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

3-Substituted Anilines as Scaffolds for the Construction of Glutamine Synthetase and DXP-Reductoisomerase Inhibitors

Marius Mutorwa [a] , Sheriff Salisu [a] , Gregory L. Blatch [b c] , Colin Kenyon [d] & Perry T. Kaye [a c]

[a] Department of Chemistry , Rhodes University , Grahamstown, South Africa

[b] Department of Biochemistry, Microbiology, and Biotechnology, Rhodes University , Grahamstown, South Africa

[c] Centre for Chemico- and Biomedicinal Research , Rhodes University , Grahamstown, South Africa

[d] CSIR BIO/CHEMTEK, Modderfontein , South Africa

Published online: 26 Jun 2009.

Synthetic Communications®, 39: 2723–2736, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802663444

Taylor & Francis
Taylor & Francis Group

3-Substituted Anilines as Scaffolds for the Construction of Glutamine Synthetase and DXP-Reductoisomerase Inhibitors

Marius Mutorwa,[1] Sheriff Salisu,[1] Gregory L. Blatch,[2,3] Colin Kenyon,[4] and Perry T. Kaye[1,3]

[1]Department of Chemistry, Rhodes University, Grahamstown, South Africa
[2]Department of Biochemistry, Microbiology, and Biotechnology, Rhodes University, Grahamstown, South Africa
[3]Centre for Chemico- and Biomedicinal Research, Rhodes University, Grahamstown, South Africa
[4]CSIR BIO/CHEMTEK, Modderfontein, South Africa

Abstract: Access to a series of truncated ATP analogs, as potential anti-tuberculosis agents, has been explored via alkylation and acylation of 3-amino-phenol, whereas chloroacetylation, using chloroacetyl chloride, and subsequent Arbuzov phosphonation of a series of 3-substituted anilines have afforded a series of phosphonate derivatives as potential antimalarial agents.

Keywords: Aniline derivatives, DXP-reductoisomerase inhibitors, glutamine synthetase, phosphonates

Malaria and tuberculosis (TB) constitute enormous health threats in the developing world. Treatment is compounded by the phenomenon of drug resistance, and the development of novel therapeutics has become a research priority. *Mycobacterium tuberculosis* (*Mtb*), the organism responsible for TB,[1] has been shown to release extracellular proteins that are vital for its replication and virulence in the host's tissues.[2–5]

Received October 27, 2008.
Address correspondence to Perry T. Kaye, Department of Chemistry, Rhodes University, Grahamstown, 6140, South Africa. E-mail: P.Kaye@ru.ac.za

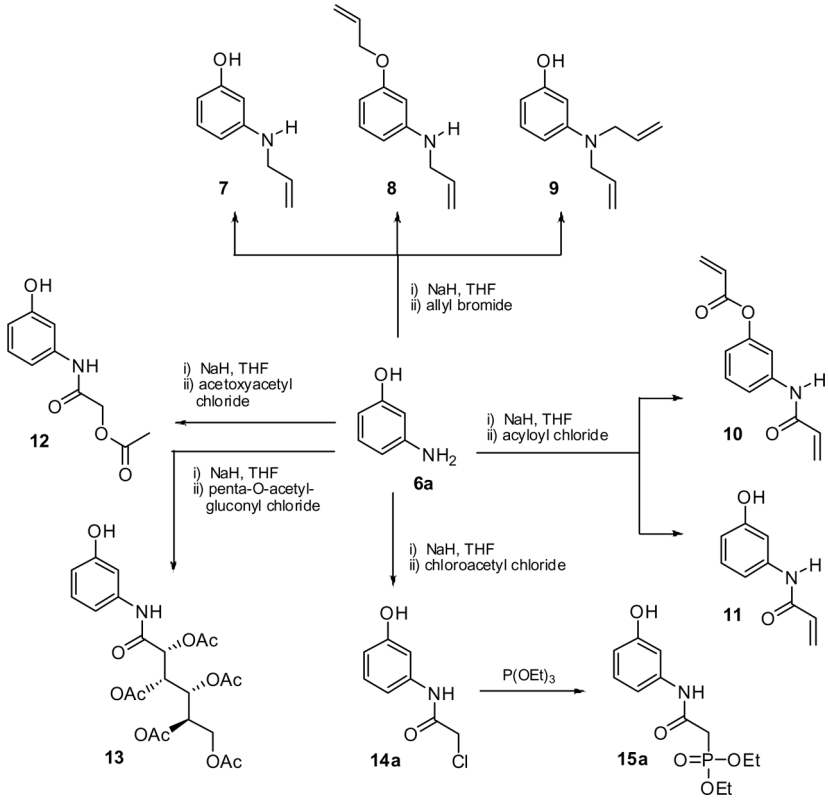
Among these proteins is the enzyme, glutamine synthetase (*Mtb*-GS), that is essential for the formation of the cell wall of *Mtb*.[6] The differences between human and bacterial GS (and in their respective modes of regulation[7]) has led to the identification of *Mtb*-GS as a therapeutic target[4] and to the investigation of adenine triphosphate (ATP) analogs as potentially selective inhibitors of *Mtb*-GS.[8]

Plasmodium falciparum (*Pf*), on the other hand, is the parasite responsible for the most dangerous form of human malaria. The enzyme 1-deoxy-1-D-xylulose-5-phosphate (DXP)–reductoisomerase is involved in a parasite-specific, isoprenoid biosynthetic pathway, for which fosmidomycin[9] and FR900098[10] act as inhibitors. In parallel programs in our laboratories, attention has been given to designing and synthesising ATP **1** and DXP **2** analogs as potential *Mtb*-GS and DXP-reductoisomerase inhibitors, respectively. In this article, we report the preparation of a range of 3-substituted aniline derivatives as DXP and truncated ATP mimics.

It was envisaged that benzenoid compounds **4** with suitable *meta* substituents could serve as truncated mimics (Fig. 1) of the 6-aminopurine (adenine) nucleus **3** and that reaction with various electrophiles (as outlined in Scheme 1) could provide convenient access to novel and effective ATP analogs (e.g., compound **5** as illustrated in Fig. 1).

Treatment of 3-aminophenol **6a** with NaH and a series of alkylating and acylating agents afforded the range of substitution products illustrated in Scheme 1. Given the presence of two nucleophilic functional groups (phenolic and amino) in the substrate **6a,** alkylation and/or acylation of either was not unexpected. The reaction with allyl bromide, in fact, afforded three products, viz., the mono-allylated product **7** and the bis-allylated isomers **8** and **9**. Mass spectrometric (MS) analysis revealed a molecular ion at m/z 149 (as the base peak) for the mono-allylated product **7**, whereas the di-allylated products **8** and **9** each exhibited a molecular ion at m/z 189 (95% and 100% relative abundance, respectively). The allylation sites in each of the products were established by comparison of the experimental chemical shifts of the methylene ^{13}CNMR signals, and the assignments were supported by the corresponding Modgraph-predicted[11] values. Moreover, in the ^{1}H NMR spectra of *N*-allyl-3-hydroxyaniline **7**, *N*-allyl-3-allyloxyaniline **8,** and *N,N*-diallyl-3--hydroxyaniline **9**, the *N*-methylene protons have similar chemical shift values (ca. 3.8 ppm), whereas the *O*-methylene protons in the *O*-allylated moiety **8** resonate downfield at 4.51 ppm because of the greater deshielding effect of the oxygen atom (Fig. 2). Unfortunately, attempts to dihydroxylate the mono-allylated product **7** using cetyltrimethylammonium permanganate (CTAP), $KMnO_4$, and $NaIO_4$ all proved unsuccessful.

The mono- and di-acylated products (**10** and **11**, respectively) were isolated in very poor yields when the substrate **6a** was treated with



Scheme 1. Alkylation and acylation reactions.

NaH and acryloyl chloride. Remarkably, however, only the corresponding *N*-mono-acylated products (**12, 13,** and **14**) were isolated from the acylation reactions involving chloroacetyl chloride, acetoxyacetyl chloride, and penta-*O*-acetyl-D-gluconyl chloride.

2-Acetoxy-*N*-(3-hydroxyphenyl)acetamide **12** exhibited phenolic and residual amino proton NMR signals at 9.39 ppm and 9.92 ppm, respectively, confirming mono-*N*-acylation, while the amide and ester carbonyl carbons resonated at 165.2 ppm and 169.9 ppm, respectively, as determined from the correlations between corresponding proton and carbon signals in the heteronuclear multiple bond correlation (HMBC) spectrum. 2,3,4,5,6-Pentaacetyl-*N*-(3-hydroxyphenyl)gluconamide **13** was isolated successfully from the reaction between 3-aminophenol **6a** and pentacetylated gluconyl chloride.[12] The five acetyl methyl groups resonated as a series of singlets, integrating for 15 protons, between 2.01 and 2.24 ppm in the ^{1}H NMR spectrum, while in the ^{13}C NMR spectrum,

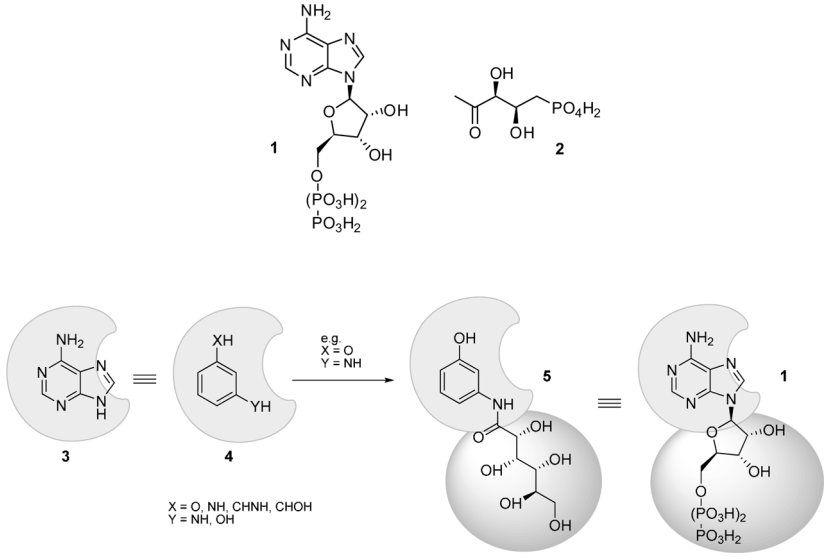


Figure 1. General approach to novel truncated ATP mimics.

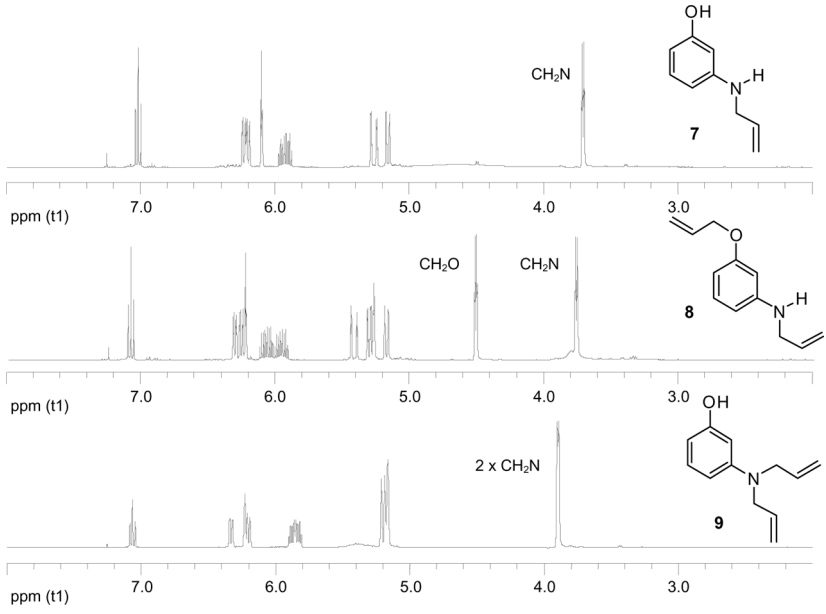
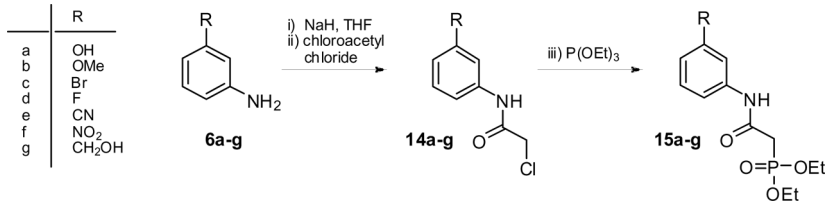


Figure 2. The 400 ^{1}H NMR spectra of allylated derivatives **7, 8**, and **9** in $CDCl_3$.



Scheme 2. Access to 3-substituted anilides.

coincidence of two of the methyl signals resulted in four carbon signals corresponding to the five methyl carbons. High-resolution mass spectrometric (HRMS) analysis confirmed the formation of compound **13**, with the base peak corresponding to the molecular ion at m/z 497.450192.

2-Chloro-*N*-(3-hydroxyphenyl)acetamide **14a** was obtained in 76% yield, with the correlation between the NH proton and the carbonyl carbon in the HMBC spectrum confirming acylation of the amino rather than the phenolic group. Arbuzov phosphonation of compound **14a** with triethyl phosphite[13] afforded the diethyl phosphonate ester **15a** in 48% yield. In the respective ^{1}H and ^{13}C NMR spectra, the CH_2P proton and carbon nuclei resonate as doublets as a result of coupling to the ^{31}P nucleus. Serendipitously, the phosphonate ester **15a** was selected as a trial substrate for a preliminary protein NMR study of ligand binding to the DXP-reductoisomerase enzyme of the malaria parasite *Plasmodium faciparum* (*Pf*DXR). The results of the saturation transfer difference (STD)[14] NMR experiment clearly indicated binding of compound **15a** to the protein, and the protein–ligand interaction was supported by in vitro inhibition of *Pf* DXR. Thus, although the phosphonate ester **15** was prepared as a potential *Mtb*-GS inhibitor, its capacity to inhibit *Pf* DXR prompted us to explore the analogous systems **15b–g** (Scheme 2) as novel antimalarials. (In vivo hydrolysis of the ester moieties is expected to release the corresponding phosphonic acids as the more active species.) Progress in this ongoing study on the synthesis of further analogs and the results of enzyme-binding and enzyme-inhibition assays will be published in due course.

EXPERIMENTAL

^{1}H, ^{13}C, and ^{31}P NMR experiments were conducted on Bruker AMX 400-MHz and Avance 600-MHz spectrometers. Chemical shifts are reported relative to the residual protonated solvent signals. Low-resolution mass spectra (LRMS) were recorded on Finnigan-MAT

GCQ or LCQ mass spectrometers, and HRMS data were obtained by the University of the Witwatersrand, University of the Northwest (Potchefstroom), or Stellenbosch University. Compounds **14a**–**g**[15–20] and **15b**[21] are known. Illustrative experimental procedures and characterization data for new compounds are detailed next.

N-Allyl-(3-hydroxy)aniline 7, *N*-Allyl-3-(allyloxy)aniline 8, and *N,N*-Diallyl-3-hydroxyaniline 9

NaH (60% dispersion in mineral oil; 1.1 g, 28 mmol) was added in small portions to a stirred solution of 3-aminophenol **6a** (3.0 g, 28 mmol) in dry tetrahydrofuran (THF) (30 mL) under nitrogen to permit controlled evolution of hydrogen. Allyl bromide (2.4 mL, 28 mmol) was then added through a septum, and the resulting solution was refluxed for ca. 4.5 h. The reaction was quenched by the addition of water (50 mL). The organic solvent was evaporated in vacuo, and the aqueous residue was extracted with EtOAc (2×50 mL). The combined organic extracts were washed sequentially with water (2×100 mL) and brine (2×100 mL). The aqueous washings were extracted with EtOAc, and the organic layers were combined and dried (anhydr. $MgSO_4$). Flash chromatography [on silica gel; elution with hexane–EtOAc (8:2)] afforded three fractions.

N-Allyl-(3-hydroxy)aniline **7**

Dark brown oil (680 mg, 17%) (found: $\mathbf{M}^+$ 149.083104; $C_9H_{11}NO$ requires *M* 149.084064); ν_{max} (thin film/cm^{-1}) 3388 (NH); δ_H/ppm (400 MHz; $CDCl_3$) 3.70 (2H, dt, $J = 5.4$ and 1.6 Hz, 1′-CH_2), 5.16 (1H, qd, $J = 10.3$ and 1.4 Hz, CH=CH_Z), 5.26 (1H, qd, $J = 17.2$ and 1.6 Hz, CH=CH_E), 5.92 (1H, m, 2′-H), 6.10 (1H, t, $J = 2.3$ Hz, 2-H), 6.20 (1H, dd, $J = 8.0$ and 2.3 Hz, 6-H), 6.23 (1H, dd, $J = 8.1$ and 2.1 Hz, 4-H), and 7.02 (1H, t, $J = 8.0$ Hz, 5-H); δ_C/ppm (100 MHz; $CDCl_3$) 46.6 (C-1′), 100.3 (C-2), 105.0 (C-6), 106.2 (C-4), 116.4 (C-3′), 130.1 (C-5), 135.1 (C-2′), 149.4 (C-1), and 156.6 (C-3).

N-Allyl-3-(allyloxy)aniline **8**

Dark brown oil (270 mg, 5.2%) (found: $\mathbf{M}^+$ 189.115840; $C_{12}H_{15}NO$ requires *M* 189.115364); ν_{max} (thin film/cm^{-1}) 3406 (NH_2); δ_H/ppm (400 MHz; $CDCl_3$) 3.77 (2H, dt, $J = 5.4$ and 1.6 Hz, 1′-CH_2), 4.51 (2H, td, $J = 5.3$ and 1.5 Hz, 1″-CH_2), 5.18 (1H, m, 3′-H_a), 5.30 (2H, m,

3′-H_b and 3″-H_a), 5.42 (1H, m, 3″-H_b), 5.97 (1H, m, 2′-H), 6.07 (1H, m, 2″-H), 6.23 (1H, t, $J = 2.3$ Hz, 2-H), 6.26 (1H, dd, $J = 8.0$ and 2.2 Hz, 6-H), 6.31 (1H, dd, $J = 8.1$ and 2.3 Hz, 4-H), and 7.08 (1H, t, $J = 8.1$ Hz, Hz, 5-H); δ_C/ppm (100 MHz; $CDCl_3$) 46.5 (C-1′), 68.6 (C-1″), 99.7 (C-2), 103.4 (C-4), 106.3 (C-6), 116.1 (C-3′), 117.3 (C-3″), 129.8 (C-5), 133.5 (C-2″), 135.3 (C-2′), 149.4 (C-1), and 159.8 (C-3).

N,N-Diallyl-3-(hydroxy)aniline **9**

Dark brown oil (830 mg, 16%) (found: $\mathbf{M}^+$ 189.114166, $C_{12}H_{15}NO$ requires *M* 189.115364); ν_{max} (thin film/cm^{-1}) 3363 (NH); δ_H/ppm (400 MHz; $CDCl_3$) 3.89 (4H, m, 1′-CH_2 and 1″-CH_2), 5.18 (4H, m, 3′-CH_2 and 3″-CH_2), 5.85 (2H, m, 2′-H and 2″-H), 6.19 (1H, m, 6-H), 6.22 (1H, s, 2-H), 6.32 (1H, m, 4-H), and 7.06 (1H, t, $J = 8.1$ Hz, 5-H); δ_C/ppm (100 MHz; $CDCl_3$) 52.7 (C-1′ and C-1″), 99.6 (C-2), 103.5 (C-6), 105.3 (C-4), 116.0 (C-3′ and C-3″), 129.9 (C-5), 133.8 (C-2′ and C-2″), 150.2 (C-1) and 156.4 (C-3).

3-(Acrylamido)phenyl acrylate 10 and *N*-(3-hydroxyphenyl)acrylamide 11

NaH (60% dispersion in mineral oil; 0.11 g, 4.6 mmol) was added in small portions to a stirred solution of 3-aminophenol **6a** (0.50 mg, 4.6 mmol) in dry THF (15 mL) under nitrogen to permit controlled evolution of hydrogen. Acryloyl chloride (0.37 mL, 4.6 mmol) was then added through a septum, and the resulting solution was refluxed for ca. 6 h. The reaction was quenched by the addition of water (20 mL). The organic solvent was evaporated in vacuo, and the aqueous residue was extracted with EtOAc (2×40 mL). The combined organic extracts were washed sequentially with water (2×80 mL) and brine (2×80 mL). The aqueous washings were extracted with EtOAc, and the organic layers were combined and dried (anhydr. $MgSO_4$). Preparative-layer chromatography [on silica gel; elution with hexane–EtOAc (4:6)] afforded two fractions.

N-(3-Hydroxyphenyl)acrylamide **11**

Yellow oil (5.4 mg, 0.72%) (found: $\mathbf{M}^+$ 163.076095; $C_9H_9NO_2$ requires *M* 163.063329); ν_{max} (thin film/cm^{-1}) 3419 (OH) and 1667 (C=O); δ_H/ppm (400 MHz; $CDCl_3$) 6.01 (1H, d, $J = 10.5$ Hz, 3′-H_a), 6.30 (1H, dd, $J = 17.3$ and 10.5 Hz, 2′-H), 6.60 (1H, d, $J = 17.3$ Hz, 3′-H_b), 6.89 (1H, d, $J = 7.0$ Hz), 7.34 (2H, m, 5-H and 6-H) and 7.50 (1H, s, 2-H); δ_C/ppm

(150 MHz; $CDCl_3$) 113.5 (C-2), 117.1 (C-6), 17.6 (C-4), 127.8 (C-2′), 129.7 (C-5), 132.9 (C-3′), 138.5 (C-1), 150.9 (C-3) 164.6 and 167.7 (C=O).

3-(Acrylamido)phenyl acrylate **10**

Yellow oil (12 mg, 1.2%) (found: $\mathbf{M}^+$ 217.072324; $C_{12}H_{11}NO_3$ requires *M* 217.073893); ν_{max} (thin film/cm^{-1}) 1731 (OC=O) and 1663 (NHC=O); δ_H/ppm (400 MHz; $CDCl_3$) 5.70 (1H, d, $J = 10.2$ Hz, 3″-H_a), 6.03 (1H, d, $J = 10.4$ Hz, 3′-H_a), 6.16 (1H, dd, $J = 16.8$ and 10.3 Hz, 2″-H), 6.32 (2H, m, 2′-H and 3″-H_b), 6.60 (1H, d, $J = 17.3$ Hz, 3′-H_b), 6.82 (1H, d, $J = 7.09$ Hz, 6-H), 7.24 (2H, m, 4-H and 5-H), 7.58 (1H, s, 2-H) and 7.95 (1H, s, NH); δ_C/ppm (100 MHz; $CDCl_3$) 113.5 (C-2), 117.2 (C-4), 117.3 (C-6), 127.7 (C-2′), 127.9 (C-3″), 129.6 (C-5), 130.9 (C-1), 133.1 (C-3′), 139.1 (C-3), 150.7 (C-1), 163.7 (OC=O), and 165.0 (NHC=O).

2-Acetoxy-*N*-(3-hydroxyphenyl)acetamide 12

To permit controlled evolution of hydrogen NaH (60% dispersion in mineral oil; 60 mg, 2.5 mmol) was added in small portions to a stirred solution of 3-aminophenol **6a** (150 mg, 1.4 mmol) in dry THF (10 mL) under nitrogen at 0°C. Acetoxyacetyl chloride (160 μL, 2.5 mmol) was then added through a septum, and the resulting solution was refluxed for ca. 5 h. The reaction was quenched by the addition of water (20 mL). The organic solvent was evaporated in vacuo, and the aqueous residue was extracted with EtOAc (2×40 mL). The combined organic extracts were washed sequentially with water (2×80 mL) and brine (2×80 mL). The aqueous washings were extracted with EtOAc, and the organic layers were combined and dried (anhydr. $MgSO_4$). Evaporation of the solvent in vacuo and chromatography of the residue [flash chromatography on silica; elution with EtOH–$CHCl_3$–hexane (0.5:1.5:2.5)] afforded *2*-acetoxy-*N*-(3-hydroxyphenyl)acetamide **12** as a grey powder (70 mg, 24%), mp 154–156°C (found: $\mathbf{M}^+$ 209.068446; $C_{10}H_{11}NO_4$ requires *M* 209.068808); ν_{max} (solid deposit/cm^{-1}) 3424 (OH), 1734 (CH_3C=O) and 1678 (NHC=O); δ_H/ppm (400 MHz; DMSO-d_6) 2.11 (3H, s, CH_3), 4.61 (2H, s, CH_2), 6.46 (1H, dd, $J = 7.9$ and 2.2 Hz, 6′-H), 6.93 (1H, d, $J = 8.3$ Hz, 4′-H), 7.07 (1H, t, $J = 8.06$ Hz, Hz, 5′-H), 7.13 (1H, t, $J = 2.0$ Hz, 2′-H), 9.39 (1H, br s, OH) and 9.92 (1H, s, NH); δ_C/ppm (100 MHz; DMSO-d_6) 20.4 (CH_3), 62.5 (CH_2), 106.3 (C-2′), 109.9 (C-4′), 110.5 (C-6′), 129.3 (C-5′), 139.3 (C-1′), 157.5 (C-3′), 165.2 (NHC=O) and 169.9 (CH_3C=O).

2,3,4,5,6-Pentaacetyl-*N*-(3-hydroxyphenyl)-D-gluconamide 13

NaH (60% dispersion in mineral oil; 0.041 g, 0.92 mmol) was added in small portions to a solution of 3-aminophenol **6a** (0.10 g, 0.92 mmol) in pyridine (2 mL) to permit controlled evolution of hydrogen. 2,3,4,5,6-Pentaacetyl-D-gluconoyl chloride[23] (0.40 g, 0.92 mmol) was then added, and the reaction mixture was stirred at room temperature for ca. 2.5 days. The solvent was evaporated in vacuo, and the residue was dissolved in EtOAc (30 mL). This solution was washed with water (2×30 mL) and brine (2×30 mL). The organic layer was then dried (anhydr. $MgSO_4$), and the solvent was evaporated in vacuo to afford a reddish brown oil. Flash chromatography [on silica gel; elution with hexane–EtOAc (4:6)] afforded 2,3,4,5,6-pentaacetyl-*N*-(3-hydroxyphenyl)-D-gluconamide **13** as a reddish brown oil (93 mg, 20%) (found: $\mathbf{M}^+$ 497.15132; $C_{22}H_{27}NO_{12}$ requires M 497.45019); ν_{max} (solid deposit/cm^{-1}) 3427 (OH), 1740 ($CH_3C{=}O$) and 1605 (NHC=O); δ_H/ppm (400 MHz; $CDCl_3$) 2.06 (12H, series of singlets, $4 \times CO.CH_3$), 2.22 (3H, s, 6-$OCO.CH_3$), 4.12 (1H, dd, $J = 12.4$ and 5.5 Hz, 6-H_a), 4.34 (1H, dd, $J = 12.4$ and 3.3 Hz, 6-H_b), 5.06 (1H, dt, $J = 5.9$ and 3.4 Hz, 5-H), 5.34 (1H, d, $J = 5.4$ Hz, 2-H), 5.47 (1H, dd, $J = 6.5$ and 4.7 Hz, 4-H), 5.70 (1H, t, $J = 5.0$ Hz, 3-H), 6.63 (1H, dd, $J = 8.1$ and 2.0 Hz, 4′-H), 6.81 (1H, dd, $J = 8.0$ and 1.1 Hz, 6′-H), 7.13 (1H, t, $J = 8.1$ Hz, 5′-H), 7.33 (1H, s, 2′-H) and 8.10 (1H, s, NH); δ_C/ppm (100 MHz; $CDCl_3$) 20.4, 20.6, 20.66, and 20.72 ($5 \times CO.CH_3$), 61.7 (C-6), 68.9 (C-3), 69.0 (C-5), 69.2 (C-4), 71.8 (C-2), 107.4 (C-2′), 111.6 (C-6′), 112.4 (C-4′), 130.0 (C-5′), 137.6 (C-3′), 156.9 (C-1′), 164.6 (NHC=O), 169.6, 169.9, 170.0, 170.3, and 170.9 ($5 \times C{=}O$); $m/z = 496$ (M − 1, 28%) and 412 (100).

2-Chloro-*N*-(3-hydroxyphenyl)acetamide 14a

NaH (60% dispersion in mineral oil; 1.2 g, 50 mmol) was added in small portions to a stirred solution of 3-aminophenol **6a** (3.0 g, 28 mmol) in THF (30 mL) under nitrogen to permit controlled evolution of hydrogen. Chloroacetyl chloride (2.2 mL, 28 mmol) was then added through a septum, and the resulting solution was stirred for ca. 6 h. The solvent was evaporated in vacuo, and the residue was dissolved in EtOAc (2×50 mL). The organic extract was washed sequentially with satd. aq. $NaHCO_3$ (2×100 mL), water (2×100 mL), and brine (2×100 mL). The aqueous washings were extracted with EtOAc, and the combined organic solutions were dried (anhydr. $MgSO_4$). Evaporation of the solvent in vacuo afforded 2-chloro-*N*-(3-hydroxyphenyl)acetamide **14a** as a grey solid (3.9 g, 76%), mp 119–120°C (lit.[16] 134.5–136°C); ν_{max} (solid

deposit/cm^{-1}) 3360 (OH) and 1642 (C=O); δ_H/ppm (400 MHz; DMSO-d_6) 4.22 (2H, s, CH_2), 6.48 (1H, dd, $J = 8.0$ and 2.0 Hz, 6′-H), 6.94 (1H, d, $J = 8.5$ Hz, 4′-H), 7.09 (1H, t, $J = 8.1$ Hz, 5′-H), 7.17 (1H, t, $J = 2.0$ Hz, 2′-H), 9.48 (1H, s, OH) and 10.18 (1H, s, NH); δ_C/ppm (100 MHz; DMSO-d_6) 43.6 (CH_2), 106.3 (C-2′), 110.0 (C-6′), 110.9 (C-4′), 129.5 (C-5′), 139.5 (C-1′), 157.6 (C-3′), and 164.4 (C=O).

Diethyl [*N*-(3-hydroxyphenyl)carbamoyl]methylphosphonate 15a

Triethyl phosphite (2.6 mL, 15 mmol) was added through a septum to 2-chloro-*N*-(3-hydroxyphenyl)acetamide **14a** (500 mg, 30 mmol) in an oven-dried, round-bottomed flask, equipped with a reflux condenser under nitrogen. The resulting mixture was refluxed for ca. 9 h during which time the reaction was monitored by thin-layer chromatography (TLC). The cooled mixture was then stirred with hexane (20 mL) for ca. 10 min followed by decantation of the hexane layer to remove the excess phosphite; this was repeated twice. Evaporation of the solvent in vacuo afforded diethyl [*N*-(3-hydroxyphenyl)carbamoyl]methylphosphonate **15a** as white crystals (370 mg, 48%), mp 115–117°C (found: $\mathbf{M}^+$ 287.093363; $C_{12}H_{18}NO_5P$ requires *M* 287.092261); ν_{max} (solid deposit/cm^{-1}) 3263 (OH), 1667 (C=O), and 1230 (P=O); δ_H/ppm (400 MHz; $CDCl_3$) 1.32 (6H, t, $J = 6.8$ Hz, $2 \times CH_3$), 3.05 (2H, d, $J_{P-H} = 21.1$ Hz, 1-CH_2), 4.17 (4H, m, $2 \times CH_3CH_2$), 6.60 (1H, d, $J = 8.0$ Hz, 4′-H), 6.80 (1H, d, $J = 7.9$ Hz, 6′-H), 7.09 (1H, t, $J = 8.0$ Hz, 5′-H), 7.46 (1H, s, 2′-H), 7.99 (1H, s, OH) and 8.96 (1H, s, NH); δ_C (100 MHz; $CDCl_3$) 16.3 (d, $J_{P-C} = 6.0$ Hz, $2 \times CH_3$), 36.4 (d, $J_{P-C} = 130.4$ Hz, 1-CH_2), 63.3 (d, $J_{P-C} = 6.6$ Hz, $2 \times CH_3CH_2$), 107.3 (C-2′), 111.1 (C-6′), 112.1 (C-4′), 129.8 (C-5′), 138.5 (C-1′), 157.3 (C-3′) and 162.7 (d, $J_{P-C} = 4.1$ Hz, C=O); δ_P/ppm (162 MHz; $CDCl_3$) 24.2 (P=O).

Other Analytical Data

Diethyl [*N*-(3-bromophenyl)carbamoyl]methylphosphonate **15c**

Yellowish-brown solid (0.25 g, 62%), mp 73–75°C; υ_{max} (solid deposit/cm^{-1}) 1683 (C=O) and 1238 (P=O); δ_H/ppm (400 MHz; $CDCl_3$) 1.34 (6H, t, $J = 6.8$ Hz, $2 \times CH_3$), 1.64 (1H, s, OH) 3.01 (2H, d, $J_{P-H} = 20.4$ Hz, Hz, 1-CH_2), 4.17 (4H, m, $2 \times CH_3CH_2$), 6.63 (1H, d, $J = 8.4$ Hz, 4′-H), 7.01 (1H, d, $J = 8.0$ Hz, 6′-H), 7.18 (1H, t, $J = 8.0$ Hz, 5′-H), 7.23 (1H, s, 2′-H), and 8.83 (1H, s, NH); δ_C (100 MHz; $CDCl_3$) 16.3 (d, $J_{P-C} = 5.7$ Hz, $2 \times CH_3$), 35.6 (d, $J_{P-C} = 129.1$ Hz, 1-CH_2), 63.0 (d, $J_{P-C} = 6.6$ Hz,

$2 \times CH_3CH_2$), 112.4 (C-2′), 117.8 (C-6′), 122.3 (C-4′), 126.8 (C-5′), 129.8 (C-1′), 139.2 (C-3′) and 162.2 (d, $J_{P-C} = 4.4$ Hz, C=O).

Diethyl [*N*-(3-fluorophenyl)carbamoyl]methylphosphonate **15d**

Brown solid (0.26 g, 56%), mp 83–85°C (found: $\mathbf{M}^+$ 289.086707. $C_{12}H_{17}FNO_4P$ requires *M* 289.239842); υ_{max} (solid deposit/cm^{-1}) 1680 (C=O) and 1228 (P=O); δ_H/ppm (400 MHz; $CDCl_3$) 1.35 (6H, t, $J = 7.2$ Hz, $2 \times CH_3$), 1.65 (1H, s, OH) 3.04 (2H, d, $J_{P-H} = 20.8$ Hz, 1-CH_2), 4.17 (4H, m, $2 \times CH_3CH_2$), 6.73 (1H, t, $J = 8.0$ Hz, 4′-H), 7.09 (1H, d, $J = 8.4$ Hz, 6′-H), 7.16 (1H, t, $J = 6.4$ Hz, 5′-H), 7.44 (1H, d, $J = 11.2$ Hz, 2′-H), and 9.23 (1H, s, NH); δ_C (100 MHz; $CDCl_3$) 16.3 (d, $J_{P-C} = 6.0$ Hz, $2 \times CH_3$), 35.5 (d, $J_{P-C} = 127$ Hz, 1-CH_2), 63.0 (d, $J_{P-C} = 6.5$ Hz, $2 \times CH_3CH_2$), 107.0 (C-2′), 111.0 (C-6′), 114.9 (C-4′), 129.8 (C-5′), (C-1′), 162.1 (C-3′), and 164.0 (C=O).

Diethyl [*N*-(3-cyanophenyl)carbamoyl]methylphosphonate **15e**

Yellowish-brown solid (0.21 g, 48%), mp 83–85°C (found: $\mathbf{M}^+$ 296.090709; $C_{13}H_{17}N_2O_4P$ requires *M* 296.258840); υ_{max} (solid deposit/cm^{-1}) 1686 (C=O) and 1217 (P=O); δ_H/ppm (400 MHz; $CDCl_3$) 1.37 (6H, t, $J = 7.2$ Hz, $2 \times CH_3$), 3.01 (2H, d, $J_{P-H} = 20.8$ Hz, 1-CH_2), 4.19 (4H, q, $J = 7.6$ Hz, $2 \times CH_3CH_2$), 7.30 (2H, d, $J = 5.6$ Hz, 4′-H and 6′-H), 7.59 (1H, m, 5′-H), 7.93 (1H, s, 2′-H), and 9.50 (1H, s, NH); δ_C (100 MHz; $CDCl_3$) 16.3 (d, $J_{P-C} = 6.0$ Hz, $2 \times CH_3$), 36.9 (d, $J_{P-C} = 129.3$ Hz, , 1-CH_2), 63.3 (d, $J_{P-C} = 7.2$ Hz, $2 \times CH_3CH_2$), 112.6 (C≡N), 118.4 (C-1′), 122.4 (C-2′), 123.2 (C-6′), 127.2 (C-4′), 129.4 (C-5′), 138.8 (C-3′) and 162.5 (C=O).

Diethyl [*N*-(3-nitrophenyl)carbamoyl]methylphosphonate **15f**

Dark brown oil (0.42 g, 72%) (found: $\mathbf{M}^+$ 316.082395; $C_{12}H_{17}N_2O_6P$ requires *M*, 316.247489); υ_{max} (thin film/cm^{-1}) 1684 (C=O) and 1262 (P=O); δ_H/ppm (400 MHz; $CDCl_3$) 1.36 (6H, t, $J = 7.2$ Hz, $2 \times CH_3$), 3.06 (2H, d, $J_{P-H} = 21.2$ Hz, 1-CH_2), 4.20 (4H, q, $J = 7.6$ Hz, $2 \times CH_3CH_2$), 7.29 (1H, t, $J = 8.4$ Hz, 5′-H), 7.85 (1H, m, 4′-H and 6′-H), 8.29 (1H, s, 2′-H), and 9.87 (1H, s, NH); δ_C (100 MHz; $CDCl_3$) 16.3 (d, $J_{P-C} = 6.2$ Hz, $2 \times CH_3$), 35.6 (d, $J_{P-C} = 128.2$ Hz, 1-CH_2), 63.6 (d, $J_{P-C} = 5.8$ Hz, $2 \times CH_3CH_2$), 114.1 (C-2′), 118.5 (C-6′), 124.8 (C-4′), 124.9 (C-5′), 129.5 (C-1′), 139.1 (C-3′), and 162.6 (C=O).

Diethyl {*N*-[3-(hydroxymethyl)phenyl]carbamoyl}methylphosphonate **15g**

Yellow oil (0.29 g, 65%) (found: $\mathbf{M}^+$ 301.108030; $C_{13}H_{20}NO_5P$ requires *M* 301.275361); υ_{max} (solid deposit/cm^{-1}) 3274 (OH), 1684 (C=O), and 1376 (P=O); δ_H/ppm (400 MHz; $CDCl_3$) 1.35 (6H, t, $J = 6.8$ Hz, $2 \times CH_3$), 2.03 (1H, s, OH), 3.01 (2H, d, $J_{P-H} = 21.2$ Hz, 1-CH_2), 4.18 (4H, q, $J = 7.2$ Hz, $2 \times CH_3CH_2$), 4.59 (2H, s, 7-CH_2OH), 7.00 (1H, d, $J = 7.6$ Hz, 4′-H), 7.20 (1H, t, $J = 8.0$ Hz, 5′-H), 7.42 (1H, s, 2′-H), 7.45 (1H, d, 8.0 Hz, 6′-H), and 9.20 (1H, s, NH); δ_C (100 MHz; $CDCl_3$), 16.3 (d, $J_{P-C} = 5.8$ Hz, $2 \times CH_3$), 36.7 (d, $J_{P-C} = 128.4$ Hz, 1-CH_2), 63.0 (d, $J_{P-C} = 7.2$ Hz, $2 \times CH_3CH_2$), 64.7 (C-7), 118.1 (C-2′), 118.7 (C-6′), 122.6 (C-4′), 128.9 (C-5′), 138.0 (C-1′), 141.9 (C-3′), and 163.5 (C=O).

ACKNOWLEDGMENTS

The authors thank the Medical Research Council of South Africa, the Innovation Fund Programme of the South African Department of Science and Technology, and Rhodes University for generous financial support.

REFERENCES

1. Beers, M. H.; Berkow, R. *The Merck Manual of Diagnosis and Therapy,* 7th ed.; Merck & Co., Inc.: Whitehouse Station, NJ, 1999; p. 1193; (b) Kim, J. Y.; Shakow, A.; Mate, K.; Vanderwarker, C.; Gupta, R.; Farmer, P. Limited good and limited vision: Multidrug-resistant tuberculosis and global health policy. *Soc. Sci. Med.* **2005**, *61* (4), 847–859.
2. Raynaud, C.; Etienne, G.; Peyron, P.; Lanéelle, M.; Daffé, M. Extracellular enzyme activities potentially involved in the pathogenicity of *Mycobacterium tuberculosis*. *Microbiology* **1998**, *144*, 577–587.
3. Harth, G.; Horwitz, M. A. Expression and efficient export of enzymically active *Mycobacterium tuberculosis* glutamine synthetase in *Mycobacterium smegmatis* and evidence that the information for export is contained within the protein. *J. Biol. Chem.* **1997**, *272* (36), 22728–22735.
4. Harth, G.; Horwitz, M. A. J. 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. *Exp. Med.* **1999**, *189* (9), 1425–1435.
5. Harth, G.; Clemens, D. L.; Horwitz, M. A. Glutamine synthetase of *Mycobacterium tuberculosis*: Extracellular release and characterization of its enzymic activity. *Proc. Natl. Acad. Sci. USA* **1994**, *91* (20), 9342–9346.
6. Hirschfield, G. R.; McNeil, M.; Brennan, P. J. Peptidoglycan-associated polypeptides of *Mycobacterium tuberculosis*. *J. Bacteriol.* **1990**, *172* (2), 1005–1013.

7. Eisenberg, D.; Gill, H. S.; Pfluegl, G. M. U.; Rotstein, S. H. Structure–function relationships of glutamine synthetases. *Biochim. Biophys. Acta.* **2000**, *1477* (1–2), 122–145.
8. Salisu, S. T. *ATP Mimics as Glutamine Synthetase Inhibitors—An Exploratory Synthetic Study* (PhD Thesis, Rhodes University, 2008).
9. Jomaa, H.; Wiesner, J.; Sanderbrand, S.; Altincicek, B.; Weidemeyer, C.; Hintz, M.; Turbachova, I.; Eberl, J.; Zeidler, J.; Lichtenthaler, H. K.; Soldati, D.; Beck, E. Inhibitors of the nonmevalonate pathway of isoprenoid biosynthesis as antimalarial drugs. *Science* **1999**, *285* (5433), 1573–1576.
10. Reichenberg, A.; Wiesner, J.; Weidemeyer, C.; Dreiseidler, E.; Sanderbrand, S.; Altincicek, B.; Beck, E.; Schlitzer, M.; Jomaa, H. Diaryl ester prodrugs of FR900098 with improved in vivo antimalarial activity. *Bioorg. Med. Chem. Lett.* **2001**, *11* (6), 833–835.
11. HOSE code prediction. http://www.modgraph.co.uk/product_nmr-HOSE.htm (accessed December 20, 2007).
12. Robins, M. J.; Hatfield, P. W. Nucleic acid related compounds, 38: Smooth and high-yield iodination and chlorination at C-5 of uracil bases and p-tolyl-protected nucleosides. *Can. J. Chem.* **1982**, *60* (5), 547–553.
13. Thomas, B. N.; Lindermann, C. M.; Corcoran, R. C.; Cotant, C. L.; Kirsch, J. E.; Persichini, P. J. Phosphonate lipid tubules II. *J. Am. Chem. Soc.* **2002**, *124* (7), 1227–1233.
14. Uhrin, D.; Prasad, A. V. K.; Brisson, J.; Bundle, D. R. Carbohydrate–antibody interactions by NMR for a ^{13}C-labeled disaccharide ligand. *Can. J. Chem.* **2002**, *80* (8), 904–907.
15. Jacobs, W. A.; Heidelberger, M. The quaternary salts of hexamethylenetetramine, III: Monohalogenacylated aromatic amines and their hexamethylenetetraminium (hexamethylenetetrammonium) salts. *J. Bio. Chem.* **1915**, *21*, 103–143.
16. Matulenko, M. A.; Hakeem, A. A.; Kolasa, T.; Nakane, M.; Terranova, M. A.; Uchic, M. E.; Miller, L. N.; Chang, R.; Donnelly-Roberts, D. L.; Namovic, M. T.; Moreland, R. B.; Brioni, J. D.; Stewart, A. O. Synthesis and functional activity of (2-aryl-1-piperazinyl)-N-(3-methylphenyl)acetamides: Selective dopamine D4 receptor agonists. *Bioorg. Med. Chem.* **2004**, *12* (13), 3471–3483.
17. Khanna, S.; Madan, M.; Vangoori, A.; Banerjee, R.; Thaimattam, R.; Basha, S. K. J. S.; Ramesh, M.; Casturi, S. R.; Pal, M. Evaluation of glycolamide esters of indomethacin as potential cyclooxygenase-2 (COX-2) inhibitors. *Bioorg. Med. Chem.* **2006**, *14* (14), 4820–4833.
18. Bhatia, P. A.; Daanen, J. F.; Hakeem, A. A.; Kolasa, T.; Matulenko, M. A.; Mortell, K. H.; Patel, M. V.; Stewart, A. O.; Wang, X.; Xia, Z.; Zhang, H. Q. Preparation of piperazinyl, piperidinyl, and related acetamides and benzamides as dopamine D4 receptor agonists useful in treating sexual dysfunction. U.S. Pat. Appl. Publ., US2004029887 A1 20040212, 2004. Cont.-in-part of U.S. Ser. No. 154,373.
19. Desai, A. D.; Chikhalia, K. H. Synthesis and studies of N-aryl-2-[4-(4-methyl-1-piperazinyl)anilino]acetamides. *E-J. Chem.* **2005**, *2* (6), 15–20.

20. Nakao, N.; Ohashi, K.; Ogihara, T.; Okano, A.; Matsumura, Y.; Nakano, T. Therapeutic agent for urinary incontinence. PCT Int. Appl., WO 2003063852 A1 20030807, 2003.
21. Ando, K.; Tsuji, E.; Ando, Y.; Kunitomo, J.-I.; Kobayashi, R.; Yokomizo, T.; Shimizu, T.; Yamashita, M.; Ohta, S.; Nabe, T.; Kohno, S.; Ohishi, Y. Synthesis of 2-, 4-, and 5-(2-alkylcarbamoyl-1-methylvinyl)-7-alkyloxybenzo[b]furans and their leukotriene B4 receptor antagonistic activity. *Org. Biomol. Chem.* **2005**, *3* (11), 2129–2139.
22. Braune, C. E.; Cook, C. D. 2,3,4,5,6-Penta-O-acetyl-D-gluconic acid and 2,3,4,5,6-penta-O-acetyl-d-gluconyl chloride. *Org. Synth.* **1961**, *41*, 79–82.