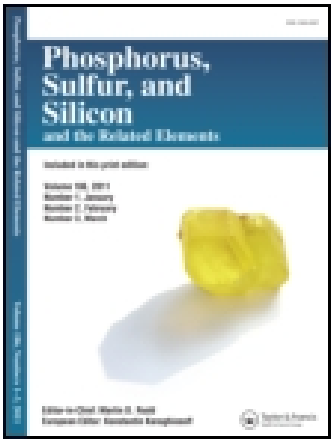

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Synthesis and Antimicrobial Activity of Novel 3-Benzyloxy-4-Substituted-2-Azetidinones: Formation of a Hydrophobic Layer Via a Self-Organization Effect

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NOVEL 3-BENZYLOXY-4-SUBSTITUTED-2-AZETIDINONES: FORMATION OF A HYDROPHOBIC LAYER VIA A SELF-ORGANIZATION EFFECT

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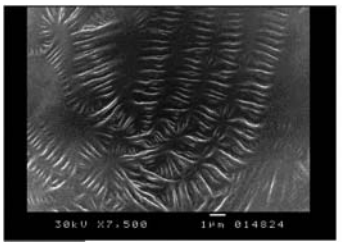
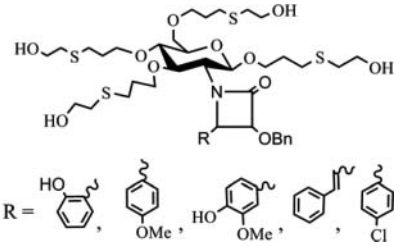
GRAPHICAL ABSTRACT





Abstract *We report the synthesis of new persulfide-spacer N-substituted-2-azetidinone-D-glucosamine in an attempt to potentially provide new antibiotics. The Schiff base ligands considered for this study were derived from D-glucosamine and 2-hydroxybenzaldehyde, 4-methoxy-benzaldehyde, cinnamaldehyde, 4-chlorobenzaldehyde, and 4-hydroxy-3-methoxy-benzaldehyde. Staudinger [2+2] cycloaddition of benzyloxyacetyl chloride to the newly reported per-O-allyl-N-substituted benzylidene-2-deoxy-β-D-glucosamine provided the sugar-based monocyclic β-lactams in moderate yields. Radical addition of 2-mercaptoethanol catalyzed by azobisisobutyronitrile to the per-O-allyl-N-substituted-2-azetidinone-D-glucosamine led to the corresponding persulfide-spacers in good yields. All new compounds were characterized by spectroscopic and spectrometric methods. The scanning electron microscopy image of 1,3,4,6-tetra-O-[3-(hydroxythioethyl)-propyl]-2-deoxy-2-N-[(3-benzyloxy-4-(4-chloropenyl)-2-azetidinone]-β-D-glucopyranoside, as a representative example, demonstrated a super hydrophobic layer formed via highly organized thioether spacers on gold as the adsorbate system through the formation of sulfur–gold bonds. The reported glucosides showed a moderate antifungal activity against Candida albicans while being slightly to moderately active against gram-positive and gram-negative bacteria used in this investigation at a concentration of 1 mg/mL dissolved in dimethyl sulfoxide.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords D-Glucosamine; sulfide spacer; antibiotics

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INTRODUCTION

The successful development of any medicinal compound relies on specific and potent pharmacological activity combined with efficient delivery of the molecule to its target site. Many potential drugs and medicinal peptides fail to reach the marketplace due to poor bioavailability and factors such as molecular size, charge, hydrophilicity, hydrogen bonding potential, and enzymatic lability. Their potential therefore rests on the design of effective and stable drug delivery systems. Formulation is one means by which the absorption of a drug can be enhanced, using surfactants, penetration enhancers, or through ion pairing.[1,2] Chemical modification is another means, although a compromise between introducing and modifying structural features of a drug moiety that optimizes biopharmaceutical properties (e.g., membrane permeability and metabolism) and those that optimize pharmacological activity (e.g., enzyme or receptor binding) must be sought.

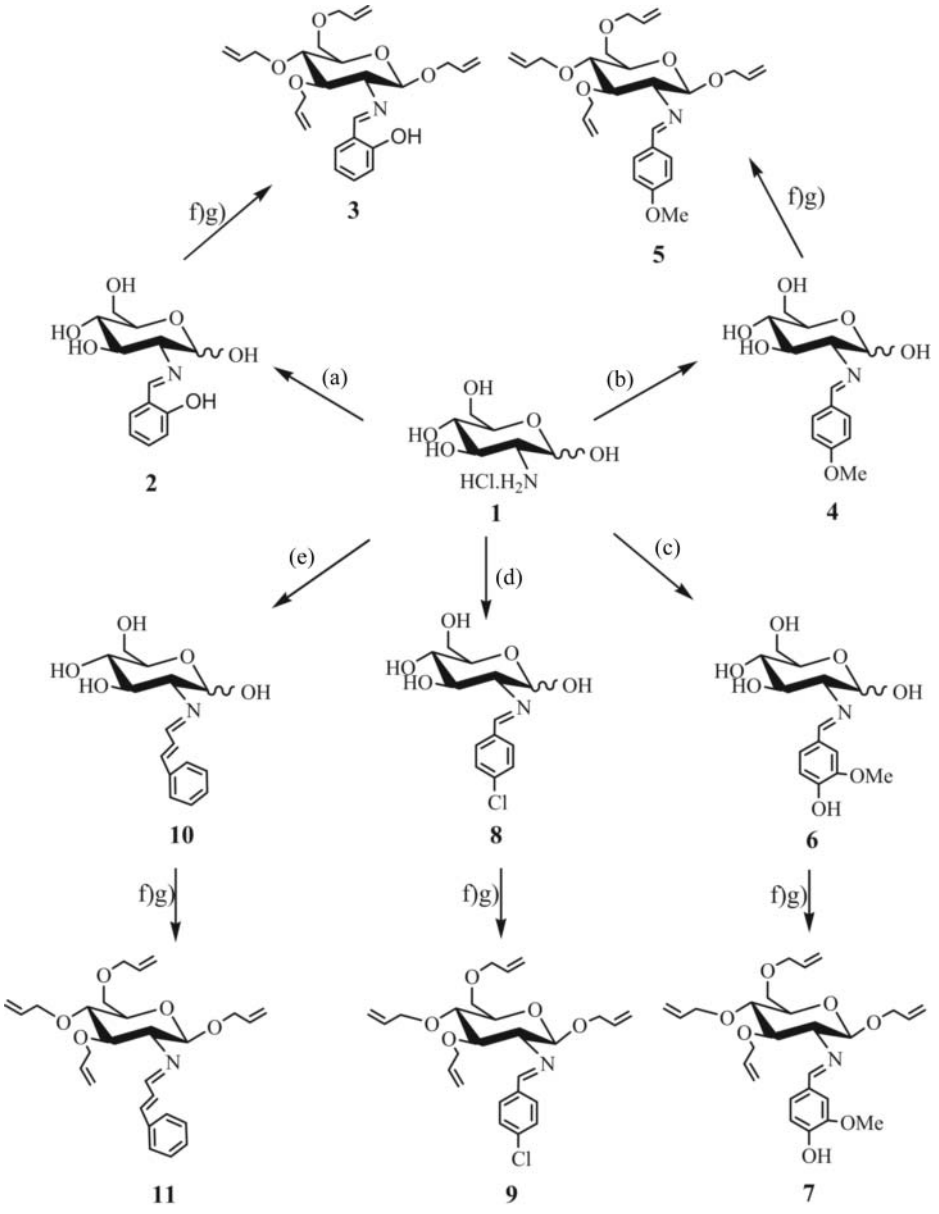
Sugar-based surfactants have been studied as antimicrobial agents.[3] Such surface-active agents are known to disrupt cell membranes because they dissolve in both the extracellular fluid and the lipid membrane. This lowers the surface tension of the membrane, allowing water to flow into the cell and ultimately resulting in lysis and bactericidal action. The primary factors that influence the activity of these molecules are the structure of the carbohydrates moiety, the presence of the hydrophobic tail, and the length of the alkyl chain and the latter factor being more important.[4] The most frequent types of linkage between the hydrophilic and hydrophobic moieties are of ester, amine, amide, and glycosidic nature.[5] Surprisingly, the basic carbohydrate structures recognized by carbohydrate-binding proteins are simple, with at best a trisaccharide or tetrasaccharide moiety being deeply involved in the protein's active sites,[6] unless conformational epitopes are involved. The innate immune system recognizes the structure of carbohydrate on bacteria through their carbohydrate-binding protein as the first defense mechanism against this type of infectious agents.[7] Alternatively, bacteria possess proteins that also recognize and bind to the carbohydrate of host human tissues as the premise for bacterial infections.[8]

[2 + 2] Cycloaddition reactions between ketenes, bearing amino, oxy, or halo groups, and imines are recognized as being among the most important and direct routes to β-lactams, and by the virtue of this way, β-lactams with a widely varying substitution pattern at 1, 3, and 4 positions of the ring are constructed stereoselectively.[9] Appropriate substituents on the monocyclic azetidin-2-one led to the discovery of new biologically active monocyclic β-lactam compounds displaying either antibiotic or nonantibiotic activities[10] and this discovery prompted us to construct new derivatives of such compounds. We postulated that radical addition of 2-mercaptoethanol, as a spacer arm, to per-*O*-allyl-2-amino-2-deoxy-glycoside carrying monocyclic azetidin-2-one with a varying substitution at position 4 of the β-lactam ring[11] could be useful for the construction of potent lipophilic sulfide-spacer carbohydrates. Such types of spacer arms contain two functional groups, which can interact with receptors independently. The terminal hydroxyl groups of these spacers are available for either direct attachment to specific receptors or covalently modify into another functional group for subsequent binding.[12] In this report, we describe the preparation of a new type of symmetrically substituted persulfide-spacer 2-amino-2-deoxy-glucoside containing 3-hydroxy-4-substituted-2-azetidinone and evaluate their antimicrobial and antifungal activity against *Staphylococcus aureus*, *Enterococcus fecalis*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Candida albicans*.

RESULTS AND DISCUSSION

The importance of amino sugars as constituents of aminoglycosides antibiotics, antigenic determinants, glycoproteins, and glycolipids is well recognized. A large number of imines or Schiff bases have been reported by the reaction of sugar aldehydes with amines or by the reaction of amino sugars such as 2-amino-2-deoxy-sugars with aldehydes.[9,11] The Schiff base ligands considered for this study are derived from 2-hydroxybenzaldehyde (salicylaldehyde), 4-methoxybenzaldehyde, cinnamaldehyde, 4-chlorobenzaldehyde, and 4-hydroxy-3-methoxybenzaldehyde (vanillin). The *N*-substituted benzylidene-D-glucosamines **2**,[13] **4**,[14] **6**,[15] **8**,[16] and **10**[17] were obtained by refluxing equimolar quantities of D-glucosamine hydrochloride **1**, NaOH, and appropriate aldehyde in MeOH solution for 2 h following the literature procedures[18] (Scheme 1). The structures of the resulted imines were confirmed by mass spectrometry, IR, and elemental analysis. The perallyl-substituted benzylidene β-D-glucosides **3**, **5**, **7**, **9**, and **11** were prepared according to the literature procedures.[19] Thus, peracetylation of imines **2**, **4**, **6**, **8**, and **10** using $Ac_2O/HClO_4$ followed by treatment with red P/Br_2 according to a reported method[20] provided the respective α-glucoside bromides. Koenigs–Knorr glycosidation with allyl alcohol/AgOTf[21] followed by *O*-deacetylation using NH_4OH/CH_3OH (2:1 v/v) provided the allyl-β-D-glucosides that were further reacted with NaH/allyl bromide/*N,N*-dimethylformamide (DMF) mixture to furnish the target intermediates, i.e., per-*O*-allyl β-D-glucosides **3**, **5**, **7**, **9**, and **11** in moderate overall yields. The structures of the prepared per-*O*-allyl-β-D-glucosides **3**, **5**, **7**, **9**, and **11** were fully characterized by spectroscopic and spectrometric analysis methods. IR spectra (film, NaCl) showed bands around υ 3010 and 1610 cm^{-1}, which correspond to the υ_{str} (C=C) of the allyl groups and strong bands around υ 1650 cm^{-1} due to the imine υ_{str} (C=N) groups. ^{1}H- and ^{13}C-NMR spectroscopic data for the allylated glucosides were in agreement with the published chemical shifts and coupling constant values for related analogues.[22,23] The anomeric proton (H-1) resonated around δ 5.20 ppm ($J = 6.1$ Hz) confirming the indicated β-stereochemistry. The olefinic protons appeared as two multiplet signals within δ 4.95–6.00 ppm range and the imine proton (N=C*H*) resonated at δ 10.50 ppm.

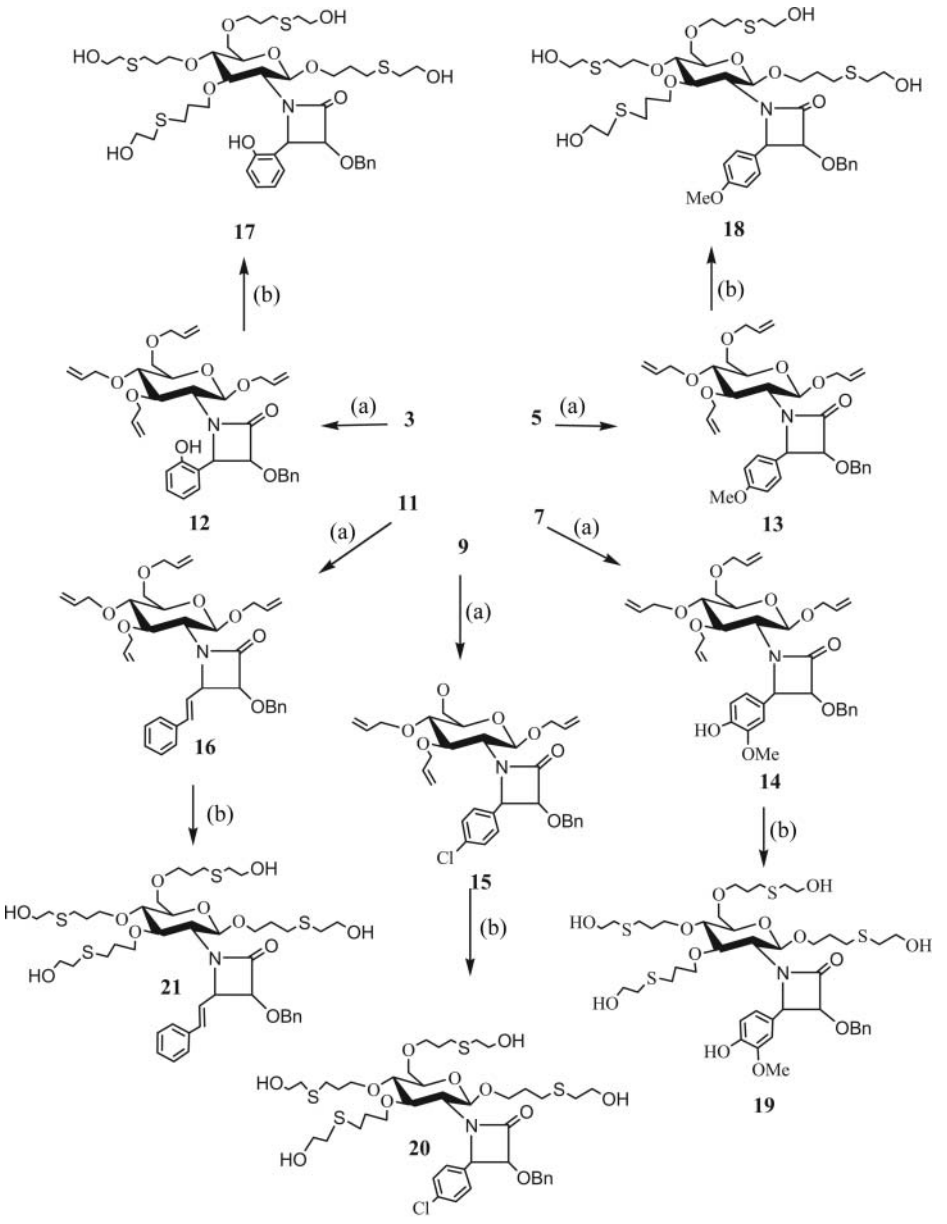
The reaction of per-*O*-allyl-*N*-substituted benzylidene-2-deoxy-β-D-glucosamines **3**, **5**, **7**, **9**, and **11** with benzyloxyacetyl chloride in the presence of triethylamine according to the method described by Manhas et al.[24] resulted in the respective per-*O*-allyl-*N*-substituted-2-azetidinone-D-glucosamines **12–16** (Scheme 2) in good yields. The structures of the prepared monocyclic β-lactams **12–16** were fully characterized by spectroscopic and spectrometric analysis methods. It is noteworthy that the NMR spectra of the crude reaction products revealed the presence of an inseparable mixture of *cis*- and *trans*-stereoisomers in nearly equal ratios. The synthesis of the targeted persulfide-spacer glycosides **17–21** were accomplished by the addition of 2-mercaptoethanol to the per-*O*-allyl-*N*-substituted-2-azetidinone-D-glucosamines **12–16** in good yields. Various methods are known to conduct the free radical addition reactions mostly by exposure to UV radiation or by the addition of chemical initiators. The first case requires a special apparatus and in this work, adducts **17–21** were obtained by the use of azobisisobutyronitrile (AIBN) as a radical initiator.[25] Elongated persulfide-spacer glycosides exhibited similar spectroscopic behaviors. IR spectra (film, NaCl) showed a broad band around υ 3400 cm^{-1}, which correspond to the free terminal OH groups and a strong band at υ 2920 cm^{-1} due to the alkyl groups. The ^{1}H-NMR spectra are characterized by a number of overlapping broad band peaks due to many magnetically equivalent ($-CH_2$) and ($-CH-$) groups on each molecule. ^{1}H-NMR spectra



Key: a) 1N NaOH, 2-Hydroxybenzaldehyde, 1h; b) 1N NaOH, 4-Methoxybenzaldehyde, 1h; c) 1N NaOH, 3-Methoxy-4-hydroxybenzaldehyde, 1h; d) 1N NaOH, 4-Chlorobenzaldehyde, 1h; e) 1N NaOH, Cinamaldehyde, 1h; f) i- Ac_2O, $HClO_4$, ii- Red P/Br_2, iii- AgOTf, Allyl alcohol, 24 h, iv- NH_4OH/CH_3OH (2:1 *v/v*); g) NaH, Allylbromide, DMF, 24 h

Scheme 1

of either persulfide-spacer glycosides revealed the presence of signals at δ 1.91–1.74 (m, 8H, 4 × CH_2), 2.69–2.59 (m, 8H, 4 × $-CH_2S-$), 2.81 (m, 8H, 4 × SCH_2-), 3.69–3.57 (m, 10H, 4 × OCH_2, 2 × H-6), and 3.77 (m, 8H, 4 × CH_2OH), which correspond to thio-spacer protons, whereas anomeric protons of the carbohydrates resonated at δ 5.62 (d, 1H, $J = 7.6$ Hz, H-1, β-configuration).



Key: a) $BnOCH_2COCl$, Et_3N, $CHCl_3$, 14 h; b) 2-mercaptoethanol, AIBN, 1,4-dioxane, 80°C

Scheme 2

We then focused on the role played by the symmetrically arranged thioether spacers on the morphology of the surface. Figure 1 shows the scanning electron microscopy (SEM) image of 1,3,4,6-tetra-*O*-[3-(hydroxylthioethyl)-propyl]-2-deoxy-2-N-[(3-benzyloxy-4-(4-chloropenyl)-2 azetidinone]-β-D-glucopyranoside **20**, as a representative example, demonstrating a super hydrophobic layer formed via highly organized thioether spacers on gold as the adsorbate system. Self-assembled monolayers (SAMs) are the simplest form of self-assembled material. Their construction is driven by the thermodynamically favored

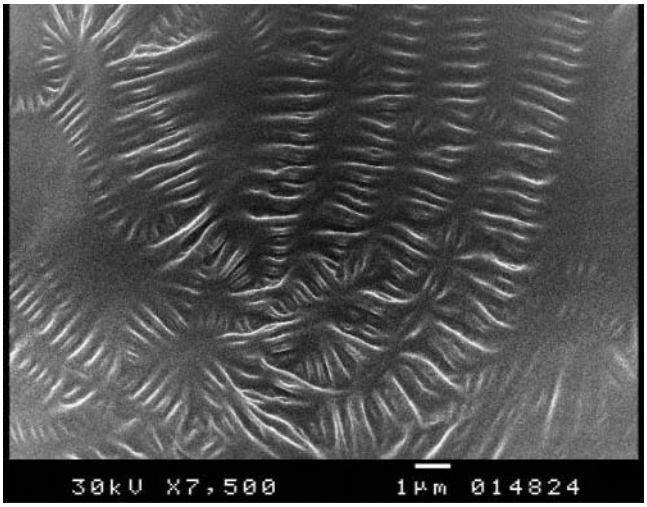


Figure 1 The SEM image of **20** demonstrating a super hydrophobic layer formed via highly organized thioether spacers on gold as the adsorbate system.

segregation of molecules to a phase boundary, most typically the surface of a solid in contact with a liquid or other ambient environment. The interest in these materials has developed greatly in recent years in no small part as a direct response to the needs of technology.[26,27]

SAMs are typically formed by small organic molecules, which in some way are amphiphilic; they are typically limited to dimensions of less than a few nanometers. The amphiphilic or dual solubility character of a compound implies that it (1) adsorbs at any polar–apolar interface, reducing the interfacial tension, that is, the amount of work required to increase the area of the interface at standard conditions and (2) self-organizes in bulk into aggregates containing many molecules and having well-defined average shape and size. The main thermodynamic driving force for both adsorption and self-assembly is the *hydrophobic effect*.[28] The best defined materials currently available for the study are the SAMs formed by various organosulfur compounds, especially alkanethiols, on metal surfaces such as those formed by Au, Ag, and to a lesser degree Cu.[29] Figure 2 shows

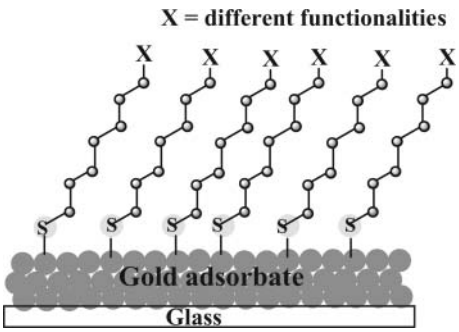


Figure 2 The general schematic structure of an organothiol used in forming firmly anchored SAMs on the gold substrate via a sulfur–gold bond.

a generic depiction that captures the essential aspects of the molecular structure of a thiolate SAM on Au. The organothiol consists of three essential units: the thio function (−S−), employed as the anchor group; a linker unit such as alkyl chains $(-CH_2-)_n$[30] or oligophenylenes $(-C_6H_4-)_n$,[31] and a functional terminal group (−X). Critically important for the generation of organic surfaces using SAMs is that the terminal group X of the corresponding organothiol determines the surface of the organic ultrathin layers.

The generation and fundamental characteristics of these molecular "furs" have been discussed[31] and the precise geometric arrangement at the thiolate–gold interphase was a topic of an intense debate.[32] The production of the monomolecular layers is achieved by immersing gold substrates in the corresponding organothiol solutions. In most cases, ethanol is the solvent; however, depending on the organothiol, other solvents (e.g., water, acetone, and dichloromethane) were employed. As a rule, a highly organized layer will form on the substrate immersed in the solution in as little as a few hours.[30] Several organosulfur compounds bearing different functionalities and studies of the highly organized thiolate SAMs on Au as the adsorbate system have been reported.[33]

The imaging of compound **20** by an SEM involves sputter coating the sample with gold prior to examination. The thioether-spacer moieties generate sulfur–gold bonds, either by direct adsorption or by in situ cleavage of a thioether bond,[34] and a self-organization effect that easy surface segregation to form a rough surface nanostructure to exhibit superhydrophobicity.[27a]

Biological Screening: Antimicrobial Activity Tests

There has been a suggestion that the bacteria may utilize a carbohydrate uptake mechanism, which allows a better transport of the monocyclic β-lactams across the membrane. The prepared perallylated and persulfide-spacer glucosides were screened in vitro against gram-positive bacteria *Staphylococcus aureus* (S) ATCC6538P and gram-negative bacteria *Enterococcus fecalis* (Ent) ATCC29212, *Klebsiella pneumonia* (Kl) ATCC10031, *Pseudomonas aeruginosa* (Ps) ATCC9027, and *Escherichia coli* (E) ATCC8739. The compounds were also screened against *Candida albicans* (C) ATCC2091 fungi. The antibacterial and antifungal activities of test compounds were performed using the filter paper disc method.[35] Screening results are summarized in Table S1 (supplemental materials). The antimicrobial screening against test strains showed slight to moderate activity against the tested bacteria strains for all compounds at a concentration of 1 mg/mL. Interestingly, the reported compounds showed a broad spectrum of antifungal activity against *Candida albicans*.

EXPERIMENTAL SECTION

General Procedures

All solvents were dried and distilled using standard procedures prior to use. All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. AIBN was recrystallized in dry methanol before use. Evaporation was performed under vacuum with a water bath temperature below 40 °C. Reactions were monitored by thin layer chromatography on silica gel 60 F_{254} plates with detection by UV at 254 nm and by charring with 5% ethanolic H_2SO_4. Column chromatography was performed on silica gel 60 (EM Science, 70–230 mesh). Optical rotations were measured

at 20 °C on an Optika polarimeter (WXG-4). IR spectra (film, NaCl) were recorded on a Perkin-Elmer 781 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR were recorded on JOEL 500 MHz spectrometers equipped with Sun off-line editing workstation. Chemical ionization mass spectrometry (CIMS) measurements were determined using a Finnigan SSQ 7000 spectrometer attached to digital DEC 300 workstation at the central scientific services unit, National Research Center, Dokki, Cairo, Egypt. Methane, the ionizing gas, was introduced directly into the source of the mass spectrometer and the pressure of the gas in the source was approximately 0.5 torr. Under these conditions, essentially all of the charged ions originate from methane. Elemental analyses were determined at the Chemistry Department, Faculty of Science, Cairo University, Egypt. The image of compound **20** was observed by an SEM (JEOL-JSM5300) at the E-Microscope Unit, Faculty of Science, Alexandria University, Egypt. The dilute methanolic solution was air-dried on a cover glass and sputter coated with gold prior to examination. Antimicrobial and antifungal evaluations were determined by the Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Alexandria University, Egypt. The supplemental materials contain example spectra of compounds **3**, **12**, and **17**.

Preparation of N-Substituted Benzylidene-D-Glucosamines 2, 4, 6, 8, and 10 (General Methods)[14]

Method 1[14]. D-Glucosamine hydrochloride (10 g, 46.5 mmol) was dissolved in NaOH (55 mL, 1N) and substituted benzaldehyde (48 mmol) was slowly added while stirring. A yellow solid soon precipitated and after approximately 2 h it was filtered off, washed carefully with little methanol and water, and dried under vacuum for 2 days.

Method 2. A mixture of equimolar quantities of D-2-glucosamine hydrochloride in NaOH and respective aldehyde in MeOH solution was refluxed for 2 h according to the literature procedure.[18]

N-(2-Hydroxy-Benzylidene)-D-Glucosamine 2[13]. Yield (9 g, 70%), mp = 183 °C–185 °C. FT-IR (KBr, cm^{-1}): υ 3387, 2934, 2888, 2764, 1632, 1493, 1408, 1340, 1279, 1224, 1153, 1098, 1016, 899, 876, 768, 741, 712, 595. CI-MS [*m*/*z* (%)]: 283 (M^{+}) (2), 279 (3), 266 (2), 252 (3), 246 (2), 237 (2), 232 (2), 228 (2), 226 (2), 218 (4), 216 (7), 206 (12), 203 (3), 202 (4), 192 (15), 181 (6), 177 (6), 166 (6), 164 (13), 155 (13), 148 (16), 141 (22), 137 (9), 131 (12), 127 (21), 124 (15), 122 (16), 120 (15), 117 (49), 114 (19), 110 (33), 108 (23), 104 (35), 102 (31), 98 (18), 94 (69), 91 (43), 76 (57), 56 (100), 50 (56). Calc.: $C_{13}H_{17}NO_6$ (283); C: 55.12, H: 6.05, N: 4.94; found: C: 54.77, H: 5.80, N: 4.61.

N-(4-Methoxy-Benzylidene)-D-Glucosamine 4[14]. Following the general method described, the known imine **4** was obtained: yield (9.5 g, 74%), mp 165 °C. Calc.: $C_{14}H_{19}NO_6$ (297); C: 56.56, H: 6.44, N: 4.71; found: C: 55.94, H: 6.11, N: 4.30.

N-(3-Methoxy-4-Hydroxy-Benzylidene)-D-Glucosamine 6[15]. Yield (9.5 g, 70%), mp = 184 °C (decomp.). FT-IR (KBr, cm^{-1}): υ 3218 br, 2850, 1665, 1592, 1519, 1461, 1363, 1304, 1266, 1206, 1174, 1132, 1062, 1018, 862, 824, 731, 679, 613, 599. CI-MS [*m*/*z* (%)]: 306 (2), 298 (2), 253 (2), 249 (2), 243 (3), 232 (3), 230 (2), 228 (2), 225 (3), 217 (4), 213 (5), 206 (2), 203 (5), 202 (4), 192 (7), 188 (6), 179 (6), 166 (6), 164 (8), 155 (3), 148 (14), 141 (9), 137 (14), 131 (7), 127 (7), 124 (12), 122 (31), 117 (6), 112 (8), 110 (20), 108 (37), 104 (23), 97 (35), 94 (27), 91 (14), 76 (19), 56 (64), 54 (49), 45 (100). Calc.: $C_{14}H_{19}NO_7$ (313); C: 53.67, H: 6.11, N: 4.47; found: C: 52.41, H: 5.60, N: 4.01.

N-(4-Chloro-Benzylidene)-D-Glucosamine 8[16]. Yield (10.5 g, 81%), mp = 133 °C. FT-IR (KBr, cm^{-1}): υ 3492, 3302, 3197, 2940, 2885, 2845, 1694, 1646, 1591,

1491, 1429, 1385, 1321, 1281, 1250, 1207, 1147, 1076, 1031, 896, 884, 829, 708, 638, 579, 541, 505. CI-MS [*m/z* (%)]: 302 (M^+) (3), 287 (3), 266 (3), 246 (5), 229 (10), 227 (26), 217 (8), 203 (16), 192 (45), 181 (6), 177 (12), 166 (10), 164 (28), 155 (26), 148 (18), 140 (38), 137 (94), 130 (20), 127 (28), 124 (34), 117 (29), 114 (21), 110 (50), 104 (24), 102 (43), 98 (16), 95 (100), 91 (63), 88 (26), 76 (43), 57 (78), 54 (62), 50 (74).

N-(3-Phenyl-Allylidene)-D-Glucosamine 10[17]. Yield (10.5 g, 84%), mp = 137 °C. FT-IR (KBr, cm^{-1}): υ 3467, 3297, 3197, 2855, 1674, 1629, 1492, 1448, 1384, 1329, 1251, 1204, 1124, 1069, 1025, 976, 883, 750, 689, 644, 609, 580, 508. CI-MS [*m/z* (%)]: 295 (M^+ +2) (4), 294 (M^+ +1) (3), 293 (M^+) (2), 264 (5), 249 (4), 244 (23), 192 (16), 181 (29), 177 (13), 166 (19), 164 (20), 153 (49), 147 (30), 143 (25), 130 (40), 127 (45), 116 (29), 114 (43), 104 (51), 102 (65), 96 (30), 94 (26), 90 (71), 88 (16), 76 (100), 56 (57), 54 (48), 50 (58). Calc.: $C_{15}H_{19}NO_5$ (293); C: 61.42, H: 6.53, N: 4.78; found: C: 60.90, H: 6.03, N: 4.20.

Preparation of Perallyl-N-Substituted Benzylidene-2-Deoxy-β-D-Glucosamines 3, 5, 7, 9, and 11 (General Method)

The *N*-substituted benzylidene-D-glucosamines **2**, **4**, **6**, **8**, and **10** (10 mmol) were converted to the corresponding *N*-substituted benzylidene-3,4,6-tri-*O*-acetyl-α-D-glucosyl bromides according to the literature procedure.[19] The allyl β-D-glucosides were prepared from the respective α-D-glucosyl bromides via AgOTf-catalyzed Koenigs–Knorr glycosidation,[21] followed by *O*-deacetylation using NH_4OH/CH_3OH (2:1 v/v) to provide the respective unprotected glucosides. To a cold (0 °C) solution of the unprotected allyl β-D-glucosides dissolved in DMF (25 mL), NaH (1.73 g, 72 mmol, 8 × equivalent based on crude starting materials) was added portionwise. Stirring was continued at 0 °C for 15 min and for 45 min at r.t. and then the salty solution was cooled to 0 °C again. Allyl bromide (8.7 g, 72 mmol, 8 × equivalent) in DMF (10 mL) was added slowly and the clear mixture was allowed to stir at r.t. for 15 h. The organic solvent and volatiles were removed under a high vacuum and the crude product was purified on column chromatography (1:2 EtOAc/hexane).

1,3,4,6-Tetra-O-Allyl-2-Deoxy-2-N-(2-Hydroxy-Benzylidene)-β-D-Glucopyranoside 3. Yield (overall) = (1.4 g, 33%), R_f = 0.30, $[\alpha]_D$ = −4.4 (c 1.0 $CHCl_3$). FT-IR (NaCl film, cm^{-1}): υ 3415, 3077, 2978, 2918, 2866, 1679, 1642, 1597, 1487, 1452, 1422, 1389, 1287, 1240, 1110, 998, 923, 842, 757, 656, 565. ^{1}H-NMR ($CDCl_3$, 500 MHz): 10.51 (s, 1H, N = C*H*), 7.98 (s br, 1H, OH), 7.82–7.80 (m, 1H, arom.), 7.52–7.50 (m, 1H, arom.), 7.35–7.25 (m, 2H, arom.), 5.90–5.70 (m, 4H, 4 = C*H*), 5.30–4.95 (m, 8H, 4 = CH_2), 5.20 (d, *J* = 6.1 Hz, 1H, H-1), 4.40–3.94 (m, 8H, 4 × OCH_2), 3.80–3.53 (m, 6H, H-2, H-3, H-4, H-5, 2 × H-6). ^{13}C-NMR ($CDCl_3$, 125 MHz): 190.0 (C=N), 161.0 (arom.) 133.4−132.5 (CH=CH_2), 128.5 (arom.), 128.4 (arom.), 121.2 (arom.), 120.6 (arom.), 118.0 (arom.), 112.6 (CH=CH_2), 73.9–69.7 (4 × OCH_2, C-5), 69.3 (C-6), 69.2 (–OCH_2), 68.6 (C-2).

1,3,4,6-Tetra-O-Allyl-2-Deoxy-2-N-(4-Methoxy-Benzylidene)-β-D-Glucopyranoside 5. Yield (overall) = (1.6 g, 36%), R_f = 0.33, $[\alpha]_D$ = –5.1 (c 1.0 $CHCl_3$). FT-IR (NaCl film, cm^{-1}): υ 3448, 3078, 3010, 2927, 2857, 1697, 1645, 1602, 1512, 1461, 1424, 1346, 1257, 1216, 1160, 1105, 995, 923, 834, 768, 722, 641, 602, 559, 517. ^{1}H-NMR ($CDCl_3$, 500 MHz): 9.81 (s, 1H, N = C*H*), 7.77 (d, *J* = 3.68 Hz, 2H, arom.), 6.94 (d, *J* = 3.36 Hz, 2H, arom.), 5.90–5.70 (m, 4H, 4 = C*H*), 5.30–4.95 (m, 8H, 4 = CH_2), 5.20 (d, *J* = 6.1 Hz, 1H, H-1), 4.40–3.94 (m, 8H, 4 × OCH_2), 3.82 (s, 3H, OCH_3),

3.80–3.53 (m, 6H, H-2, H-3, H-4, H-5, 2× H-6). ^{13}C-NMR ($CDCl_3$, 125 MHz): 190.9 (C=N), 164.6 (arom.), 134.8, 134.7, 134.6 (3× C*H*=CH_2), 132.0 (CH=CH_2, arom.), 129.9, 129.1 (arom.), 116.9, 116.3 (arom.), 114.3 (CH=CH_2), 76.9 (C-5), 72.2–69.4 (OCH_2, C-6), 62.8 (C-2), 55.6 (OMe). CI-MS [*m*/*z* (%)]: 457 (2), 449 (7), 422 (2), 409 (5), 379 (87), 364 (8), 346 (7), 337 (28), 326 (7), 320 (7), 309 (7), 293 (8), 287 (5), 278 (11), 269 (4), 261 (17), 251 (16), 245 (6), 231 (9), 223 (20), 209 (9), 179 (38), 175 (36), 160 (12), 152 (94), 148 (53), 134 (56), 120 (32), 81 (100), 78 (39), 54 (71).

1,3,4,6-Tetra-O-Allyl-2-Deoxy-2-N-(3-Methoxy-4-Hydroxy-Benzylidene)-β-D-Glucopyranoside 7. Yield (overall) = (1.4 g, 30%), $R_f = 0.35$, $[\alpha]_D = -4.0$ (c 1.0 $CHCl_3$). FT-IR (NaCl film, cm^{-1}): υ 3458, 3078, 2978, 2918, 2867, 1682, 1644, 1590, 1511, 1455, 1420, 1338, 1267, 1131, 1037, 924, 867, 809, 782, 759, 732, 658, 589, 565. ^{1}H-NMR ($CDCl_3$, 500 MHz): 9.81 (s, 1H, N = C*H*), 7.25 (s, 1H, arom.), 6.94 (d, J = 8.4 Hz, 2H, arom.), 6.07–5.72 (m, 4H, 4 = C*H*), 5.42–4.97 (m, 9H, 4 = CH_2, H-1), 4.67–3.99 (m, 8H, 4 × OCH_2), 4.00 (s, 3H, OCH_3), 4.11–3.50 (m, 6H, H-2, H-3, H-4, H-5, 2 × H-6). ^{13}C-NMR ($CDCl_3$, 125 MHz): 191.1 (C=N), 153.5, 149.5, 134.7, 134.4, 133.0, 132.3 (4 × CH=CH_2), 132.1 (arom.), 126.63, 126.1, 125.0 (arom.), 118.8, 117.3, 116.0 (arom.), 112.1 (CH=CH_2), 111.6 (arom.), 98.6 (C-1), 78.5, 78.3, 73.9, 72.5, 70.4, 70.3, 69.9 (OCH_2), 69.8 (OCH_2), 69.7 (OCH_2), 69.3 (OCH_2), 69.2 (C-5), 69.1 (C-6), 56.1 (OMe). CI-MS [*m*/*z* (%)]: 474 (M^+ +1), 338 (2), 326 (2), 311(3), 286 (2), 269 (3), 253 (2), 246 (2), 243 (2), 232 (14), 227 (2), 225 (3), 217 (24), 208 (3), 203 (14), 200 (4), 196 (4), 190 (61), 182 (5), 178 (14), 177 (40), 164 (38), 155 (7), 150 (41), 144 (28), 137 (17), 131 (15), 127 (28), 124 (8), 122 (7), 117 (24), 112 (7), 110 (17), 108 (21), 104 (33), 97 (18), 94 (26), 91 (100), 76 (44), 56 (36), 54 (44), 50 (33).

1,3,4,6-Tetra-O-Allyl-2-Deoxy-2-N-(4-Chloro-Benzylidene)-β-D-Glucopyranoside 9. Yield (overall) = (1.5 g, 33%), R_f = 0.25, $[\alpha]_D$ = –6.1 (c 1.0 $CHCl_3$). FT-IR (NaCl film, cm^{-1}): υ 3413 br, 3079, 2979, 2922, 2868, 1725, 1644, 1596, 1489, 1412, 1347, 1270, 1092, 1011, 924, 829, 809, 759, 660, 523. ^{1}H-NMR ($CDCl_3$, 500 MHz): 9.97 (s, 1H, N = C*H*), 7.98 (d, J = 8.4 Hz, 2H, arom.), 7.81 (d, J = 8.4 Hz, 2H, arom.), 6.06–5.60 (m, 4H, 4 = C*H*), 5.27–4.90 (m, 8H, 4 = CH_2), 5.20 (d, J = 6.1 Hz, 1H, H-1), 4.47–4.00 (m, 8H, 4 × OCH_2), 3.74–3.50 (m, 6H, H-2, H-3, H-4, H-5, 2 × H-6). ^{13}C-NMR ($CDCl_3$, 125 MHz): 165.5 (arom.), 136.0, 135.4, 134.7, 133.1 (4 × CH=CH_2), 131.2 (arom.), 129.2–127.9 (arom.), 119.0–116.0 (arom.), 98.8 (C-1), 76.8 (C-4), 72.4 (C-5), 65.8 (OCH_2). CI-MS [*m*/*z* (%)]: 462.5 (M^+ +1) (4), 428 (9), 410 (6), 404 (4), 369 (9), 338 (9), 321 (40), 304 (10), 277 (6), 266 (4), 250 (5), 235 (9), 223 (8), 218 (27), 211 (12), 196 (9), 193 (10), 190 (29), 181 (25), 167 (22), 164 (38), 155 (12), 153 (17), 140 (38), 137 (100), 129 (23), 127 (27), 123 (66), 117 (7), 114 (15), 112 (21), 104 (9), 102 (7), 98 (14), 96 (14), 91 (9), 88 (8), 76 (14), 57 (33), 54 (34), 50 (14). Calc.: $C_{25}H_{32}NClO_5$ (461.5); C: 65.00, H: 6.98, N: 3.03; found: C: 64.10, H: 6.32, N: 2.91.

1,3,4,6-Tetra-O-Allyl-2-Deoxy-2-N-(3-Phenyl-Allylidene)-β-D-Glucopyranoside 11. Yield (overall) = (1.3 g, 30%), R_f = 0.42, $[\alpha]_D = -2.2$ (c 1.0 $CHCl_3$). FT-IR (NaCl film, cm^{-1}): υ 3454, 3075, 3023, 2980, 2919, 1731, 1641, 1601, 1493, 1450, 1335, 1244, 1121, 995, 923, 757, 701, 557. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.44–7.25 (m, 6H, 4*H* arom., C*H*=C*H*), 5.95–5.60 (m, 4H, 4 = C*H*), 5.28–5.05 (m, 8H, 4 = CH_2), 5.20 (d, J = 6.1 Hz, 1H, H-1), 4.30–4.09 (m, 8H, 4 × OCH_2), 4.00–3.50 (m, 6H, H-2, H-3, H-4, H-5, 2× H-6). ^{13}C-NMR ($CDCl_3$, 125 MHz): 171.3 (C=N), 134.0−130.0 (CH=CH_2, arom.), 129.8–127.3 (arom.), 119.0–116.0 (arom.), 98.5 (C-1), 76.8 (C-4), 72.3 (C-5), 68.9 (C-6), 64.6, 64.3, 64.2 (OCH_2), 60.5 (C-2). CI-MS [*m*/*z* (%)]: 454 (M^+ +1) (3), 412 (3), 409 (5), 400 (8), 394 (9), 384 (16), 378 (8), 356 (6), 352 (12), 342 (2), 327 (11), 301 (3), 299 (92),

257 (28), 251 (25), 229 (20), 223 (29), 215 (17), 211 (83), 198 (22), 192 (41), 172 (26), 169 (24), 166 (17), 164 (13), 154 (18), 151 (37), 140 (34), 143 (23), 130 (45), 127 (100), 116 (39), 114 (61), 109 (22), 104 (44), 102 (42), 96 (11), 94 (9), 91 (56), 88 (5), 76 (22), 55 (23), 50 (8).

Preparation of N-Substituted-2-Azetidinone-D-Glucosamine 12–16 (General Method)[23]

A solution of the Schiff base (**3**, **5**, **7**, **9**, and **11**; 10 mmol) and triethylamine (15 mmol) in CH_2Cl_2 (50 mL) was stirred at r.t. while a solution of benzyloxyacetyl chloride (15 mmol) in CH_2Cl_2 (25 mL) was added dropwise over a period of 1 h. The mixture was stirred at r.t. for additional 20 h. Then, the mixture was washed with water, dried, and the solvent and volatiles were removed under reduced pressure. The residue was purified over a short column of Florisil using CH_2Cl_2 as the eluent.

1,3,4,6-Tetra-O-Allyl-2-Deoxy-2-N-[(3-Benzyloxy-4-(2-Hydroxyphenyl)-2-Azetidinone]-β-D-Glucopyranoside 12. Yield (3.8 g, 65%), clear thick oil. FT-IR (NaCl film, cm^{-1}): υ 3451 br, 3075, 2978, 2918, 2868, 1755, 1687, 1642, 1598, 1487, 1451, 1390, 1284, 1238, 1121, 998, 924, 842, 753, 703, 656, 614, 573. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.82–7.25 (m, 9H, arom.), 6.08–5.88 (m, 4H, 4 = C*H*), 5.46–5.03 (m, 8H, 4 = CH_2), 4.88–4.50 (m, 11H, H-1, –CH_2Ph, 4 × OCH_2), 4.09–3.69 (m, 6H, H-2, H-3, H-4, H-5, 2× H-6). ^{13}C-NMR ($CDCl_3$, 125 MHz): 170.8 (CO), 164.7 (arom.), 137.0 (arom.), 136.0–134.0 (CH=CH_2), 132.0 (arom.), 131.4 (arom.), 128.7–127.8 (arom.), 117.2 (arom.), 113.2 (CH=CH_2), 112.6 (CH=CH_2), 74.0 (C-4), 73.4 (C-5), 72.9, 69.2 (CH_2), 67.1, 61.1 (C-6), 52.1 (C-2), 51.8 (CH). CI-MS [*m*/*z* (%)]: 593 (M^+ +2) (2), 553 (2), 523 (4), 501 (1), 496 (5), 482 (6), 471 (7), 443 (7), 412 (4), 401 (7), 377 (8), 347 (11), 341 (4), 338 (6), 325 (5), 269 (9), 266 (5), 256 (3), 244 (6), 242 (6), 227 (13), 221 (14), 216 (6), 202 (20), 189 (6), 185 (21), 181 (3), 179 (21), 171 (27), 166 (6), 164 (16), 148 (11), 146 (27), 141 (7), 137 (16), 131 (46), 127 (25), 122 (9), 119 (36), 117 (10), 114 (9), 110 (23), 109 (23), 106 (55), 104 (27), 96 (16), 95 (17), 90 (100), 76 (21), 56 (15), 50 (15).

1,3,4,6-Tetra-O-Allyl-2-Deoxy-2-N-[(3-Benzyloxy-4-(4-Methoxyphenyl)-2-Azetidinone]-β-D-Glucopyranoside 13. Yield (3.6 g, 62%), clear thick oil. FT-IR (NaCl film, cm^{-1}): υ 3491, 3078, 3010, 2927, 2858, 1753, 1697, 1645, 1602, 1512, 1456, 1425, 1348, 1257, 1211, 1119, 1033, 996, 924, 834, 741, 700, 641, 604, 560, 517. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.81–6.96 (m, 9H, arom.), 5.90–5.60 (m, 4H, 4 = C*H*), 5.30–4.86 (m, 9H, H-1, 4 = CH_2), 4.86 (s, 2H), 4.40–3.97 (m, 8H, 4 × OCH_2), 3.85–3.57 (m, 6H, H-2, H-3, H-4, H-5, 2 × H-6), 3.72 (s, 3H, OCH_3). ^{13}C-NMR ($CDCl_3$, 125 MHz): 170.9 (CO), 164.7 (arom.), 137.0 (arom.), 136.0–134.0 (CH=CH_2), 132.0 (arom.), 128.7, 128.4, 128.3, 128.0, 116.7 (arom.), 114.6 (CH=CH_2), 73.5 (C-5), 73.1 (C-4), 72.8, 72.4, 72.2 (OCH_2), 72.0 (CH_2), 67.1 (C-6), 63.0 (CH), 55.9 (OCH_3), 52.0 (C-2), 51.8 (CH). CI-MS [*m*/*z* (%)]: 605 (M^+, 1), 497 (5), 485 (4), 457 (5), 440 (5), 416 (4), 387 (6), 379 (20), 364 (9), 346 (8), 345 (8), 337 (12), 329 (13), 321 (7), 307 (12), 293 (10), 285 (7), 279 (11), 267 (13), 251 (16), 227 (16), 222 (9), 208 (16), 179 (14), 175 (50), 160 (44), 152 (55), 147 (52), 134 (100), 120 (53), 80 (95), 78 (36), 54 (56).

1,3,4,6-Tetra-O-Allyl-2-Deoxy-2-N-[(3-Benzyloxy-4-(3-Methoxy-4-Hydroxy phenyl)-2-Azetidinone]-β-D-Glucopyranoside 14. Yield (3.7 g, 60%), clear thick oil. FT-IR (NaCl film, cm^{-1}): υ 3453 br, 3077, 2978, 2917, 2868, 1755, 1682, 1643, 1590, 1511, 1455, 1422, 1343, 1268, 1129, 1034, 925, 867, 810, 782, 736, 701, 659, 617, 567. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.34–6.95 (m, 8H, arom.), 6.07–5.60 (m, 4H,

4 = C*H*), 5.33–4.70 (m, 10H, 2H, 4 = CH_2), 4.69–4.09 (m, 8H, 4 × OCH_2), 3.95–3.57 (m, 6H, H-2, H-3, H-4, H-5, 2× H-6), 3.72 (s, 3H, OCH_3). ^{13}C-NMR ($CDCl_3$, 125 MHz): 170.8 (CO), 153.5 (arom.), 149.9 (arom.), 137.0 (arom.), 135.0, 134.8, 134.2, 133.7, 132.3 (CH=CH_2), 130.2, 128.7, 128.2, 127.5, 127.0, 126.6, 119.0, 118.6, 117.2 (arom.), 112.5, 112.1, 111.7 (CH=CH_2), 109.3 (arom.), 98.7 (C-1), 74.0 (C-4), 73.4 (C-5), 73.2, 72.8, 70.5, 70.4 (OCH_2), 69.9 (CH_2), 67.3 (CH), 56.2 (OCH_3), 46.0 (C-2). CI-MS [*m*/*z* (%)]: 648 (2), 585 (2), 543 (2), 533 (2), 513 (12), 501 (4), 473 (12), 454 (6), 445 (4), 431 (8), 426 (5), 415 (26), 400 (8), 394 (9), 385 (14), 374 (15), 366 (22), 356 (14), 329 (16), 315 (12), 298 (19), 285 (52), 274 (22), 259 (12), 246 (6), 232 (81), 217 (27), 207 (7), 204 (11), 191 (77), 177 (35), 161 (100), 155 (7), 150 (29), 133 (61), 126 (17), 120 (58), 117 (21), 112 (11), 110 (44), 108 (23), 104 (34), 97 (20), 94 (24), 92 (20), 76 (19), 56 (23), 54 (39), 50 (10).

1,3,4,6-Tetra-O-Allyl-2-Deoxy-2-N-[(3-Benzyloxy-4-(4-Chloropenyl)-2-Azetidinone]-β-D-Glucopyranoside 15. Yield (3.6 g, 60%), clear thick oil. FT-IR (NaCl film, cm^{-1}): υ 3480 br, 3077, 2979, 2926, 2869, 1755, 1729, 1643, 1597, 1490, 1451, 1347, 1271, 1207, 1092, 1013, 924, 830, 740, 700, 611, 524. ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.08, 7.98 (2d, 2H, *J* = 7.6, 8.4 Hz, arom.), 7.81 (2d, *J* = 8.4 Hz, 2H, arom.), 7.58–7.16 (m, 5H, arom.), 5.90–5.66 (m, 4H, 4 = C*H*), 5.29–4.95 (m, 9H, CH, 4 = CH_2), 4.86 (d, *J* = 17.5 Hz, 1H), 4.79 (d, *J* = 6.1 Hz, 1H, H-1), 4.69–4.07 (m, 8H, 4 × OCH_2), 3.77–3.53 (m, 6H, H-2, H-3, H-4, H-5, 2 × H-6), 3.36 (d, *J* = 6.9 Hz, 1H), 3.25 (d, *J* = 6.9 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 170.8 (CO), 139.5 (arom.), 137.1 (arom.), 134.3, 134.0, 133.6, 133.0 (CH=CH_2), 131.2, 129.2–127.8, 119.0, 116.9, 116.2 (arom.), 112.2 (CH=CH_2), 98.9 (C-1), 76.4 (C-5), 73.3 (C-3), 67.1 (OCH_2), 60.9 (CH), 52.0 (C-2). Calc.: $C_{34}H_{40}NClO_7$ (610.5); C: 66.93, H: 6.61, N: 2.30; found: C: 66.21, H: 6.33, N: 1.99.

1,3,4,6-Tetra-O-Allyl-2-Deoxy-2-N-[3-Benzyloxy-4-(3-Phenyl-Vinylidene)-2-Azetidinone-β-D-Glucopyranoside 16. Yield (3.8 g, 64%), clear thick oil. FT-IR (NaCl film, cm^{-1}): υ 3488, 3071, 3026, 2979, 2920, 1748, 1731, 1641, 1601, 1493, 1449, 1276, 1206, 1122, 996, 923, 751, 701, 613, 560. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.39–7.19 (m, 10H, arom.), 5.90–5.66 (m, 6H, 6 = C*H*), 5.27–4.85 (m, 11H, C*H*, −CH_2Ph, 4 = CH_2), 4.22–3.96 (m, 8H, 4 × OCH_2), 3.78–3.69 (m, 6H, H-2, H-3, H-4, H-5, 2 × H-6). ^{13}C-NMR ($CDCl_3$, 125 MHz): 170.9 (CO), 139.5 (arom.), 137.0 (arom.), 134.9−133.0 (CH=CH_2), 128.7–127.8, 119.0, 118.4, 117.7 (arom.), 116.0 (CH=CH_2), 73.4 (C-5), 67.1 (CH_2), 64.3, 64.1, 63.8 (OCH_2), 61.1 (C-6), 59.7 (OCH_2), 51.8 (CH), 45.6 (C-2). CI-MS [*m*/*z* (%)]: 585 (M^+ +16) (2), 567 (1), 557 (2), 536 (1), 485 (3), 453 (2), 412 (2), 409 (2), 400 (4), 395 (3), 385 (4), 379 (3), 371 (8), 356 (2), 351 (4), 342 (6), 325 (8), 300 (9), 279 (13), 258 (4), 244 (12), 238 (16), 227 (16), 223 (13), 215 (8), 211 (28), 204 (28), 195 (31), 183 (19), 171 (43), 166 (16), 164 (17), 154 (20), 152 (30), 148 (4), 140 (31), 130 (61), 128 (78), 116 (38), 114 (54), 109 (8), 104 (70), 102 (48), 96 (11), 94 (10), 91 (100), 88 (7), 76 (39), 66 (17), 50 (13).

General Procedure for Radical Elongations: Preparation of Compounds 17–21

A solution of perallyl *N*-substituted-2-azetidinone-D-glucosamines **12–16** (3 mmol), AIBN (0.1–0.2 mmol), and 2-mercaptoethanol (10 mL) in 1,4-dioxane (10 mL) was degassed by bubbling N_2 gas in solution before heating at 75 °C (preheated oil bath). Stirring was continued for 10 h and then concentrated to dryness. Coevaporation was carried out twice with toluene and the residue was purified on silica gel column chromatography (EtOAc and then 9:4:2 EtOAc/^{i}PrOH/H_2O).

1,3,4,6-Tetra-O-[3-(Hydroxythioethyl)-Propyl]-2-Deoxy-2-N-[(3-Benzyloxy-4-(2-Hydroxyphenyl)-2-Azetidinone]-β-D-Glucopyranoside 17. Yield (2 g, 75%), clear thick oil. FT-IR (NaCl film, cm^{-1}): υ 3333 br, 2920, 2868, 1755, 1661, 1598, 1487, 1451,1414, 1286, 1243, 1159, 1046, 1010, 935, 819, 757, 658. ^{1}H-NMR (CD_3OD, 500 MHz): 7.56–6.93 (m, 9H, arom.), 5.62 (d, 1H, $J = 7.6$ Hz, H-1), 5.58 (d, $J = 13.7$ Hz, 1H, –CH_2Ph), 5.55 (d, $J = 13.7$ Hz, 1H, –CH_2Ph), 4.60 (s br, 1H), 4.30–3.90 (m, 6H), 3.77 (m, 8H, 4 × CH_2OH), 3.69–3.57 (m, 10H, 4 × OCH_2, 2 × H-6), 3.29–3.28 (m, 1H, H-4), 2.81 (m, 8H, 4 × SCH_2—), 2.69–2.59 (m, 8H, —CH_2S—), 2.13–2.05 (m, 4H, 4 × OH), 1.91–1.74 (m, 8H, 4 × CH_2). ^{13}C-NMR (CD_3OD, 125 MHz): 155.3, 128.7, 128.5, 128.3, 111.7 (arom.), 66.4, 61.3, 61.0, 60.9, 60.8 (CH_2), 60.1, 59.9, 59.7, 59.0 (CH_2OH), 58.7 (C-2), 40.7 (CH), 34.3–33.5 (—S—*CH_2*—), —*CH_2*—S), 29.8–28.0 (—*CH_2*—CH_2—). Calc.: $C_{42}H_{65}NO_{12}S_4$ (904); S: 14.18; found: S: 14.53.

1,3,4,6-Tetra-O-[3-(Hydroxythioethyl)-Propyl]-2-Deoxy-2-N-[(3-Benzyloxy-4-(4-Methoxyphenyl)-2-Azetidinone]-β-D-Glucopyranoside 18. Yield (1.7 g, 63%), clear thick oil. FT-IR (NaCl film, cm^{-1}): υ 3454, 2918, 2858, 1753, 1662, 1611, 1510, 1416, 1286, 1046, 941, 833, 634. ^{1}H-NMR (500 MHz, CD_3OD): δ 7.36 (d, $J =$ 6.8 Hz, 2H, arom.), 7.10–6.90 (m, 5H, arom.), 6.86 (d, $J = 6.8$ Hz, 2H, arom.), 5.51 (s br, 1H, H-1), 5.42 (s br, 1H, CH), 5.10 (s, 2H, CH_2Ph), 4.90 (d, $J = 5.1$ Hz, 1H, CH), 4.60 (s br, 1H, CH), 4.25–4.10 (m, 2H, H-2, H-5), 3.80–3.75 (m, 8H, 4 × C*H_2*OH), 3.75 (s, 3H, OCH_3), 3.70–3.65 (m, 8H, 4 × OCH_2), 3.60 (m, 1H, H-5), 2.85–2.80 (m, 8H, 4 × SC*H_2*), 2.69–2.64 (m, 8H, 4 × CH_2S), 1.88–1.82 (m, 8H, 4 × CH_2). ^{13}C-NMR (125 MHz, CD_3OD): δ 148.7, 128.8–128.3, 109.1, 98.9, 71.8–70.1 (—O*CH_2*—), 61.3–61.1 (—*CH_2*—OH), 53.5, 53.4, 52.8–51.5, 34.3–32.7 (—S—*CH_2*—), 30.8–30.2 (—*CH_2*—S), 29.5–29.0 (—*CH_2*—CH_2—). Calc.: $C_{43}H_{67}NO_{12}S_4$ (918); S: 13.97; found: S: 14.41.

1,3,4,6-Tetra-O-[3-(Hydroxythioethyl)-Propyl]-2-Deoxy-2-N-[(3-Benzyloxy-4-(3-Methoxy-4-Hydroxyphenyl)-2-Azetidinone]-β-D-Glucopyranoside 19. Yield (1.9 g, 69%), clear thick oil. FT-IR (NaCl film, cm^{-1}): υ 3453 br, 2920, 2868, 1755, 1641, 1595, 1511, 1453, 1416, 1266, 1229, 1134, 1044, 937, 814, 755, 638. ^{1}H-NMR (CD_3OD, 500 MHz): 7.56–6.93 (m, 9H, arom.), 5.62 (d, 1H, $J = 7.6$ Hz, H-1), 5.58 (d, J = 13.75 Hz, 1H, –CH_2Ph), 5.55 (d, $J = 13.75$ Hz, 1H, –CH_2Ph), 4.06 (s br, 1H), 4.30–3.90 (m, 6H), 3.77 (m, 8H, 4 × CH_2OH), 3.69–3.57 (m, 10H, 4× OCH_2, 2× H-6), 3.29–3.28 (m, 1H, H-4), 2.81 (m, 8H, 4 × SCH_2—), 2.69–2.59 (m, 8H, —CH_2S—), 2.13–2.05 (m, 4H, 4 × OH), 1.91–1.74 (m, 8H, 4 × CH_2). ^{13}C-NMR (CD_3OD, 125 MHz): 148.7, 147.3, 146.0, 132.7, 128.0, 127.0, 119.6, 111.9 (arom.), 86.0 (CH, C-5), 66.2 (CH_2), 60.7, 60.3, 59.5, 59.1 (OCH_2), 52.2 (C-2), 40.1 (CH), 39.9, 39.7, 33.5, 33.3, 33.9 (—S*CH_2*—), 29.0–27.0 (—*CH_2*—CH_2—). Calc.: $C_{43}H_{67}NO_{13}S_4$ (934); S: 13.73; found: S: 14.02.

1,3,4,6-Tetra-O-[3-(Hydroxythioethyl)-Propyl]-2-Deoxy-2-N-[(3-Benzyloxy-4-(4-Chloropenyl)-2-Azetidinone]-β-D-Glucopyranoside 20. Yield (1.9 g, 70%), clear thick oil. FT-IR (NaCl film, cm^{-1}): υ 3353 br, 2920, 2869, 1755, 1644, 1413, 1284, 1220, 1047, 1009, 940, 825, 635. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.63–6.92 (m, 9H, arom.), 5.62 (d, 1H, $J = 7.6$ Hz, H-1), 5.58 (d, $J = 13.75$ Hz, 1H, —CH_2Ph), 5.55 (d, $J = 13.75$ Hz, 1H, —CH_2Ph), 4.60–3.95 (m, 7H), 3.77 (m, 8H, 4 × CH_2OH), 3.69–3.57 (m, 10H, 4 × OCH_2, 2 × H-6), 3.29–3.28 (m, 1H, H-4), 2.81 (m, 8H, 4 × SCH_2—), 2.70–2.50 (m, 8H, —CH_2S—), 1.91–1.74 (m, 8H, 4 × CH_2). ^{13}C-NMR (CD_3OD, 125 MHz): 155.3, 128.7, 128.5, 128.3, 111.7 (arom.), 66.4 (CH_2), 61.3, 60.8, 60.1 (C-6), 59.7, 59.0, 58.7 (OCH_2), 41.1 (C-2), 40.7 (CH), 34.3–33.5 (S*CH_2*), 29.8–28.0 (*CH_2*—CH_2—). Calc.: $C_{42}H_{64}NClO_{11}S_4$ (922.5); C: 54.67, H: 6.99, N: 1.52, S: 13.90; found: C: 53.40, H: 6.17, N: 1.03, S: 13.62.

1,3,4,6-Tetra-O-[3-(Hydroxythioethyl)-Propyl]-2-Deoxy-2-N-[3-Benzyloxy-4-(3-Phenyl-Vinylidene)-2-Azetidinone]-β-D-Glucopyranoside 21. Yield (1.9 g, 70%), clear thick oil. FT-IR (NaCl film, cm^{-1}): υ 3328 br, 2917, 1728, 1712, 1695, 1665, 1644, 1601, 1554, 1535, 1448, 1414, 1285, 1220, 1044, 940, 819, 761, 703, 660. ^{1}H-NMR (500 MHz, CD_3OD): δ 7.50–7.25 (m, 10H, arom.), 6.94 (d, J = 16.4 Hz, 1H, C*H*=CH_{trans}), 5.50 (s br, 1H, H-1), 5.42 (s br, 1H, CH), 4.82 (s, 2H, CH_2Ph), 4.20–3.90 (m, 4H, H-2, H-5, 2 × CH), 3.80–3.60 (m, 8H, 4 × CH_2OH), 3.60–3.40 (m, 8H, 4 × OCH_2), 2.82–2.80 (m, 8H, 4 × SCH_2), 2.64–2.60 (m, 8H, 4 × CH_2S), 1.84–1.70 (m, 8H, 4 × CH_2). ^{13}C-NMR (CD_3OD, 125 MHz): δ 154.1 (arom.), 128.7–127.3 (arom.), 111.7, 71.78–69.95 (−O−CH_2−), 61.36–60.90 (−CH_2−OH, C-6), 53.53 (CH), 51.83 (C-2), 34.60–32.79 (−SCH_2−), 30.81–30.22 (−CH_2−S), 29.46–28.37 (−CH_2−CH_2−). Calc.: $C_{44}H_{67}NO_{11}S_4$ (914); S: 14.03; found: S: 13.97.

CONCLUSIONS

The synthesis of new persulfide-spacer *N*-substituted-2-azetidinone-D-glucosamine in the attempt to potentially provide new antibiotics is described. Staudinger [2+2] cycloaddition of benzyloxyacetyl chloride to the newly reported per-*O*-allyl-*N*-substituted benzylidene-2-deoxy-β-D-glucosamines **3**, **5**, **7**, **9**, and **11** provided the sugar-based monocyclic β-lactams **12–16** in good yields. Radical addition of 2-mercaptoethanol to per-*O*-allyl-*N*-substituted-2-azetidinone-D-glucosamine led to the persulfide spacers **17–21** in good yields. All new compounds were characterized by spectroscopic and spectrometric methods. The reported glucosides showed a moderate antifungal activity against *Candida albicans* while being slightly active against gram-positive and gram-negative bacteria used in this work. The SEM image of 1,3,4,6-tetra-*O*-[3-(hydroxythioethyl)-propyl]-2-deoxy-2-N-[(3-benzyloxy-4-(4-chloropenyl)-2-azetidinone]-β-D-glucopyranoside, as a representative example, demonstrated a super hydrophobic layer formed via highly organized thioether spacers on gold as the adsorbate system through the formation of sulfur–gold bonds. The formation of self-assembled hydrophobic layer of carbohydrate-containing thioether spacers on gold with a high degree of structural order is an important class of model substrates for the mechanistic investigation of biomolecules and they might have potential application as platforms for studies of cell adhesion due to their flexibility.[36,37]

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