m, 4 × $POCH_2CH_3$), 73.5 ($CHCH_2OP$), 109.6 (C-4), 120.5 (C-7), 122.5 (C-5), 123.3 (C-6), 133.9 (C-3a), 143.6 (C-2) and 143.7 (C-7a); $\delta_P$ (162 MHz; $CDCl_3$) −0.63 and −1.27; *m/z* 464 (*M*, 12.7%) and 156 (100%).

Other new compounds prepared in this study are as follows:

### 1-(3,4-Dihydroxybutyl)benzimidazole 8

The experimental procedure (method A) employed for the synthesis of *N*-(2,3-dihydroxypropyl)benzimidazole **7** was followed, using 1-(but-3-enyl)benzimidazole

**5** (0.55 g, 3.2 mmol) in *t*-BuOH (2.6 ml), CTAP (1.3 g, 3.2 mmol) in $H_2O$-*t*-BuOH [1:4 (16 ml)], $CHCl_3$ (32 ml), and 5% aq. NaOH (10 ml). The reaction mixture was stirred for 6.5 h, and the aqueous layer was then extracted with $CHCl_3$ ($3 \times 32$ ml). The solvent was removed in vacuo, and the residual oil was purified by radial chromatography [on silica gel; elution with EtOH-$CHCl_3$ (1:4)] to afford, as white crystals, 1-(3,4-dihydroxybutyl)benzimidazole **8** (0.172 g, 26%), mp 150–152 °C (found: $M^+$, 206.10361; $C_{11}H_{14}N_2O_2$ requires *M*, 206.10553); $\delta_H$ (400 MHz; DMSO-$d_6$) 1.70 and 2.01 (2H, m, $CH_2$CHOH), 3.25 (1H, dd, $J = 6.6$ and 11.8 Hz, 4′-$CH_a$OH), 3.33 (2H, m, 4′-$CH_b$OH and 3′-CHOH), 4.34 (2H, t, $J = 7.1$ Hz, $NCH_2$), 4.60 (1H, t, $J = 5.4$ Hz, $CH_2OH$), 4.83 (1H, d, $J = 4.7$ Hz, CHOH), 7.20 (1H, t, $J = 7.4$ Hz, 6-H), 7.25 (1H, t, $J = 7.4$ Hz, 5-H), 7.59 (1H, d, $J = 7.9$ Hz, 4-H), 7.65 (1H, d, $J = 7.9$ Hz, 7-H), and 8.20 (1H, s, 2-H); $\delta_C$ (100 MHz; DMSO-$d_6$) 33.6 ($CH_2$CHOH), 41.0 ($NCH_2$), 65.7 ($CH_2OH$), 68.3 (CHOH), 110.3 (C-4), 119.3 (C-7), 121.3 (C-6), 122.1 (C-5), 133.7 (C-3a), 143.4 (C-7a) and 144.0 (C-2); *m/z* 206 ($M^+$, 74.3%) and 132 (100%).

### 1-(3-Methyl-2,3-dihydroxybutyl)benzimidazole 9

The experimental procedure (method A) employed for the synthesis of *N*-(2,3-dihydroxypropyl)benzimidazole **7** was followed, using 1-(3-methylbut-2-enyl) benzimidazole **6** (0.239 g, 1.29 mmol) in *t*-BuOH (1 ml), CTAP (0.503 g, 1.29 mmol) in $H_2O$-*t*-BuOH (1:4; 6.5 ml), $CHCl_3$ (13 ml), and 5% NaOH (3.9 ml). The reaction mixture was stirred for 6.5 h, and the aqueous layer was then extracted with $CHCl_3$ ($3 \times 13$ ml). The residual oil was purified by flash chromatography [on silica; elution with EtOH-$CHCl_3$ (1:4)] to afford, as cream needles, 1-(3-methyl-2,3-dihydroxybutyl)benzimidazole **9** (0.093 g, 33%), mp 144–146 °C (found: $M^+$, 220.12083; $C_{12}H_{16}N_2O_2$ requires *M*, 220.12118); $\delta_H$ (400 MHz; DMSO-$d_6$) 1.15 and 1.18 (6H, s, $2 \times CH_3$), 3.46 (1H, m, 2′-H), 4.02 (1H, dd, $J = 10.0$ and 14.2 Hz, 1′-$H_a$), 4.52 (1H, d, $J = 1.4$ and 14.2 Hz, 1′-$H_b$), 4.65 (1H, s, 3′-OH), 5.11 (1H, d, $J = 6.2$ Hz, 2′-OH), 7.19 (1H, t, $J = 7.4$ Hz, 6-H), 7.25 (1H, t, $J = 7.4$ Hz, 5-H), 7.54 (1H, d, $J = 7.9$ Hz, 4-H), 7.64 (1H, d, $J = 7.9$ Hz, 7-H), and 8.13 (1H, s, 2-H); $\delta_C$ (100 MHz; DMSO-$d_6$) 23.6 and 27.5 ($2 \times CH_3$), 46.6 (C-1′), 71.0 (C-2′), 75.8 (C-3′), 110.4 (C-4), 119.2 (C-7), 121.1 (C-6), 121.9 (C-5), 133.9 (C-3a), 143.4 (C-7a), and 144.8 (C-2); *m/z* 220 ($M^+$, 75.5%) and 118 (100%).

### 1-[(2-Acetoxyethoxy)methyl]benzimidazole 13[23]

The experimental procedure employed for the synthesis of 1-allylbenzimidazole **4** was followed using benzimidazole **3** (1.025 g, 8.686 mmol), 60% NaH (0.6940 g, 28.92 mmol), 2-(bromomethoxy)ethyl acetate **12** (2.0614 g, 10.46 mmol), and THF (15 mL). The mixture was boiled under reflux for 24 h, and the residue was purified by radial chromatography [on silica; elution with EtOH-$CHCl_3$ (1:9)] to afford, as a yellow oil, 1-[(2-acetoxyethoxy)methyl]benzimidazole **13** (0.709 g, 34.9%) (found: $M^+$ 234.09929; $C_{12}H_{14}N_2O_3$ requires *M*, 234.10044); $\delta_H$ (400 MHz; $CDCl_3$) 1.95 (3H, s, $CH_3$), 3.59 (2H, t, $J = 4.6$ Hz, $OCH_2CH_2OCO$), 4.13 (2H, t, $J = 4.6$ Hz, $OCH_2CH_2OCO$), 7.31 (2H, m, 5- and 6-H), 7.52 (1H, d, $J = 6.2$ Hz, 4-H), 7.79 (1H, d, $J = 6.2$ Hz, 7-H) and 7.80 (1H, s, 2-H); $\delta_C$ (100 MHz; $CDCl_3$) 20.6 ($CH_3$),

62.7 ($OCH_2CH_2OCO$), 66.5 ($OCH_2CH_2OCO$), 74.7 ($NCH_2O$), 110.1 (C-4), 120.4 (C-7), 122.8 (C-6), 123.6 (C-5), 133.4 (C-3a), 142.8 (C-2), 144.0 (C-7a) and 170.7 (C=O); $m/z$ 235 ($M+1$, 100%).

### 1-[(2-Hydroxyethoxy)methyl]benzimidazole 14[23]

A solution of 1-[(2-acetoxyethoxy)methyl]benzimidazole **13** (0.4450 g, 1.90 mmol) in dry THF (2 ml) was added dropwise to a suspension of LAH (0.0796 g, 2.1 mmol) in dry THF (5 ml) under nitrogen, and the mixture was heated at 60 °C for 9 h. The reaction mixture was cooled to room temperature, and EtOAc was then added to destroy excess LAH. Excess solvent was removed in vacuo, and the residual oil was purified by flash chromatography [on silica; elution with EtOH-$CHCl_3$-hexane (1:1.5:2.5)] to afford, as a golden oil, 1-[(2-hydroxyethoxy)methyl]benzimidazole **14** (77.8 mg, 21.3%) (found: $M^+$, 192.09042; $C_{10}H_{12}N_2O_2$ requires $M$, 192.08988); $\delta_H$ (400 MHz; $CDCl_3$) 3.52 and 3.71 (4H, 2 × t, $J=4.6$ Hz, $OCH_2CH_2OH$), 5.72 (2H, s, $NCH_2$), 7.31 (2H, m, 5- and 6-H), 7.5 (1H, m, 4-H), 7.7 (1H, m, 7-H) and 7.92 (1H, s, 2-H); $\delta_C$ (100 MHz; $CDCl_3$) 61.1 ($OCH_2CH_2OH$), 70.1 ($OCH_2CH_2OH$), 74.8 ($NCH_2O$), 110.2 (C-4), 120.1 (C-7), 122.8 (C-5), 123.6 (C-6), 133.3 (C-3a), 143.0 (C-2), and 143.5 (C-7a); $m/z$ 193 ($M+1$, 100%).

### 1-[2-(2-Hydroxyethoxy)ethyl]benzimidazole 16[24]

The experimental procedure employed for the synthesis of *N*-allylbenzimidazole **4** was followed using benzimidazole **3** (1.007 g, 8.481 mmol), 60% NaH (0.6697 g, 27.9 mmol), 2-(chloroethoxy)ethanol **15** (1.2737 g, 10.22 mmol), and THF (20 ml). The residual oil was purified by flash chromatography [on silica; elution with EtOH-$CHCl_3$-hexane (1:1.5:2.5)] to afford, as a pale yellow oil, 1-[2-(2--hydroxyethoxy)ethyl]benzimidazole **16** (0.4089 g, 23.4%) (found: $M^+$ 206.10432; $C_{11}H_{14}N_2O_2$ requires $M$, 206.10553); $\delta_H$ (400 MHz; $CDCl_3$) 2.15 (1H, s, OH), 3.50 (2H, t, $J=4.6$ Hz, $CH_2$), 3.66 (2H, t, $J=4.6$ Hz, $CH_2$), 3.82 (2H, t, $J=5.2$ Hz, $CH_2$), 4.33 (2H, t, $J=5.2$ Hz, $CH_2$), 7.25–7.29 (2H, m, 5- and 6-H), 7.40 (1H, d, $J=6.4$ Hz, 4-H), 7.79 (1H, d, $J=6.4$ Hz, 7-H), and 7.96 (1H, s, 2-H); $\delta_C$ (100 MHz; $CDCl_3$) 45.0 ($NCH_2CH_2O$), 61.6 ($OCH_2CH_2OH$), 69.4 ($NCH_2CH_2O$), 72.6 ($OCH_2$-$CH_2OH$), 109.4 (C-4), 120.3 (C-7), 122.2 (C-5), 122.9 (C-6), 133.8 (C-3a and C-7a), and 143.5 (C-2); $m/z$ 207 ($M+1$, 65.2%) and 132 (100%).

### 1-[(2-Hydroxyethoxy)methyl]benzimidazole diethyl phosphate 17

The experimental procedure employed for the synthesis of compound **21** was followed, using 1-[(2-hydroxyethoxy)methyl]benzimidazole **14** (0.250 g, 1.30 mmol), BuLi (1.6 M in hexane; 0.85 ml, 1.36 mmol), diethyl chlorophosphate (190 µl, 1.31 mmol), and THF (13 ml). The reaction mixture was stirred overnight at room temperature, and the residual oil was purified by flash chromatography [on silica; elution with EtOH/$CHCl_3$/hexane (1:1.5:2.5)] to afford, as a yellow oil, 1-[(2-hydroxyethoxy)methyl]benzimidazole diethyl phosphate **17** (0.0998 g, 23.3%); $\delta_H$ (400 MHz; $CDCl_3$) 1.25–1.28 (6H, m, $POCH_2CH_3$), 3.86–4.14 [6H, m, $OCH_2CH_2OP$ and $P(OCH_2CH_3)_2$], 4.67 (2H, s, $NCH_2O$), 7.24–7.31 (2H, m, 5- and 6-H), 7.39

(1H, d, $J = 8.2$ Hz, 4-H), 7.78 (1H, d, $J = 8.2$ Hz, 7-H), and 7.97 (1H, s, 2-H); $\delta_C$ (100 MHz; $CDCl_3$) 16.3 (d, $J = 7.3$ Hz, $POCH_2CH_3$), 61.7 (d, $J = 5.6$ Hz, $POCH_2CH_3$), 64.1 (d, $J = 6.9$ Hz, $OCH_2CH_2OP$), 66.2 ($OCH_2CH_2OP$), 94.7 (NCHO), 110.0 (C-4′), 119.3 (C-7), 123.0 (C-5), 123.6 (C-6), 132.9 (C-3a), 140.8 (C-7a) and 143.2 (C-2); $\delta_P$ (162 MHz, $CDCl_3$) −0.46.

### 1-[2-(2-Hydroxyethoxy)ethyl]benzimidazole diethyl phosphate 18

The experimental procedure employed for the synthesis of compound **21** was followed, using *N*-[2-(2-hydroxyethoxy)ethyl]benzimidazole **16** (0.309 g, 1.50 mmol), 1.6 M BuLi in hexane (0.95 ml, 1.52 mmol), diethyl chlorophosphate (217 µl, 1.52 mmol), and THF (15 ml). The residual oil was purified by flash chromatography [on silica; elution with EtOH/$CHCl_3$/hexane (1:1.5:2.5)] to afford, as a yellow oil, 1-[2-(2-hydroxyethoxy)ethyl]benzimidazole diethyl phosphate **18** (0.129 g, 30%) (found: $M^+$, 342.13495; $C_{15}H_{23}N_2O_5P$ requires *M*, 342.13446); $\delta_H$ (400 MHz; $CDCl_3$) 1.25 (6H, t, $J = 7.2$ Hz, $POCH_2CH_3$), 3.48–3.51 (2H, m, $OCH_2CH_2OP$), 3.53–3.58 (2H, m, $OCH_2CH_2OP$), 3.78–3.80 (2H, m, $NCH_2CH_2O$), 3.97–4.09 (4H, m, $POCH_2CH_3$), 4.30 (2H, t, $J$ =Hz, $NCH_2CH_2O$), 7.21–7.25 (2H, m, 5- and 6-H), 7.35 (1H, d, $J = 6.8$ Hz, 4-H), 7.73 (1H, d, $J = 6.8$ Hz, 7-H) and 7.92 (1H, s, 2-H); $\delta_C$ (100 MHz; $CDCl_3$) 16.0 ($POCH_2CH_3$), 44.9 ($NCH_2CH_2O$), 63.8 ($POCH_2CH_3$), 69.3 ($NCH_2CH_2O$), 70.0 ($OCH_2CH_2OP$), 70.5 ($OCH_2CH_2OP$), 109.5 (C-4), 120.1 (C-7), 122.0 (C-5), 122.8 (C-6), 133.7 (C-3a), 143.4 (C-7a), and 143.5 (C-2); $\delta_P$ (162 MHz, $CDCl_3$) −0.48.

### 1-(3,4-Dihydroxybutyl)benzimidazole bis(diethyl phosphate) 22

The experimental procedure employed for the synthesis of compound **21** was followed, using 1-(3,4-dihydroxybutyl)benzimidazole **8** (0.2140 g, 1.039 mmol), BuLi (1.6 M in hexane; 0.65 ml, 1.1 mmol), diethyl chlorophoshate (39 µl, 1.1 mmol), and THF (8 ml). The residual oil was purified by radial chromatography [on silica; elution with EtOH/$CHCl_3$/hexane (1:1.5:2.5)] to afford, as a yellow oil, 1-(3,4-dihydroxybutyl)benzimidazole bis(diethyl phosphate) **22** (24.2 mg, 4.87%) (found: $M^+$, 478.16403; $C_{19}H_{32}N_2O_8P_2$ requires *M*, 478.16339); $\delta_H$ (400 MHz; $CDCl_3$) 1.26–1.37 (12H, m, $POCH_2CH_3$), 1.90–2.05 and 2.23–2.67 (2H, m, 2′-$CH_2$), 4.04–4.16 {10H, m, $[P(OCH_2CH_3)_2]_2$ and 4′-$CH_2$}, 4.31–4.38 (2H, m, 1′-$CH_2$), 4.47–4.49 (1H, m, 3′-CH), 7.26–7.31 (1H, m, 5- and 6-H), 7.40 (1H, d, $J = 7.2$ Hz, 4-H), 7.79 (1H, d, $J = 7.2$ Hz, 7-H) and 8.05 (1H, s, 2-H); $\delta_C$ (100 MHz; $CDCl_3$) 15.6–16.1 ($POCH_2CH_3$), 32.1 (d, $J = 8.1$ Hz, C-2′), 40.7 (C-1), 64.0 and 64.2 [$P(OCH_2CH_3)_2$], 66.3 (d, $J = 10.2$ Hz, C-4′), 71.3 (d, $J = 9.9$ Hz, C-3′), 109.5 (C-7). 120.0 (C-4), 122.0 (C-5), 122.9 (C-6), 133.4 (C-7a), 143.4 (C-2) and 143.6 (C-7a); $\delta_P$ (162 MHz; $CDCl_3$) −5.27 and −5.43.

## ACKNOWLEDGMENTS

We are grateful to the South African Department of Science and Technology (DST) Innovation Fund for a bursary (B.S.B.G.), the DST and Rhodes University for generous financial support, and Ms. Y. C. Lee for running additional NMR spectra.

## REFERENCES


1. Zhang, Y.; Amzel, L. M. Tuberculosis drug targets. *Curr. Drug Targets* **2002**, *3*, 131–154.
2. World Health Organization. Emergence of XDR-TB. Available at http://www.who.int/mediacentre/news/notes/2006/np23/en/print.html
3. Waksman, S. A.; Henrici, A. T. The nomenclature and classification of the actinomycetes. *J. Bact.* **1943**, *46*, 337–341.
4. Fox, H. H. Chemical approach to the control of tuberculosis. *Science (New York)* **1952**, *116*, 129–135.
5. Bernstein, J.; Lott, W. A.; Steinberg, B. A.; Yale, Harry L. Chemotherapy of experimental tuberculosis, V: Isonicotinic acid hydrazide (Nydrazid) and related compounds. *Am. Rev. Tuberc.* **1952**, *65*, 357–364.
6. Steenken Jr., W.; Wolinsky, E. Antituberculous properties of hydrazines of isonicotinic acid (rimifon, marsilid). *Am. Rev. Tuberc.* **1952**, *65*, 365–375.
7. Yeager, R. L.; Munroe, W. G. C.; Dessau, F. I. Pyrazinamide (aldinamide) in the treatment of pulmonary tuberculosis. *Am. Rev. Tuberc.* **1952**, *65*, 523–534.
8. Aquinas, M. Short-course therapy for tuberculosis. *Drugs* **1982**, *24*(2), 118–132.
9. Frieden, T. R.; Sterling, T. R.; Munsiff, S. S.; Watt, C. J.; Dye, C. Tuberculosis. *Lancet* **2003**, *362*, 887–899.
10. Kuehl Jr., F. A.; Wolf, F. J.; Trenner, N. R.; Peck, R. L.; Buhs, R. P.; Putter, I.; Ormond, R.; Lyons, J. E.; Chaiet, L.; Howe, E.; Hunnewell, B. D.; Downing, G.; Newstead, E.; Folkers, K. D-4-Amino-3-isoxazolidinone, a new antibiotic. *J. Am. Chem. Soc.* **1955**, *77*, 2344–2345.
11. De Souza, M. V. N. New fluoroquinolones: A class of potent antibiotics. *Rev. Med. Chem.* **2005**, *5*, 1009–1017.
12. Cole, S. T.; Brosch, R.; Parkhill, J.; Garnier, T.; Churcher, C.; Harris, D.; Gordon, S. V.; Eiglmeier, K.; Gas, S.; Barry III, C. E.; Tekaia, F.; Badcock, K.; Basham, D.; Brown, D.; Chillingworth, T.; Connor, R.; Davies, R.; Devlin, K.; Feltwell, T.; Gentles, S.; Hamlin, N.; Holroyd, S.; Hornsby, T.; Jagels, K.; Krogh, A.; McLean, J.; Moule, S.; Murphy, L.; Oliver, K.; Osborne, J.; Quail, M. A.; Rajandream, M.-A.; Rogers, J.; Rutter, S.; Seeger, K.; Skelton, J.; Squares, R.; Squares, S.; Sulston, J. E.; Taylor, K.; Whitehead, S.; Barrell, B. G. Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. *Nature* **1998**, *393*, 537–544.
13. Gill, H. S.; Eisenberg, D. The crystal structure of phosphinothricin in the active site of glutamine synthetase illuminates the mechanism of enzymatic inhibition. *Biochemistry* **2001**, *40*, 1903–1912.
14. Harth, G.; Horwitz, M. A. An inhibitor of exported *Mycobacterium tuberculosis* glutamine synthetase selectively blocks the growth of pathogenic mycobacteria in axenic culture and in human monocytes: Extracellular proteins as potential novel drug targets. *J. Exp. Med.* **1999**, *189*, 1425–1435.
15. Cook, G. C. Use of benzimidazole chemotherapy in human helminthiases: Indications and efficacy. *Parasitol. Today* **1990**, *6*, 113–136.
16. Tan, K. L.; Vasudevan, A.; Bergman, R. G.; Ellman, J. A.; Souers, A. J. Microwave-assisted C−H bond activation: A rapid entry into functionalized heterocycles. *Org. Lett.* **2003**, *5*, 2131–2134.
17. Fessenden, R. J.; Fessenden, J. S. *Techniques and Experiments for Organic Chemistry*; Willard Grant Press: Boston, 1983; pp. 248–251.
18. Bhushan, V.; Rathore, R.; Chandrasekaran, S. A simple and mild method for the cis-hydroxylation of alkenes with cetyltrimethylammonium permanganate. *Synthesis* **1984**, 431–433.

19. Kanayama, T.; Yoshida, K.; Miyabe, H.; Kimachi, T.; Takemoto, Y. Synthesis of β-substituted α-amino acids with use of iridium-catalyzed asymmetric allylic substitution. *J. Org. Chem.* **2003**, *68*, 6197–6201.
20. Petrushkina, E. A.; Gavrilenko, V. V.; Oprunenko, Y. F.; Akhmedov, N. G. Control of the regioselectivity of isoprene telomerization with benzimidazole catalyzed by palladium complexes. *Akhmedov, Zh. Obshch. Khim.* **1996**, *66*, 1864–1870; CAN 126:144225.
21. Marasco Jr., C. J.; Piantadosi, C.; Meyer, K. L.; Morris-Natschke, S.; Ishaq, K. S.; Small, G. W.; Daniel, L. W. Synthesis and biological activity of novel quaternary ammonium derivatives of alkylglycerols as potent inhibitors of protein kinase C. *J. Med. Chem.* **1990**, *33*, 985–992.
22. Robins, M. J.; Hatfield, P. W. Nucleic acid related compounds, 37: Convenient and high-yield syntheses of N-[(2-hydroxyethoxy)methyl]heterocycles as "acyclic nucleoside" analogs. *Can. J. Chem.* **1982**, *60*, 547–553.
23. Yavorskii, A. E.; Stetsenko, A. V.; Gogoman, I. V.; Boiko, V. N.; Zavgorodnii, S. G.; Sobko, A. I.; Tatskaya, V. N.; Kvachev, V. G.; Florent'ev, V. L. Acyclic analogs of nucleosides: Synthesis of hydroxyalkyl derivatives of 2-trifluoromethyl- and 2-(trifluoromethylthio)benzimidazoles. *Khim. Geterotsikl. Soedin.* **1988**, *2*, 198–202; CAN 110:114751.
24. Garuti, L.; Ferranti, A.; Giovanninetti, G.; Scapini, G.; Franchi, L.; Landini, M. P. Studies on potential antiviral compounds, XXII: Synthesis and in vitro antiviral activity of 1-(hydroxyalkyl)-1H-benzimidazoles. *Arch. Pharm.* **1982**, *315*, 1007–1013.