Phenylethanoid and Lignan Glycosides from Polar Extracts of *Lantana*, a Genus of Verbenaceous Plants Widely Used in Traditional Herbal Therapies

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Many references to the use of *Lantana* spp. can be found in the ethnopharmacological literature from locations around the globe. This study was focused on examining constituents from the polar extracts of *Lantana radula* Sw. and *Lantana canescens* Kunth, for which no prior chemical investigations had been reported. A new phenylethanoid glycoside, raduloside, and lignan glycoside, radulignan, were identified along with the known compounds alyssonoside, arenarioside, calceolarioside E, isonuomioside, samioside, and verbascoside.

Surprisingly little is known about the chemical profiles of *Lantana* spp. (Verbenaceae) despite their widespread native distributions and modern-day emergence as invasive weeds into many new locations. Certain members of this genus, such as *Lantana camara* L., are well recognized for their significant toxicity, which has been the cause of several reported livestock poisonings.[1] The toxicity of *L. camara* is attributed to a series of oleane-type triterpenes known as the lantadenes, and studies of these metabolites have confirmed their abilities to induce liver and kidney dysfunctions and cause photosensitization.[1−3] Additional compounds that have been reported from *Lantana* include GR133487 and GR133686, and these euphane-type triterpenes were formerly pursued by Glaxo Wellcome (now GlaxoSmithKline PLC) for their inhibitory properties against human α-thrombin.[4,5]

Our group had become intrigued by the large number of ethnopharmacological uses ascribed to various *Lantana* spp., including *L. camara.*[6] These plants have been reportedly used to treat infections, ulcerations, tumors, rheumatism, fevers, and other conditions in Africa,[7−9] the Bahamas,[10] India,[11−13] Jordan,[14] Mexico,[15] Venezuela,[16] and Brazil.[17,18] While no studies have specifically addressed the extent to which the lantadenes are distributed throughout the genus *Lantana*, there is evidence suggesting that certain toxins such as lantadene A (also known as rehmannic acid) occur in most *L. camara* varieties[19−21] and are found in other taxa such as *Lippia turbinata* Griseb. (Verbenaceae)[22] and *Cordia multispicata* Cham. (Boraginaceae).[23] One explanation for the apparent lack of overt toxicity associated with human ingestion of *Lantana* extracts is likely attributable to the method in which herbal medicines are traditionally prepared. Most herbal extracts and tinctures are made by steeping plant material in water or aqueous alcohol, respectively, which favors the extraction of hydrophilic compounds while excluding many hydrophobic substances. Lantadene A and other structurally similar triterpenes have poor predicted solubility in aqueous solvents,[24] which would limit their incorporation into medicinal preparations. Having considered these features, we were interested in investigating the types of metabolites that would be obtained from *Lantana* under polar extraction conditions since no such study had been previously reported. We anticipated that this approach would help us characterize the secondary metabolites encountered in *Lantana*-derived medicinal preparations and assist us in targeting these specific compound classes during future bioassay studies.

Two *Lantana* spp., *L. radula* Sw. and *L. canescens* Kunth, for which no prior chemical investigations have been reported, were selected for investigation. Dried root materials of both plants were extracted with 95% EtOH, and after removal of the solvent from each sample, the resultant organic extracts were subjected to a modified Kupchan partitioning scheme with hexanes, CH_2Cl_2, and EtOAc. The remaining aqueous-soluble materials were dried and fractionated by passing over HP-20SS resin (gradient MPLC: 100% H_2O to 100% MeOH). Profiling of the fractions by TLC, HPLC, and NMR drew our attention to several samples that appeared to contain phenolic constituents based on chemical and spectroscopic evidence (positive color change with phosphomolybdic acid, strong UV absorbance at 254 nm, and ^{1}H NMR resonances from δ_H 6.5 to 7.5).

One of the phenolic-containing fractions from *L. radula* yielded a compound with an *m*/*z* of 897.2651 $[M + Na]^+$ by HRESIMS, leading us to assign compound **1** a molecular formula of $C_{38}H_{50}O_{23}$. Analysis of ^{1}H NMR (Table 1), ^{1}H−^{1}H COSY, and ^{1}H−^{1}H TOCSY data allowed for the discernment of two phenolic substructures in **1** that were readily assigned as (*E*)-caffeoyl [δ_H 7.50 (d, J = 15.4 Hz, H-β), 7.05 (d, J = 1.8 Hz, H-2), 7.01 (dd, J = 8.3 and 1.8 Hz, H-6), 6.77 (d, J = 8.3 Hz, H-5), and 6.26 (d, J = 15.4 Hz, H-α)] and 3,4-dihydroxyphenethyl [δ_H 6.64 (d, J = 2.0 Hz, H-2), 6.58 (d, J = 8.2 Hz, H-5), 6.51 (dd, J = 8.2 and 2.0 Hz, H-6), 3.87/3.61 (each m, H-α_a and H-α_b), and 2.69 (m, H-β_a and H-β_b)] residues (Table 1). The remaining ^{1}H NMR resonances were attributable to four sugar residues that included distinctive anomeric proton signals for β-glucose [δ_H 4.39 (d, J = 7.8 Hz, H-1‴)], β-xylose [δ_H 4.15, H-1″)], and two β-apiose units [δ_H 5.19 (d, J = 2.7 Hz, H-1⁗) and 4.80 (d, J = 2.9 Hz, H-1′)], suggesting that compound **1** had a tetrasaccharide core. These assignments were substantiated by analysis of the acid hydrosylate of **1**, which resulted in the liberation of glucose, xylose, and apiose, all presumably possessing D-configurations. The positions of the glycosidic bonds were determined by an HMBC experiment (Table 1) showing $^3J_{H-C}$ correlations from H-1′ → C-4″, H-1⁗ → C-6‴, and H-1⁗ → C-4‴ (Figure 1). This established the structure of the tetrasaccharide moiety as β-D-Api-(1→4)-β-D-Xyl-(1→6)-β-D-Glc-(4→1)-β-D-Api (Figure 1). Additional HMBC correlations (Table 1) were instrumental for assigning the positions of the 3,4-dihydroxyphenethyl (H-α_a and H-α_b → C-1‴) and (*E*)-caffeoyl (H-4‴ → C=O$_{caffeoyl}$) subunits (Figure 1). This established the structure of compound **1** as shown, and we have assigned it the trivial name raduloside in

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Table 1. NMR Data (DMSO-d_6) for Raduloside (**1**)[a]

position	δ_C	δ_H mult. (J in Hz)	HMBC (H→C)
aglycone			
1	129.9		
2	116.3	6.64 d (2.0)	C-1, C-3, C-β
3	144. 0		
4	146.0		
5	116.8	6.58 d (8.2)	C-1, C-3, C-4
6	119.4	6.51 dd (8.2, 2.0)	C-1, C-4, C-β
α	70.83	3.61 m, 3.87 m	C-1, C-1‴, C-β
β	35.66	2.69 m	C-1, C-6, C-α
caffeoyl			
1	126.4		
2	115.1	7.05 d (1.8)	C-1, C-3
3	146.1		
4	148.8		
5	116.2	6.77 d (8.3)	C-1, C-3, C-4
6	122.2	7.01 dd (8.3, 1.8)	C-4, C-β
α	114.1	6.26 d (15.4)	C-1, C-β, C=O
β	146.0	7.50 d (15.4)	C-2, C-α, C=O
C=O	166.7		
Api 1			
1′	109.2	4.80 d (2.9)	C-2′, C-3′, C-4″
2′	73.6	2.96 m	C-4′
3′	79.2		
4′	73.8	3.56 m, 3.78 m	C-2′, C-3′, C-5′
5′	63.9	3.35 m	C-3′, C-4′
Xyl			
1″	104.2	4.15[b]	C-3″, C-6‴
2″	73.6	2.96 m	C-3″
3″	76.7	3.68 m	C-4″, C-5‴
4″	69.7	3.25 m	C-2″
5″	68.3	3.45 m, 3.66 m	C-1″, C-3″
Glc			
1‴	102.7	4.39 d (7.8)	C-3‴, C-α
2‴	76.6	3.08 m	C-4‴
3‴	73.5	3.66 m	C-2‴
4‴	69.2	4.71 m	C-3‴, C=O
5‴	76.6	3.08 m	C-3‴, C-4‴
6‴	66.0	2.98 m, 3.66 m	C-1″, C-5‴
Api 2			
1⁗	109.9	5.19 d (2.7)	C-2⁗, C-3⁗, C-4‴
2⁗	74.4	3.24 m	C-1⁗, C-4⁗
3⁗	79.1		
4⁗	74.0	3.56 m, 3.78 m	C-3⁗, C-5⁗
5⁗	63.9	3.35 m	C-4⁗

[a] NMR experiments were performed at 500 (^{1}H and HMBC) and 100 MHz (^{13}C). [b] This resonance appeared under the residual H_2O, preventing the determination of its multiplicity.

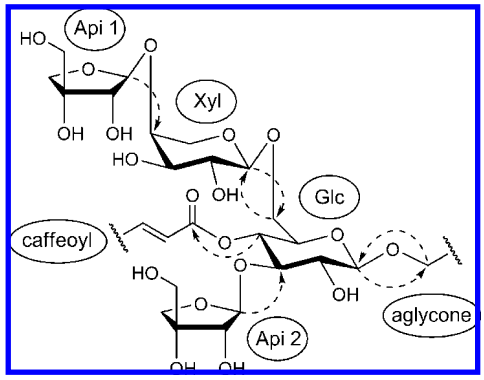
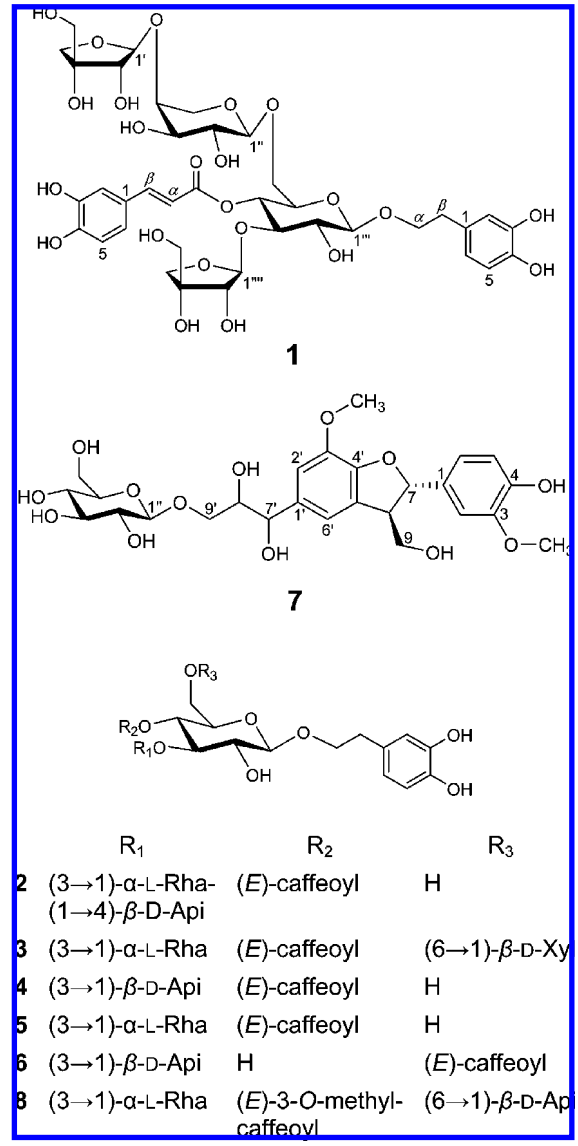


Figure 1. Key HMBC $^{2-3}J_{H\rightarrow C}$ correlations (dashed arrows) used to establish the structure of the tetrasaccharide core, as well as the aglycone and caffeoyl substituent positions for raduloside (**1**).

recognition of its biogenetic source. Very few phenylethanoid tetraglycosides like compound **1** have been reported (e.g., lunaroside,[25] marruboside,[26] magnolioside C,[27] ballotetroside,[28] trichosanthoside B,[29] and velutinosides I and II[30]). Five additional phenylethanoid glycosides were also isolated from *L. radula*, and these were identified as the known compounds samioside[31] (**2**), arenarioside[32] (**3**), calceolarioside E[33] (**4**), verbascoside[34] (**5**), and isonuomioside A[35] (**6**). On the basis of this study, *L. radula* appears to be a rich source of phenylethanoid glycosides. Phenylethanoid glycoside metabolites from several different plant species have been previously investigated for a variety of potential therapeutic applications including antimicrobial and blood-platelet aggregation-modulating effects.[36,37]



Compound **7** was also isolated from *L. radula* roots. It exhibited an m/z of 577.1912 $[M + Na]^+$ by HRESIMS and was assigned a molecular formula of $C_{26}H_{34}O_{13}$. ^{1}H NMR data for **7** (Table 2) revealed several high-field spins that were distinct from those observed in the phenylethanoid glycosides, suggesting that this isolate belonged to a different class of metabolites. Five aromatic proton [δ_H 6.91 (1H, d, J = 1.8 Hz, H-2), 6.86 (2H, s, H-2′ and H-6′), 6.75 (1H, dd, J = 8.1 and 1.8 Hz, H-6), and 6.74 (1H, d, J = 8.1 Hz)] and 12 carbon [δ_C 109.7, 110.6, 114.4, 114.8, 117.7, 128.2, 132.3, 136.1, 142.6, 146.1 (×2), and 147.2] resonances were observed, accounting for two substituted benzene rings in **7**. The four furthest downfield resonances in the ^{13}C NMR spectrum [δ_C 142.6, 146.1 (×2, overlapping), and 147.2] were rationalized as belonging to two sets of *ortho*-oxygenated aromatic carbons, as was later confirmed by a ^{1}H−^{13}C HMBC experiment (H-2 → C-3 and C-4, H-2′ → C-3′ and C-4′) (Table 2). Two of these oxygen atoms were deduced as having attached methyl groups (δ_C 55.2 and 55.3) whose protons [δ_H 3.74 (s) and 3.77 (s), respectively]

Table 2. NMR Data (DMSO-d_6) for Radulignan (**7**)[a]

position	δ_C	δ_H mult. (*J* in Hz)	HMBC (H→C)
1	132.3		
2	109.7	6.91 d (1.8)	C-3, C-4
3	146.1		
3-OCH_3	55.2	3.74 s	C-3
4	147.2		
4-OH		9.00 s	C-3, C-5
5	114.8	6.74 d (8.1)	C-3
6	117.7	6.75 dd (8.1; 1.8)	C-1, C-4
7	86.6	5.42 d (6.8)	C-1, C-8, C-9
8	52.7	3.42 m	C-7, C-4′
9	62.6	3.59 m, 3.69 dd (15.5; 5.3)	C-7, C-8
9-OH		4.99 m	
1′	136.1		
2′	110.6	6.86 s[b]	C-3′, C-4′
3′	146.1		
3′-OCH_3	55.3	3.77 s	C-3′
4′	142.6		
5′	128.2		
6′	114.4	6.86 s[b]	C-8
7′	71.9	4.52 t (4.7)	C-6′
7′−OH		4.99 m	
8	73.2	3.67 m	C-9′
8′-OH		4.54 d (5.8)	
9′	70.4	3.51 dd (10.5; 5.0), 3.56 dd (10.5, 6.4)	C-7′, C-8′, C-1″
1″	102.7	4.12 d (8.4)	C-2″, C-9′
2″	73.1	2.98 dt (8.4, 4.4)	C-3″
2″-OH		5.01 d (4.4)	
3″	76.1	3.13 ddd (9.08, 7.8; 5.0)	C-4″, C-1″, C-2″
3″-OH		4.92 d (5.0)	
4″	69.6	3.04 ddd (9.08, 9.08, 5.5)	C-5″, C-3″
4″-OH		4.89 d (5.5)	
5″	76.4	3.07 ddd (9.08; 5.6; 2.2)	C-4″, C-3″, C-6″
6″	60.6	3.41 ddd (16.0; 5.8; 5.6), 3.65 ddd (16.0; 5.8; 2.2)	C-4″, C-5″
6″-OH		4.49 t (5.8)	

[a] NMR experiments were performed at 800 (^{1}H and HMBC) and 150 MHz (^{13}C). [b] Despite partially overlapping, these resonances were distinguishable from one another at 18.8 T for HSQC and HMBC experiments.

showed strong $^3J_{H-C}$ couplings to overlapping carbon spins (δ_C 146.1) (Table 2). ^{1}H and ^{13}C NMR shift data (Table 2) indicated the presence of a β-glucose, and this was presumed to possess a D-configuration by comparison of the residue from the acid hydrolysis of **7** to an authentic sample of the sugar. The remaining six carbon atoms in **7** (δ_C 52.7, 62.6, 70.4, 71.9, 73.2, and 86.6) were readily assigned by a ^{1}H−^{13}C HMBC experiment to two separate groups (group 1: H-7 → C-8 and H-9 → C-7, group 2: H-9′ → C-7′ and H-9′ → C-8′) (Table 2). The first set of three carbons (C-7, C-8, and C-9) served as a bridge linking the two aromatic rings, while the second group of carbons (C-7′, C-8′, and C-9′) joined an aromatic ring to the β-D-glucose. Thus, the structure of this isolate was determined to be the new glucosylated lignan **7**.

Interestingly, NMR chemical shift data for the aglycone of **7** were found to be comparable to values reported for sisymbrifolin, which had been isolated from *Solanum sisymbrifolium*.[38] However, the ^{1}H−^{1}H coupling between H-7′ and H-8′ was dissimilar for the two compounds (J = 4.7 Hz for compound **7** versus $J \approx 7$ Hz for sisymbrifolin penta- and tetra-acetates). The configurations of both stereogenic centers had not been previously assigned, and despite our attempts to rationalize this problem using $^3J_{HH}$ coupling and ^{1}H−^{1}H ROESY experiments, we could not define their relative configurations with confidence. In contrast, we were successful in analyzing the C-7 and C-8 stereogenic centers, which were assigned as 7*S**,8*R** on the basis of proton coupling data ($^3J_{H\text{-}7,H\text{-}8}$ = 6.8 Hz) and ^{1}H−^{1}H ROESY experiment (correlation observed between H-2/H-6 → H-8 and H-7 → H-9). Examination of **7** by circular dichroism showed a strong positive Cotton effect at 290 nm (+5.02) for the ^1L_b band, which has been previously shown in C-3 methoxy-containing lignans to be indicative of a 7*S*,8*R* configuration.[39] Thus, the structure of this new metabolite was deduced as that shown for **7**, and we have given this compound the trivial name radulignan.

Our subsequent analysis of the polar root extract from *L. canescens* showed a very different set of metabolites in this plant. The only detected phenylethanoid glycoside was determined to be the compound alyssonoside (**8**) on the basis of comparisons of its ESIMS, NMR, and chemical degradation data to published values.[40] Therefore, we suspect that *Lantana* spp. exhibit significant diversity in their polar secondary metabolites and that this will greatly influence the pharmacological properties of extracts and tinctures made from these plants. We did not detect any of the previously noted toxic olean-type triterpenes in the polar extracts of *Lantana* roots, adding further confirmatory evidence that species/strain plant selection and preparation methods play important roles in ensuring the safety and efficacy of plants used in traditional medical settings. Furthermore, compounds **1** and **7** were tested for cytotoxicity against several cell lines (HL-60, K562, U937, CEM, KG-1, Jurkat, U266, and NCI-H929) and were determined to not inhibit cell viability at 10 μM. Additional studies will be needed to more thoroughly scrutinize the distribution of phenylethanoid glycosides in *Lantana* spp., as well as determine their potential contributions to the therapeutic effects ascribed to these plants.

Experimental Section

General Experimental Methods. Optical rotations were measured on a Rudolph Research Autopol III automatic polarimeter, while CD spectra were recorded on an Aviv model 202-01 instrument. Nuclear magnetic resonance experiments were performed on Varian Inova (600 and 800 MHz instruments with triple resonance and broadband probes, respectively) and VNMRS (400 and 500 MHz instruments with broadband and triple resonance probes, respectively) spectrometers at 20 ± 0.5 °C with samples prepared in DMSO-d_6. ESIMS data were acquired on a LCT Premier (Waters Corp.) time-of-flight instrument. HPLC separations were performed on a Shimadzu system using a SCL-10A VP system controller and Gemini 5 μm C-18 column (110 Å, 250 × 21.2 mm) with flow rates of 1 to 10 mL/min. All solvents were of ACS grade or better.

Plant Material. Roots (*L. radula* and *L. canescens*) were collected in Joao Pessoa, State of Pernambuco, Brazil, in January 2006. The plants were identified by Dr. Rita de Cassia Pereira. Voucher specimens of *L. radula* and *L. canescens* were deposited under numbers 70004 and 74048, respectively, at the Herbarium Dárdano de Andrade Lima, in Empresa Pernambucana de Pesquisa Agropecuaria (IPA), State of Pernambuco, Brazil.

Extraction and Isolation. Dried and powdered roots (5.5 kg) of *Lantana radula* were extracted with 95% EtOH (×3) at room temperature. The EtOH was evaporated at 40 °C under reduced pressure, affording 454 g of crude extract. A portion of the crude extract (250 g) was dissolved in H_2O and successively partitioned with hexanes, CH_2Cl_2, and EtOAc. The aqueous phase was subjected to MPLC over HP-20SS resin at 70 psi pressure using a step-gradient of MeOH−H_2O mixtures (100% H_2O to 100% MeOH). The MPLC fraction eluting with 1:1 MeOH−H_2O was further separated by gradient HPLC (mobile phase 10% to 30% MeCN in H_2O), yielding **1** (10 mg), **2** (8 mg), and **3** (5 mg). The MPLC fraction eluting with 100% MeOH was further separated by HPLC (10% to 100% acetonitrile in H_2O), yielding **7** (6 mg), **4** (12 mg), **5** (8 mg), and **6** (10 mg). The EtOH extract of *L. canescens* (100 g) was first passed over a silica gel column with increasing amounts of MeOH in EtOAc. Several of the late eluting fractions were pooled and further purified by HPLC (10% to 100% MeCN in H_2O), yielding **8** (5 mg).

Acid Hydrolysis. Hydrolysis experiments were performed on **1** and **7** by dissolving compounds in 10 mL of 2 N HCl and heating the mixture at 100 °C for 2 h. The cooled reaction mixtures were then extracted twice with EtOAc (20 mL), and the aqueous phases were added to HP-20 resin in H_2O. After equilibrating, the resin samples were washed with H_2O and the bound organic materials were removed with 1:1 MeOH−H_2O. Solvent was evaporated from each sample under reduced pressure, and the residues were spotted on analytical TLC plates along with carbohydrate standards. Plates were developed using 100:11:11:26 EtOAc−AcOH−formic acid−H_2O, and spots were visualized

using a sulfuric acid−vanillin spray reagent. Due to limited amounts of the samples and degradation of the hydrolysis products following TLC examination, determination of the carbohydrate residues was based on NMR and TLC analyses.

Cytotoxicity Assay. The cytotoxicity assay was performed according to a previously described method.[41] Briefly, cells (HL-60, K562, U937, CEM, KG-1, Jurkat, U266, and NCI-H929) were distributed into 96-well plates containing growth medium (RPMI 1640 supplemented with 10% fetal calf serum and 10 units/mL penicillin−streptomycin). Cells were cultured for 24 h (37 °C in a humidified atmosphere with 5% CO_2) before being treated with compounds dissolved in DMSO (final concentration <1% by vol). After 48 h of incubation, 20 μL of resazurin solution (Promega CellTiter-Blue cell viability assay kit) was added to each well and the cells were incubated an additional 2 h prior to fluorescence measurements with a microplate fluorometer (λ_{Ex} 560 nm, λ_{Em} 590 nm). All experiments were performed in triplicate.

Raduloside (1): amorphous, pale yellow solid; $[\alpha]_D^{20}$ −9.8 (*c* 0.1, MeOH); ^{1}H NMR and ^{13}CNMR data, see Table 1; HRESIMS *m/z* 897.2651 $[M + Na]^+$ (calcd for $C_{38}H_{50}O_{23}Na$, 897.2641).

Radulignan (7): amorphous, pale yellow solid; $[\alpha]_D^{20}$ −135.9 (*c* 0.1, MeOH); CD (*c* 0.05, MeOH) λ ($\Delta\varepsilon$) 290 (+5.0), 238 (+10.9); ^{1}H NMR and ^{13}CNMR data, see Table 2; HRESIMS *m/z* 577.1912 $[M + Na]^+$ (calcd for $C_{26}H_{34}O_{13}Na$, 577.1897).

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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