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Optically active sugar thioamides from δ-gluconolactone

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Abstract

This paper describes a facile and rapid approach to *N*-alkyl- and *N*-aryl-thiogluconamides employing δ-gluconolactone as starting material. The protocol involves a three-step sequence to afford the corresponding thioamides as crystalline substances in moderate to good yields. The Lawesson reagent was found to be the reagent of choice to accomplish the key transformation amide–thioamide.

1. Introduction

Carbohydrates represent the most ubiquitous source of chiral pool in nature and are therefore ideal precursors to access enantiomerically pure targets. Carbohydrate templates are available in a wide variety of chain lengths, cyclic and acyclic structures, and remarkably they are endowed with a plethora of stereochemical and conformational features which can be exploited in synthesis.[1] Moreover, methods for the transformation of sugar molecules into synthetically useful, yet chiral derivatives are likewise relevant.[1a,b] Recently, we have developed several syntheses of sugar thioamides,[2,3] which serve as suitable precursors of optically active heterocycles[4] and of other functional groups.[5–7] Traditional methods have been based on the reaction of glycosyl cyanides with hydrogen sulfide,[8] and more recently, on the condensation of aldonodithioates with heterocyclic amines[9] and reactions of aminosugars with dithiocarboxylic esters or *O*-ethyl thioformate.[10] These protocols have been applied to cyclic sugars, especially glycopyranosyl or ribopyranosyl derivatives to nucleosides and their analogs.

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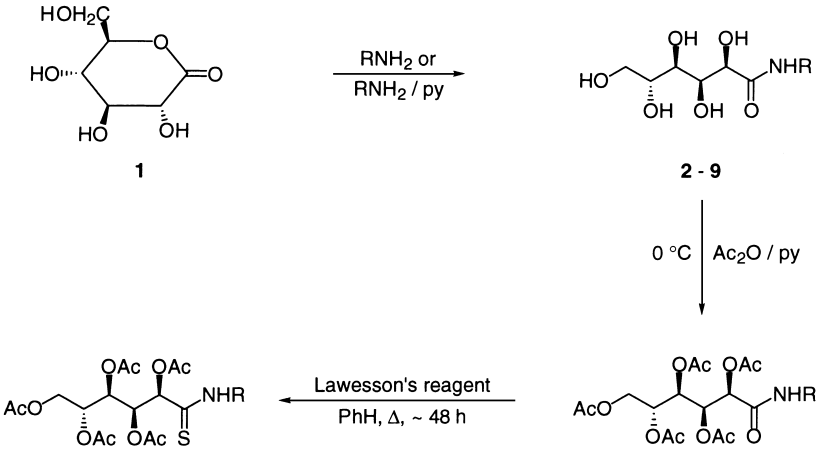
2. Results

2.1. Syntheses

Herein we describe a short synthesis of *O*-protected *N*-alkyl and *N*-arylthiogluconamides starting from δ-gluconolactone, which is an inexpensive and readily available monosaccharide derivative (Scheme 1).[11] It is known that aldonolactones undergo ring opening by aminolysis of the lactone group. However, the process has largely been restricted to reactions with ammonia, *N*,*N*-dialkylamines,[12] and long-chain primary amines in the search of emulsifying agents,[13,14] or liquid crystals.[15] Some gluconamides also exhibit biological activity.[16] We have extended the transformation to a series of alkyl and arylamines to yield the unprotected gluconamides in high yields. Reactions of δ-gluconolactone with aromatic amines (neat or in 50% pyridine–amine mixtures) were faster than those of alkyl derivatives, although they were essentially complete within 24 h in all cases. Conventional *O*-protection with acetic anhydride gave the acetylated sugars as crystalline solids in good yields. The apparently trivial transformation of converting the carbonyl group into a thiocarbonyl was difficult to carry out, as several reaction conditions gave only partial conversions. The thermal reaction of gluconamides with P_4S_{10} in benzene proceeded slowly. Reasoning that a major drawback arises from the heterogeneous character of the reaction mixture, we attempted to accelerate the mass transfer by ultrasonic irradiation in THF at 40°C, a strategy which proved to be successful for simple amides[17] and glycopyranosyl amides.[3] Nevertheless, reactions in an ultrasonic bath were unpractical, albeit they could be improved using a sonic probe (20 kHz, 600 W, ~50% conversion).



2, **10**, **18** R = CH_3
3, **11**, **19** R = C_2H_5
4, **12**, **20** R = *n*-C_3H_7
5, **13**, **21** R = *i*-C_3H_7
6, **14**, **22** R = *c*-C_6H_{11}
7, **15**, **23** R = C_6H_5
8, **16**, **24** R = 4-$CH_3OC_6H_4$
9, **17**, **25** R = 4-BrC_6H_4

Scheme 1.

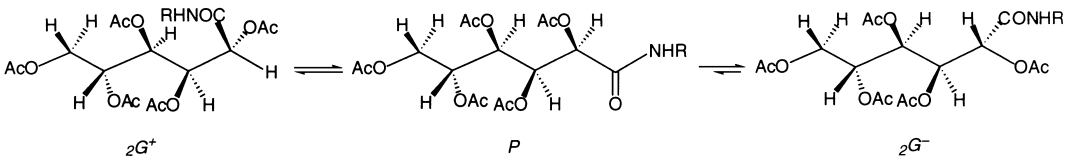
Next, we turned our attention to the Lawesson reagent, 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, one of the most efficient thiation reagents.[18,19] Reactions of the latter with the corresponding gluconamides in refluxing benzene for 24 h resulted in complete conversions as detected by TLC and NMR monitoring. The use of HMPA as solvent,[18a] instead of benzene, gave dark and complex reaction mixtures. These O/S-exchange reactions, mediated by the Lawesson reagent, can also be conducted under milder conditions using an ultrasonic bath (~35 kHz, THF, 40–50°C), although conversions were never greater than 50%. The fact that ultrasonic agitation is less efficient than conventional heating is also consistent with the ionic mechanism assumed for this transformation, since ionic processes are insensitive to the chemical role of ultrasound and only a physical component, in the case of heterogeneous processes, should be expected ('false sonochemistry').[20]

3. Discussion

3.1. Structural characterization

All compounds gave satisfactory combustion analyses with the sole exception of the thiogluconamide derivative **23**, which was obtained as an amorphous solid, but homogeneous by chromatography and NMR analyses. IR spectra of compounds **2**–**17** show the typical amide band at ~1650 cm^{-1},[21] which is absent in their thiogluconamide counterparts **18**–**25**. As expected, ring-opening of δ-gluconolactone does not modify the stereochemistry at C-2, and hence the sign of optical rotation is always positive, consistent with the fact that the configuration at the first stereogenic center (C-2) must be *R*.[22]

Compounds **2**–**17** show ^{13}C resonances at ~170 ppm, attributable to the amide carbonyl group, whereas thioamides **18**–**25** display the thiocarbonyl group at ~195 ppm. ^{1}H NMR spectra of gluconamides and their thioanalogs could fully be interpreted. In the case of per-*O*-acetylgluconamides, the chemical shifts of the acyclic side chain follow the order: H-3 > H-4 > H-2 > H-5 > H-6 > H-6′, while for the protected thiogluconamides the sequence of proton resonances is: H-3 > H-2 > H-4 > H-5 > H-6 > H-6′. The large chemical shift differences between amides and thioamides observed for H-2 ($\Delta\delta$ ~0.4 ppm) and for H-3 at a lesser extent ($\Delta\delta$ ~0.24 ppm), which can be attributed to the greater anisotropy exerted by the C=S group, are remarkable.[23] A further analysis of the coupling constants $J_{2,3}$, $J_{3,4}$, $J_{4,5}$, $J_{5,6}$ and $J_{5,6'}$ reveals that there is a conformational equilibrium for both the amides **10**–**17** and thioamides **18**–**25** in solution. Although the conformer $_2G^-$ should be prevalent,[24] the values of the apparent coupling constants $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ suggest a significant contribution of *P* and $_2G^+$ conformations, despite these arrangements being less stabilized owing to 1,3-interactions between the acetate groups (*P*) or between the *O*-acyl and the amide groups ($_2G^+$) at C-2 and C-4 (Scheme 2).



Scheme 2.

On the other hand, the close similarity for ^{13}C chemical shifts from C-2 to C-5 also support the existence of an acyclic structure.[25] For the protected amides **10**–**17**, ^{13}C resonances lie in the order: C-3 > C-2 > C-4 > C-5 > C-6, whereas the sequence for thioamides is C-2 > C-3 > C-4 > C-5 > C-6, again consistent with the enhanced anisotropy provided by a thioamide group.

In conclusion a concise synthesis of *N*-substituted thiogluconamides has been reported. It is hoped that these materials will be appropriate synthons in asymmetric reactions, and current efforts focus on this application.

4. Experimental

4.1. General methods

Melting points were determined with a Gallenkamp apparatus and are uncorrected. Optical rotations were measured at 20±5°C with a Perkin–Elmer 241 polarimeter. IR spectra were recorded on KBr pelletes with a Perkin–Elmer 399 spectrophotometer. TLC analyses were conducted on silica gel GF_{254} (Merck) using benzene–acetonitrile solvent mixtures (3:1, 5:1, and 10:1) as eluents, followed by detection with UV light or iodine vapor. Flash chromatography was performed on SiO_2 (Merck) using the method described by Still et al.[26] ^1H and ^{13}C NMR spectra were recorded with a Bruker AC 200-E or a Bruker 400 AC/PC spectrometer. Assignments were confirmed by ^1H–^1H COSY and ^1H–^{13}C heteronuclear techniques, and DEPT (Distortionless Enhanced Proton Transfer) experiments. Elemental microanalyses were determined on a Perkin–Elmer 240C analyzer.

4.2. N-*Alkyl(aryl)*-D-*gluconamides. General procedure*

A solution of **1** (5.0 g, 28.0 mmol) in a commercial solution of amine (0.3 mol) in the cases of methylamine (40% aqueous solution) and ethylamine, or in a 1:1 (v/v) amine–pyridine solution (40 mL, 0.3 mol) in the cases of *n*-propylamine, isopropylamine, cyclohexylamine, aniline, 4-methoxyaniline, and 4-bromoaniline, was kept at room temperature for 24 h. The solvent was evaporated and the residue was treated with ethanol and diethyl ether to afford the corresponding gluconamides as crystalline solids, which were further recrystallized from ethanol or 96% aqueous ethanol.

4.2.1. N-*Methyl*-D-*gluconamide* **2**

Yield: 96%, mp 158–160°C, $[\alpha]_D$ +29 (*c* 0.5, *N*,*N*-dimethylformamide); IR (KBr) ν_{max} 3300, 1635, 1560, 1270 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 7.67 (m, 1H, *N*-H), 4.62–3.36 (m, 11H), 2.61 (d, J = 4.7 Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 173.2 (C-1), 73.8, 72.5, 71.6, 70.3, 63.5 (C-6), 25.6 (CH_3). Anal. calcd for $C_7H_{15}NO_6$: C, 40.19; H, 7.23; N, 6.69. Found: C, 39.85; H, 7.42; N, 6.97.

4.2.2. N-*Ethyl*-D-*gluconamide* **3**

Yield: 93%, mp 138–140°C, $[\alpha]_D$ +26 (*c* 0.5, *N*,*N*-dimethylformamide); IR (KBr) ν_{max} 3300, 1665, 1550, 1310 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 7.67 (t, J = 5.6 Hz, 1H, *N*-H), 5.40–3.36 (m, 11H), 3.13 (m, 2H, CH_2), 1.02 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ

172.4 (C-1), 73.7, 72.5, 71.6, 70.2, 63.5 (C-6), 33.2 (CH_2), 15.0 (CH_3). Anal. calcd for $C_8H_{17}NO_6$: C, 43.04; H, 7.68; N, 6.27. Found: C, 43.20; H, 7.52; N, 6.10.

4.2.3. N-*Propyl-D-gluconamide* ***4***

Yield: 93%, mp 149–151°C, $[\alpha]_D$ +31 (*c* 0.5, *N*,*N*-dimethylformamide); IR (KBr) ν_{max} 3300, 1660, 1540, 1290 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 7.66 (t, $J=5.8$ Hz, 1H, *N*-H), 5.43–3.38 (m, 11H), 3.05 (q, $J=6.6$ Hz, 2H, *N*-CH_2), 1.43 (q, $J=7.3$ Hz, 3H, CH_2), 0.84 (t, $J=7.3$ Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 172.7 (C-1), 73.9, 72.7, 71.7, 70.3, 63.6 (C-6), 39.9 (*N*-CH_2), 22.3 (CH_2), 11.6 (CH_3). Anal. calcd for $C_9H_{19}NO_6$: C, 45.60; H, 8.07; N, 5.90. Found: C, 45.47; H, 8.22; N, 5.79.

4.2.4. N-*Isopropyl-D-gluconamide* ***5***

Yield: 97%, mp 179–181°C (dec.), $[\alpha]_D$ +24 (*c* 0.5, *N*,*N*-dimethylformamide); IR (KBr) ν_{max} 3300, 1640, 1565, 1320 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 7.33 (d, $J=8.2$ Hz, 1H, *N*-H), 5.37–3.37 (m, 11H), 3.89 (m, 1H, *N*-CH), 1.07 (d, $J=6.6$ Hz, 6H, CH_3), 0.84 (t, $J=7.3$ Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 171.6 (C-1), 73.6, 72.5, 71.6, 70.2, 63.5 (C-6), 40.3 (*N*-CH), 22.4 (2C, CH_3). Anal. calcd for $C_9H_{19}NO_6$: C, 45.60; H, 8.07; N, 5.90. Found: C, 45.45; H, 8.32; N, 5.93.

4.2.5. N-*Cyclohexyl-D-gluconamide* ***6***

Yield: 87%, mp 187–189°C, $[\alpha]_D$ +28 (*c* 0.5, *N*,*N*-dimethylformamide); IR (KBr) ν_{max} 3300, 1640, 1560 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 7.36 (d, $J=8.2$ Hz, 1H, *N*-H), 4.66–3.37 (m, 12H), 1.65–1.14 (m, 10H); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 171.6 (C-1), 73.7, 72.5, 71.5, 70.2, 63.5 (C-6), 47.3, 33.8, 32.4, 25.3, 24.8, 24.5. Anal. calcd for $C_{12}H_{23}NO_6$: C, 51.97; H, 8.36; N, 5.05. Found: C, 52.35; H, 8.08; N, 5.33.

4.2.6. N-*Phenyl-D-gluconamide* ***7***

Yield: 90%, mp 178–180°C, $[\alpha]_D$ +24 (*c* 0.5, *N*,*N*-dimethylformamide); IR (KBr) ν_{max} 3300, 1660, 1540, 1300 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 9.53 (s, 1H, *N*-H), 7.71–7.07 (m, 5H, Ph), 5.70–3.40 (m, 11H); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 171.7 (C-1), 138.6, 128.8 (2C), 123.6, 119.7 (2C), 74.4, 72.5, 71.7, 70.5, 63.5 (C-6). Anal. calcd for $C_{12}H_{17}NO_6$: C, 53.12; H, 6.31; N, 5.16. Found: C, 53.21; H, 6.57; N, 4.92.

4.2.7. N-*(4-Methoxyphenyl)-D-gluconamide* ***8***

Yield: 80%, mp 158–160°C (dec.), $[\alpha]_D$ +26 (*c* 0.5, *N*,*N*-dimethylformamide); IR (KBr) ν_{max} 3300, 1655, 1530, 1300 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 9.43 (s, 1H, *N*-H), 7.62–6.87 (m, 4H, Ph), 5.76–3.53 (m, 11H), 3.72 (s, 3H, OCH_3); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 171.1 (C-1), 155.3, 131.8, 121.1 (2C), 113.7 (2C), 74.2, 72.4, 71.6, 70.3, 63.4 (C-6), 55.2 (OCH_3). Anal. calcd for $C_{13}H_{19}NO_7$: C, 51.82; H, 6.35; N, 4.65. Found: C, 51.66; H, 6.17; N, 4.83.

4.2.8. N-*(4-Bromophenyl)-D-gluconamide* ***9***

Yield: 61%, mp 158–160°C (dec.), $[\alpha]_D$ +40 (*c* 0.5, pyridine); IR (KBr) ν_{max} 3300, 1650, 1520, 1350 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 9.71 (s, 1H, *N*-H), 7.72–7.48 (m, 4H, Ph), 4.74–3.36 (m, 11H); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 170.1 (C-1), 138.2, 132.1 (2C), 121.6 (2C), 115.2, 74.5, 72.4, 71.7, 70.5, 63.5 (C-6). Anal. calcd for $C_{12}H_{16}BrNO_6$: C, 41.16; H, 4.61; N, 4.00. Found: C, 41.02; H, 4.54; N, 4.00.

4.2.9. 2,3,4,5,6-Penta-O-*acetyl*-N-*alkyl(aryl)gluconamides. General procedure*

The unprotected aldonamides (3.0 g) were suspended in pyridine (10 mL), cooled at 0°C, acetic anhydride (10 mL) was added, and the mixtures were stirred for 24 h. Then the solutions were poured into ice-water, and the resulting solids were recrystallized from 96% ethanol.

4.2.10. 2,3,4,5,6-Penta-O-*acetyl*-N-*methyl-D-gluconamide* ***10***

Yield: 75% from **2**, mp 199–201°C, $[\alpha]_D$ +30 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3230, 1740, 1650, 1570, 1240 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.26 (m, 1H, *N*-H), 5.66 (t, $J=5.1$ Hz, 1H, H-3), 5.46 (dd, $J=5.1$ Hz, $J=6.5$ Hz, 1H, H-4), 5.31 (d, $J=5.1$ Hz, 1H, H-2), 5.06 (m, 1H, H-5), 4.32 (dd, $J=3.9$ Hz, $J=12.3$ Hz, 1H, H-6), 4.12 (dd, $J=5.7$ Hz, $J=12.3$ Hz, 1H, H-6′), 2.82 (d, $J=4.9$ Hz, 3H, *N*-CH_3), 2.20 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.06 (s, 3H, OAc); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.6 (CO, OAc), 169.8 (CO, OAc), 169.8 (CO, OAc), 169.6 (CO, OAc), 169.2 (CO, OAc), 166.6 (CO, amide), 71.4 (C-2), 69.2 (C-4), 69.0 (C-3), 68.6 (C-5), 61.5 (C-6), 26.1 (*N*-CH_3), 20.7 (OAc), 20.6 (OAc). Anal. calcd for $C_{17}H_{25}NO_{11}$: C, 48.68; H, 6.01; N, 3.34. Found: C, 48.69; H, 6.05; N, 3.33.

4.2.11. 2,3,4,5,6-Penta-O-*acetyl*-N-*ethyl-D-gluconamide* ***11***

Yield: 85% from **3**, mp 158–160°C, $[\alpha]_D$ +27 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3300, 1765, 1670, 1575, 1240 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.19 (t, $J=3.8$ Hz, 1H, *N*-H), 5.68 (t, $J=5.2$ Hz, 1H, H-3), 5.45 (dd, $J=5.1$ Hz, $J=6.3$ Hz, 1H, H-4), 5.30 (d, $J=5.2$ Hz, 1H, H-2), 5.04 (m, 1H, H-5), 4.32 (dd, $J=3.9$ Hz, $J=12.3$ Hz, 1H, H-6), 4.13 (dd, $J=5.5$ Hz, $J=12.3$ Hz, 1H, H-6′), 3.29 (m, 2H, *N*-CH_2), 2.21 (s, 3H, OAc), 2.12 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.13 (t, $J=7.2$ Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.5 (CO, OAc), 169.8 (2C, CO, OAc), 169.6 (CO, OAc), 169.1 (CO, OAc), 165.8 (CO, amide), 71.6 (C-2), 69.2 (C-4), 68.9 (C-3), 68.6 (C-5), 61.4 (C-6), 34.3 (*N*-CH_2), 20.7 (OAc), 20.6 (OAc), 20.3 (OAc), 14.5 (CH_3). Anal. calcd for $C_{18}H_{27}NO_{11}$: C, 49.88; H, 6.28; N, 3.23. Found: C, 49.99; H, 6.34; N, 3.23.

4.2.12. 2,3,4,5,6-Penta-O-*acetyl*-N-*propyl-D-gluconamide* ***12***

Yield: 72% from **4**, mp 130–132°C, $[\alpha]_D$ +25 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3280, 1755, 1665, 1575, 1240 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.42 (t, $J=5.5$ Hz, 1H, *N*-H), 5.69 (t, $J=5.0$ Hz, 1H, H-3), 5.46 (dd, $J=5.0$ Hz, $J=6.0$ Hz, 1H, H-4), 5.30 (d, $J=5.0$ Hz, 1H, H-2), 5.09 (m, 1H, H-5), 4.32 (dd, $J=3.8$ Hz, $J=12.2$ Hz, 1H, H-6), 4.13 (dd, $J=5.4$ Hz, $J=12.2$ Hz, 1H, H-6′), 3.23 (m, 2H, *N*-CH_2), 2.21 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.51 (q, $J=7.4$ Hz, 2H, CH_2), 0.91 (t, $J=7.4$ Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.3 (CO, OAc), 169.6 (CO, OAc), 169.5 (CO, OAc), 169.4 (CO, OAc), 168.9 (CO, OAc), 165.7 (CO, amide), 71.5 (C-2), 69.1 (C-4), 68.8 (C-3), 68.4 (C-5), 61.2 (C-6), 40.8 (*N*-CH_2), 20.4 (CH_2), 20.4 (OAc), 10.9 (CH_3). Anal. calcd for $C_{19}H_{29}NO_{11}$: C, 51.00; H, 6.53; N, 3.13. Found: C, 50.82; H, 6.57; N, 3.10.

4.2.13. 2,3,4,5,6-Penta-O-*acetyl*-N-*isopropyl-D-gluconamide* ***13***

Yield: 95% from **5**, mp 162–164°C, $[\alpha]_D$ +28 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3300, 1765, 1665, 1565, 1240 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.97 (d, $J=5.5$ Hz, 1H, *N*-H), 5.69 (t, $J=5.0$ Hz, 1H, H-3), 5.44 (dd, $J=5.0$ Hz, $J=6.0$ Hz, 1H, H-4), 5.26 (d, $J=5.0$ Hz, 1H, H-2), 5.03 (m, 1H, H-5), 4.32 (dd, $J=4.1$ Hz, $J=12.2$ Hz, 1H, H-6), 4.13 (dd, $J=5.4$ Hz, $J=12.2$ Hz, 1H, H-6′), 4.05 (m, 1H, *N*-CH), 2.21 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.06 (s, 3H,

OAc), 2.05 (s, 3H, OAc), 1.15 (d, $J=6.6$ Hz, 6H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.5 (CO, OAc), 169.7 (2C, CO, OAc), 169.5 (CO, OAc), 169.0 (CO, OAc), 164.9 (CO, amide), 71.7 (C-2), 69.2 (C-4), 68.9 (C-3), 68.6 (C-5), 61.3 (C-6), 41.4 (*N*-CH), 22.3 (CH_3), 22.2 (CH_3), 20.6 (OAc), 20.5 (OAc), 20.3 (OAc). Anal. calcd for $C_{19}H_{29}NO_{11}$: C, 51.00; H, 6.53; N, 3.13. Found: C, 50.72; H, 6.37; N, 3.11.

4.2.14. 2,3,4,5,6-Penta-O-*acetyl*-N-*cyclohexyl-D-gluconamide* ***14***

Yield: 83% from **6**, mp 166–168°C, $[\alpha]_D$ +27 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3400, 1770, 1690, 1550, 1240 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.98 (d, $J=7.9$ Hz, 1H, *N*-H), 5.69 (t, $J=5.2$ Hz, 1H, H-3), 5.44 (dd, $J=5.2$ Hz, $J=6.2$ Hz, 1H, H-4), 5.27 (d, $J=5.2$ Hz, 1H, H-2), 5.04 (m, 1H, H-5), 4.32 (dd, $J=4.2$ Hz, $J=12.2$ Hz, 1H, H-6), 4.13 (dd, $J=5.1$ Hz, $J=12.2$ Hz, 1H, H-6′), 3.75 (m, 1H, *N*-CH), 2.21 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.90–1.10 (m, 10H, cyclohexyl moiety); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.5 (CO, OAc), 169.8 (2C, CO, OAc), 169.6 (CO, OAc), 169.1 (CO, OAc), 164.9 (CO, amide), 71.8 (C-2), 69.3 (C-4), 69.0 (C-3), 68.5 (C-5), 61.3 (C-6), 48.2 (*N*-CH), 32.8, 32.6, 25.3, 24.6 (2C), 20.7 (OAc), 20.6 (OAc), 20.3 (OAc). Anal. calcd for $C_{22}H_{33}NO_{11}$: C, 54.20; H, 6.82; N, 2.87. Found: C, 54.22; H, 6.92; N, 2.74.

4.2.15. 2,3,4,5,6-Penta-O-*acetyl*-N-*phenyl-D-gluconamide* ***15***

Yield: 95% from **7**, mp 168–170°C, $[\alpha]_D$ +40 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3280, 1750, 1675, 1550, 1230 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.40 (s, 1H, *N*-H), 7.49–7.09 (m, 5H, phenyl), 5.73 (t, $J=5.0$ Hz, 1H, H-3), 5.52 (dd, $J=5.0$ Hz, $J=6.5$ Hz, 1H, H-4), 5.37 (d, $J=5.0$ Hz, 1H, H-2), 5.09 (m, 1H, H-5), 4.31 (dd, $J=3.4$ Hz, $J=12.4$ Hz, 1H, H-6), 4.11 (dd, $J=5.5$ Hz, $J=12.4$ Hz, 1H, H-6′), 2.14 (s, 3H, OAc), 2.03 (s, 12H, OAc); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.3 (CO, OAc), 169.6 (CO, OAc), 169.5 (CO, OAc), 169.5 (CO, OAc), 169.0 (CO, OAc), 164.1 (CO, amide), 136.5, 128.6 (2C), 124.5, 120.0 (2C), 71 (C-2), 68.6 (C-4), 68.4 (C-3), 68.3 (C-5), 61.2 (C-6), 20.3 (OAc), 20.2 (OAc), 20.1 (OAc), 20.0 (OAc). Anal. calcd for $C_{22}H_{27}NO_{11}$: C, 54.88; H, 5.65; N, 2.91. Found: C, 54.83; H, 5.67; N, 2.91.

4.2.16. 2,3,4,5,6-Penta-O-*acetyl*-N-*(4-methoxyphenyl)-D-gluconamide* ***16***

Yield: 83% from **8**, mp 171–173°C, $[\alpha]_D$ +40 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3260, 1740, 1665, 1540, 1220 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.98 (s, 1H, *N*-H), 7.37–6.48 (m, 4H, phenyl), 5.73 (t, $J=5.5$ Hz, 1H, H-3), 5.50 (dd, $J=5.5$ Hz, $J=6.7$ Hz, 1H, H-4), 5.36 (d, $J=5.5$ Hz, 1H, H-2), 5.08 (m, 1H, H-5), 4.32 (dd, $J=3.7$ Hz, $J=12.3$ Hz, 1H, H-6), 4.13 (dd, $J=5.3$ Hz, $J=12.3$ Hz, 1H, H-6′), 3.75 (s, 3H, OCH_3), 2.23 (s, 3H, OAc), 2.16 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.06 (s, 3H, OAc); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.6 (CO, OAc), 170.1 (CO, OAc), 169.8 (CO, OAc), 169.6 (CO, OAc), 169.2 (CO, OAc), 163.9 (CO, amide), 156.8, 129.61 (2C), 121.9 (2C), 114.0, 71.7 (C-2), 69.0 (C-4), 68.8 (C-3), 68.6 (C-5), 61.4 (C-6), 55.3 (OCH_3), 20.8 (OAc), 20.5 (OAc), 20.3 (OAc). Anal. calcd for $C_{23}H_{29}NO_{12}$: C, 54.01; H, 5.71; N, 2.74. Found: C, 54.29; H, 5.77; N, 2.74.

4.2.17. 2,3,4,5,6-Penta-O-*acetyl*-N-*(4-bromophenyl)-D-gluconamide* ***17***

Yield: 80% from **9**, mp 140–141°C, $[\alpha]_D$ +37 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3360, 1740, 1680, 1540, 1220 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H, *N*-H), 7.45–7.39 (m, 4H, phenyl), 5.73 (dd, $J=5.7$ Hz, $J=4.5$ Hz, 1H, H-3), 5.48 (dd, $J=4.5$ Hz, $J=6.6$ Hz, 1H, H-4), 5.33 (d, $J=5.7$ Hz, 1H, H-2), 5.07 (m, 1H, H-5), 4.35 (dd, $J=3.4$ Hz, $J=12.4$ Hz, 1H, H-6), 4.15 (dd,

$J = 5.2$ Hz, $J = 12.4$ Hz, 1H, H-6′), 2.25 (s, 3H, OAc), 2.11 (s, 6H, OAc), 2.08 (s, 6H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (CO, OAc), 170.2 (CO, OAc), 169.9 (2C, CO, OAc), 169.3 (CO, OAc), 164.2 (CO, amide), 135.8, 132.0 (2C), 121.6 (2C), 117.7, 77.3 (C-2), 71.6 (C-3), 69.0 (C-4), 68.7 (C-5), 61.6 (C-6), 20.7 (OAc), 20.6 (OAc), 20.4 (OAc). Anal. calcd for $C_{22}H_{26}BrNO_{11}$: C, 47.12; H, 4.77; N, 2.50. Found: C, 47.28; H, 4.65; N, 2.65.

*4.3. 2,3,4,5,6-Penta-*O*-acetyl-*N*-alkyl(aryl)thiogluconamides. General procedure*

To a solution of the per-*O*-acylated gluconamide (6.7 mmol) in anhydrous benzene (40 mL) was added the Lawesson reagent (3.0 g, 7.4 mmol). The mixture was refluxed for 24 h and then the solvent was evaporated. The resulting residue was extracted with diethyl ether and the combined organic extracts were concentrated until a final volume of 25–30 mL. The resulting thiogluconamide was purified by flash chromatography and/or crystallized on cooling. Analytical samples were obtained by recrystallization from 96% aqueous ethanol.

*4.3.1. 2,3,4,5,6-Penta-*O*-acetyl-*N*-methyl-D-thiogluconamide* ***18***

Yield: 72% yield from **10**, mp 141–142°C, $[\alpha]_D$ +63 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3280, 1750, 1560, 1240 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.23 (m, 1H, *N*-H), 5.90 (dd, $J = 4.2$ Hz, $J = 5.6$ Hz, 1H, H-3), 5.71 (d, $J = 4.2$ Hz, 1H, H-2), 5.44 (t, $J = 5.6$ Hz, 1H, H-4), 5.04 (m, 1H, H-5), 4.33 (dd, $J = 4.7$ Hz, $J = 12.1$ Hz, 1H, H-6), 4.15 (dd, $J = 5.6$ Hz, $J = 12.1$ Hz, 1H, H-6′), 3.15 (d, $J = 4.8$ Hz, 3H, *N*-CH_3), 2.24 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 195.3 (C=S), 170.5 (CO, OAc), 169.7 (CO, OAc), 169.6 (CO, OAc), 169.2 (CO, OAc), 168.9 (CO, OAc), 77.0 (C-2), 70.8 (C-3), 69.3 (C-4), 68.7 (C-5), 61.0 (C-6), 32.1 (*N*-CH_3), 20.7 (OAc), 20.5 (OAc). Anal. calcd for $C_{17}H_{25}NO_{10}S$: C, 46.89; H, 5.78; N, 3.22. Found: C, 46.86; H, 5.81; N, 3.22.

*4.3.2. 2,3,4,5,6-Penta-*O*-acetyl-*N*-ethyl-D-thiogluconamide* ***19***

Yield: 80% from **11**, mp 118–120°C, $[\alpha]_D$ +55 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3260, 1765, 1545, 1240 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.09 (m, 1H, *N*-H), 5.90 (dd, $J = 4.2$ Hz, $J = 5.7$ Hz, 1H, H-3), 5.66 (d, $J = 4.2$ Hz, 1H, H-2), 5.42 (t, $J = 5.7$ Hz, 1H, H-4), 5.03 (m, 1H, H-5), 4.33 (dd, $J = 4.6$ Hz, $J = 12.1$ Hz, 1H, H-6), 4.16 (dd, $J = 5.5$ Hz, $J = 12.1$ Hz, 1H, H-6′), 3.68 (m, 2H, *N*-CH_2), 2.24 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.04 (s, 3H, OAc), 1.25 (t, $J = 5.2$ Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 194.2 (C=S), 170.5 (CO, OAc), 169.7 (CO, OAc), 169.7 (CO, OAc), 169.2 (CO, OAc), 168.9 (CO, OAc), 77.0 (C-2), 70.8 (C-3), 69.3 (C-4), 68.7 (C-5), 61.0 (C-6), 40.0 (*N*-CH_2), 20.5 (OAc), 20.1 (OAc). Anal. calcd for $C_{18}H_{27}NO_{10}S$: C, 49.65; H, 6.25; N, 3.22. Found: C, 49.68; H, 6.35; N, 2.99.

*4.3.3. 2,3,4,5,6-Penta-*O*-acetyl-*N*-propyl-D-thiogluconamide* ***20***

Yield: 5% from **12**, mp 104–105°C, $[\alpha]_D$ +53 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3330, 1740, 1530, 1240 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.20 (m, 1H, *N*-H), 5.90 (dd, $J = 4.2$ Hz, $J = 5.9$ Hz, 1H, H-3), 5.67 (d, $J = 4.2$ Hz, 1H, H-2), 5.42 (t, $J = 5.9$ Hz, 1H, H-4), 5.02 (m, 1H, H-5), 4.33 (dd, $J = 4.7$ Hz, $J = 12.1$ Hz, 1H, H-6), 4.16 (dd, $J = 5.6$ Hz, $J = 12.1$ Hz, 1H, H-6′), 3.60 (m, 2H, *N*-CH_2), 2.24 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.70 (m, 2H, CH_2), 0.95 (t, $J = 5.8$ Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 194.5 (C=S), 170.4 (CO, OAc), 169.7 (CO, OAc), 169.6 (CO, OAc), 169.1 (CO, OAc), 168.8 (CO, OAc), 77.0 (C-2), 70.8 (C-3), 69.4 (C-4), 68.8 (C-5), 61.1 (C-6), 46.7 (*N*-CH_2), 20.8 (CH_2), 20.5 (OAc),

20.1 (OAc), 11.1 (CH_3). Anal. calcd for $C_{19}H_{29}NO_{10}S$: C, 49.23; H, 6.31; N, 3.02. Found: C, 49.22; H, 6.39; N, 3.02.

4.3.4. 2,3,4,5,6-Penta-O-*acetyl*-N-*isopropyl-D-thiogluconamide* ***21***

Yield: 60% from **13**, mp 77–79°C, $[\alpha]_D$ +50 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3300, 1640, 1565, 1320, 1240 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.62 (d, $J=8.0$ Hz, 1H, *N*-H), 5.92 (dd, $J=4.4$ Hz, $J=5.7$ Hz, 1H, H-3), 5.63 (d, $J=4.4$ Hz, 1H, H-2), 5.40 (t, $J=5.7$ Hz, 1H, H-4), 5.03 (m, 1H, H-5), 4.58 (m, 1H, *N*-CH), 4.34 (dd, $J=4.6$ Hz, $J=12.2$ Hz, 1H, H-6), 4.18 (dd, $J=5.2$ Hz, $J=12.2$ Hz, 1H, H-6′), 2.21 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.36 (d, $J=8.0$ Hz, 3H, CH_3), 1.22 (d, $J=8.0$ Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 193.1 (C=S), 170.6 (CO, OAc), 170.0 (CO, OAc), 169.8 (CO, OAc), 169.2 (CO, OAc), 168.8 (CO, OAc), 77.4 (C-2), 70.9 (C-3), 69.5 (C-4), 68.8 (C-5), 61.1 (C-6), 46.7 (*N*-CH), 20.9 (2C, CH_3), 20.8 (OAc), 20.3 (OAc); Anal. calcd for $C_{19}H_{29}NO_{10}S$: C, 49.23; H, 6.31; N, 3.02. Found: C, 49.52; H, 6.07; N, 3.35.

4.3.5. 2,3,4,5,6-Penta-O-*acetyl*-N-*cyclohexyl-D-thiogluconamide* ***22***

Yield: 65% from **14**, mp 116–118°C, $[\alpha]_D$ +52 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3310, 1750, 1530, 1220 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.66 (d, $J=8.3$ Hz, 1H, *N*-H), 5.92 (dd, $J=4.2$ Hz, $J=5.3$ Hz, 1H, H-3), 5.64 (d, $J=4.2$ Hz, 1H, H-2), 5.40 (t, $J=5.3$ Hz, 1H, H-4), 5.01 (m, 1H, H-5), 4.35 (m, 1H, *N*-CH), 4.33 (dd, $J=4.1$ Hz, $J=12.2$ Hz, 1H, H-6), 4.17 (dd, $J=5.4$ Hz, $J=12.2$ Hz, 1H, H-6′), 2.24 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.83–1.12 (m, 10H, cyclohexyl moiety); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 192.9 (C=S), 170.5 (CO, OAc), 169.9 (CO, OAc), 169.7 (CO, OAc), 169.1 (CO, OAc), 168.8 (CO, OAc), 77.5 (C-2), 70.9 (C-3), 69.5 (C-4), 68.8 (C-5), 61.1 (C-6), 53.2 (*N*-CH), 31.1, 25.2, 24.3, 20.7 (OAc), 20.6 (OAc), 20.2 (OAc). Anal. calcd for $C_{22}H_{33}NO_{10}S$: C, 52.47; H, 6.60; N, 2.78. Found: C, 52.29; H, 6.68; N, 2.75.

4.3.6. 2,3,4,5,6-Penta-O-*acetyl*-N-*phenyl-D-thiogluconamide* ***23***

Yield: 69% from **15**, mp 168–170°C, $[\alpha]_D$ +80 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3330, 1750, 1520, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H, *N*-H), 7.70–7.28 (m, 5H, phenyl), 5.95 (t, $J=4.5$ Hz, 1H, H-3), 5.77 (d, $J=4.5$ Hz, 1H, H-2), 5.48 (t, $J=4.5$ Hz, 1H, H-4), 5.06 (m, 1H, H-5), 4.35 (dd, $J=4.5$ Hz, $J=12.1$ Hz, 1H, H-6), 4.19 (dd, $J=5.2$ Hz, $J=12.1$ Hz, 1H, H-6′), 2.28 (s, 3H, OAc), 2.12 (s, 6H, OAc), 2.06 (s, 3H, OAc), 2.04 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2 (C=S), 170.7 (CO, OAc), 170.2 (CO, OAc), 169.8 (CO, OAc), 169.3 (CO, OAc), 169.1 (CO, OAc), 137.5, 129.0 (2C), 127.2, 123.1 (2C), 78.0 (C-2), 71.1 (C-3), 69.5 (C-4), 68.9 (C-5), 61.2 (C-6), 20.8 (OAc), 20.7 (OAc), 20.3 (OAc). The sample was homogeneous by TLC and NMR analyses, but no satisfactory combustion analysis could be obtained.

4.3.7. 2,3,4,5,6-Penta-O-*acetyl*-N-*(4-methoxyphenyl)-D-thiogluconamide* ***24***

Yield: 60% from **16**, mp 118–120°C, $[\alpha]_D$ +87 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3320, 1750, 1530, 1220 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H, *N*-H), 7.56–6.91 (m, 4H, phenyl), 5.95 (t, $J=4.5$ Hz, 1H, H-3), 5.77 (d, $J=4.5$ Hz, 1H, H-2), 5.48 (t, $J=4.5$ Hz, 1H, H-4), 5.05 (m, 1H, H-5), 4.35 (dd, $J=4.6$ Hz, $J=12.1$ Hz, 1H, H-6), 4.19 (dd, $J=5.3$ Hz, $J=12.1$ Hz, 1H, H-6′), 3.81 (s, 3H, OCH_3), 2.28 (s, 3H, OAc), 2.12 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.04 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0 (C=S), 170.7 (CO, OAc), 170.2 (CO, OAc), 169.8 (CO, OAc), 169.3 (CO, OAc), 169.0 (CO, OAc), 158.3, 130.4, 124.9 (2C), 114.1 (2C),

77.9 (C-2), 71.1 (C-3), 69.6 (C-4), 68.9 (C-5), 61.2 (C-6), 55.4 (OCH_3), 20.8 (OAc), 20.7 (OAc), 20.4 (OAc). Anal. calcd for $C_{23}H_{29}NO_{11}S$: C, 52.36; H, 5.54; N, 2.65. Found: C, 52.32; H, 5.50; N, 2.70.

4.3.8. 2,3,4,5,6-Penta-O-*acetyl*-N-*(4-bromophenyl)-D-thiogluconamide* **25**

Yield: 60% from **17**, mp 105–107°C, $[\alpha]_D$ +85 (*c* 0.5, chloroform); IR (KBr) ν_{max} 3300, 1740, 1580, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H, *N*-H), 7.64–7.52 (m, 4H, phenyl), 5.92 (t, $J=4.5$ Hz, 1H, H-3), 5.72 (d, $J=4.5$ Hz, 1H, H-2), 5.46 (t, $J=4.5$ Hz, 1H, H-4), 5.05 (m, 1H, H-5), 4.36 (dd, $J=4.3$ Hz, $J=12.2$ Hz, 1H, H-6), 4.19 (dd, $J=5.2$ Hz, $J=12.2$ Hz, 1H, H-6′), 2.29 (s, 3H, OAc), 2.12 (s, 6H, OAc), 2.07 (s, 3H, OAc), 2.04 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6 (C=S), 170.8 (CO, OAc), 170.3 (CO, OAc), 169.8 (CO, OAc), 169.4 (CO, OAc), 169.1 (CO, OAc), 136.6, 132.1 (2C), 124.6 (2C), 120.2, 77.8 (C-2), 71.0 (C-3), 69.5 (C-4), 68.9 (C-5), 61.3 (C-6), 20.8 (OAc), 20.7 (OAc), 20.4 (OAc). Anal. calcd for $C_{22}H_{26}BrNO_{10}S$: C, 45.84; H, 4.55; N, 2.43. Found: C, 45.88; H, 4.52; N, 2.72.

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