JOURNAL OF NATURAL PRODUCTS

pubs.acs.org/jnp

Article

Antimycobacterial Activities of the *Zanthoxylum leprieurii* Metabolite Adubangoamide and Non-Natural Fagaramide Analogues

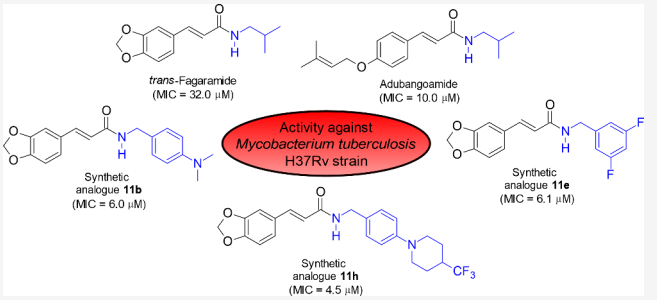
Benson Oloya,* Jane Namukobe, Mandy Krüger, Willy Ssengooba, Eric Sperlich, George Kwesiga, Kevin Komakech, Matthias Heydenreich, Robert Byamukama, and Bernd Schmidt*

Cite This: *J. Nat. Prod.* 2025, 88, 530−536

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: *trans*-Fagaramide (**1**) and adubangoamide (**2**) are natural products with a cinnamic acid amide skeleton that have recently been isolated from *Zanthoxylum leprieurii*, a medicinal plant used locally in Uganda for the treatment of tuberculosis. Insufficient quantities of material from the natural source originally prevented the antimycobacterial evaluation of the new natural product **2**. Herein, a synthesis of **2** is reported, and its antimycobacterial activity was determined using the synthetic material. Adubangoamide (**2**) is three times more active against the drug-susceptible *M. tuberculosis* strain $H_{37}Rv$ than *trans*-fagaramide (**1**), with an MIC value of 10.0 μM. In addition, we synthesized eight non-natural analogues of *trans*-fagaramide (**1**, MIC = 32.0 μM against $H_{37}Rv$ strain), in which benzylamide groups mimic the isobutylamide part of the *trans*-fagaramide structure. Five out of eight synthetic analogues are more active than the parent natural product: **11b** (MIC = 6.0 μM), **11d** (21.0 μM), **11e** (6.1 μM), **11g** (17.0 μM), and **11h** (4.5 μM).

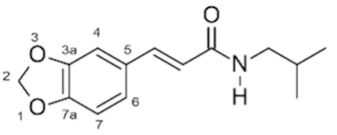


Tuberculosis (TB) is a major cause of ill health and one of the leading causes of death worldwide.[1] Reduced access to TB diagnosis and treatment due to interruptions brought in by the COVID-19 pandemic has increased TB deaths. The COVID-19 pandemic has more severely impacted TB mortality in 2020 and 2021 than HIV/AIDS.[1,2] Worldwide, the estimated number of deaths from TB increased between 2019 and 2021, reversing years of decline between 2005 and 2019. In 2021, there were an estimated 1.4 million deaths among HIV-negative people and 187,000 deaths among HIV-positive people, a combined total of 1.6 million. This was up from the best estimates of 1.5 million in 2020 and 1.4 million in 2019 and back to the level of 2017,[1] indicating a resurgence in the TB pandemic. Furthermore, the net reduction from 2015 to 2021 was 5.9%, about one-sixth of the way to the first milestone of the WHO End TB Strategy.[1] As such, the WHO End TB Strategy still needs a lot of effort to be achieved. This calls for multifaceted approaches to reverse the trend, which includes the search for alternative treatments.

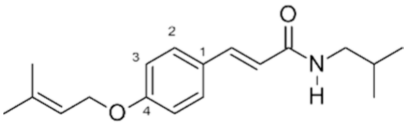
Natural products from plants often possess a number of exciting bioactivities and have therefore emerged as templates for the development of novel drugs,[3−5] including potential anti-TB agents.[6−9] Therefore, medicinal plants remain essential for finding original active drugs or new therapeutic agents. Hence, there is a need to search for new molecular structures from the plant kingdom as lead structures.[10] *Zanthoxylum leprieurii* is a tree distributed in tropical Africa that is used locally in Uganda for the treatment of TB.[11] Some of us have recently reported that the root bark extract of *Z. leprieurii* exhibits activity against *Mycobacterium tuberculosis*.[12] In two phytochemical investigations, we isolated six known natural products from the *Z. leprieurii* stem bark,[13] and 16 known and two new compounds from its root bark.[14] Among these compounds, in particular *trans*-fagaramide (**1**), a natural product previously isolated from many *Zanthoxylum* species,[15] showed a notable antimycobacterial activity against the susceptible ($H_{37}Rv$) TB strain (MIC = 7.82 $\mu g \bullet mL^{-1}$ (32 μM)).[14] Although numerous bioactivities had been reported for *trans*-fagaramide (**1**) before,[16] its notable antimycobacterial activity was unknown prior to our investigation.[13] One of the two new natural products isolated by us from the *Z. leprieurii* root bark,[14] adubangoamide (**2**), is structurally closely related to *trans*-fagaramide (**1**), as both are cinnamides of isobutylamine. Adubangoamide (**2**) could only be isolated in minute amounts (1 mg of **2** from 1 kg of plant material) from its

Received: December 3, 2024
Revised: January 31, 2025
Accepted: February 3, 2025
Published: February 11, 2025

natural source, which initially prevented an investigation into its antimycobacterial activity.



1



2

A literature search revealed that cinnamic acids and their derivatives have been intensively investigated for the treatment of tuberculosis for quite some time. The first publication in this regard dates from 1893 and reports the treatment of tuberculous rabbits with cinnamic acid.[17,18] More recently, the synergistic activity of cinnamic acid in combination with established drugs[19,20] and the antitubercular activity of natural cinnamic acids[21] and synthetic cinnamic acid derivatives has been established.[22−25] It was demonstrated that cinnamide analogues of rosmarinic acid, a caffeic acid ester, act through inhibition of UDP-galactopyranose mutase, an enzyme required for cell wall biosynthesis of *M. tuberculosis*.[26]

This literature precedence, in combination with the above-mentioned remarkable antitubercular activity of *trans*-fagaramide (**1**) and the traditional use of *Z. leprieurii* in Uganda for treating tuberculosis prompted us to synthesize the new natural product adubangoamide (**2**) to obtain sufficient amounts for antimycobacterial testing. Additionally, structural analogues of *trans*-fagaramide (**1**) were synthesized by varying the amine part of the cinnamide structure via amide coupling reactions. To gain first insights into structure−activity relationships and identify potentially more active derivatives, all compounds were tested against drug-susceptible ($H_{37}Rv$) and resistant MDR-TB strains.

RESULTS AND DISCUSSION

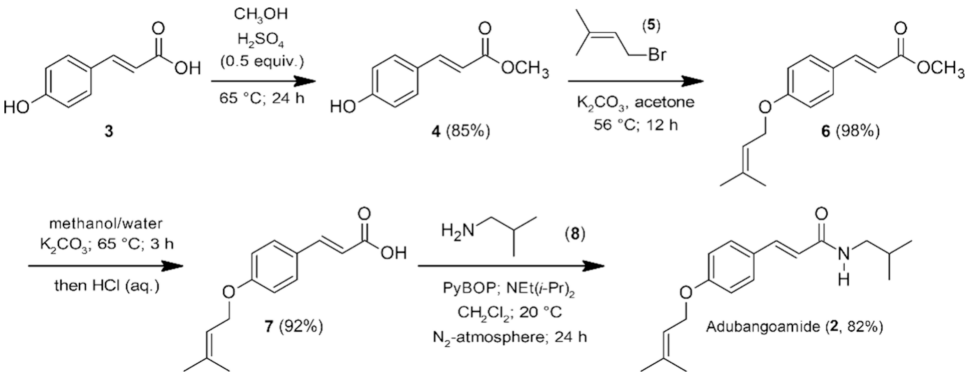
Total Synthesis of Adubangoamide (2). Adubangoamide (**2**) was synthesized in four steps from commercially available *para*-coumaric acid (**3**). The synthesis proceeds by esterification of **3** to its methyl ester **4**[27] to enable selective *O*-prenylation of the phenol with prenyl bromide (**5**) in the next step,[22] without concomitant prenylation of the carboxylate. The resulting *para*-prenyloxy methylcinnamate (**6**) was saponified to carboxylic acid **7**,[22] which was reacted with isobutylamine (**8**) using the peptide coupling reagent[28] PyBOP (benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate)[29] and Hünig's base to furnish adubangoamide (**2**) in 63% yield over four steps (Scheme 1). All analytical data of synthetic **2** match those previously reported for the compound isolated from the natural source.[14]

Synthesis of Fagaramide Analogues. The notable antimycobacterial activity of *trans*-fagaramide (**1**)[13] and its structural similarity with the new natural product **2** prompted us to synthesize amide analogues of **1**, to enable a preliminary investigation into the structure−activity relationship. To mimic the branched *N*-(2-methylpropyl) substituent present in fagaramide (**1**) and adubangoamide (**2**) we focused on amides derived from various benzylamines **10** through coupling with commercially available 3,4-(methylenedioxy)cinnamic acid (**9**). The formation of the amide bond was accomplished with PyBOP as a coupling reagent under conditions identical to those used for the synthesis of adubangoamide (**2**). Apart from six commercially available benzylamines **10a−f**, carboxylic acid **9** was also coupled with two benzylamines **10g,h**, that were synthesized based on previously published general procedures,[30] to furnish in total eight carboxamides **11a−h** (Scheme 2). Imidazo[1,2-*a*]pyridine amides,[30] pyrazolo[1,5-*a*]pyridine amides[31] and nitrobenzamides[32,33] of amines **10g** and **10h** have earlier been synthesized, and it was reported that they show high antimycobacterial activity against the same MTB $H_{37}Rv$ strain that has also been used by us.

Out of the eight *trans*-fagaramide analogues **11a-h** only compound **11a** had previously been described in the literature. It was synthesized by amide coupling of acid **9** and benzyl amine (**10a**) in 38% yield, using the coupling reagent 1-hydroxybenzotriazol (HOBt). These researchers evaluated **11a** and several other amide analogues of *trans*-fagaramide in cytotoxicity assays against various cancer cell lines, but found *trans*-fagaramide (**1**) and all analogues tested to be inactive in this regard.[16] For compounds **11b,c,f** a CAS-registry number exists, but no references or analytical data were found in a SciFinder search. All other amides **11d,e,g,h** are new compounds.

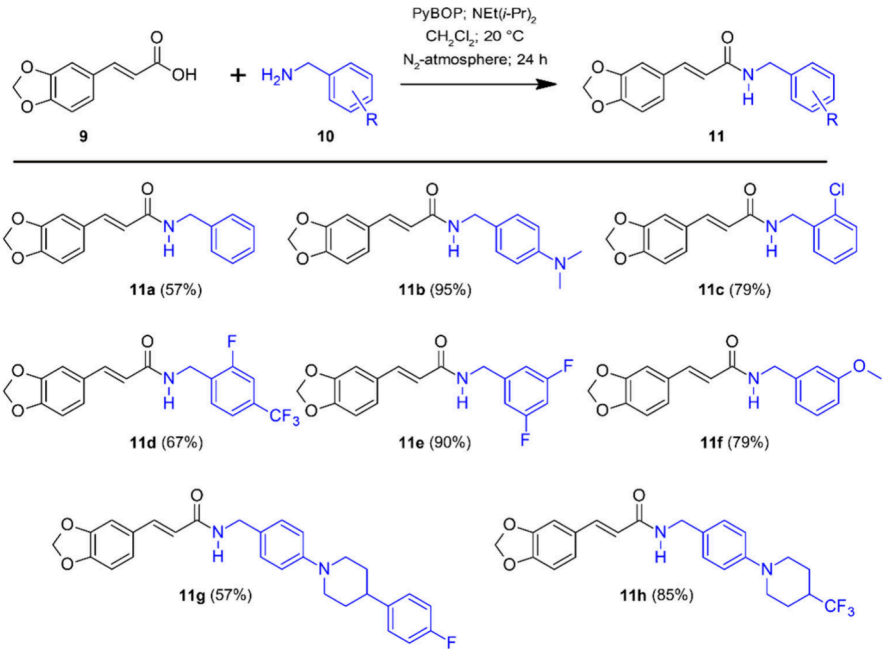
For adubangoamide (**2**) and fagaramide analogues **11b**, **11c**, and **11e** a full signal assignment of ^{1}H- and ^{13}C NMR data was performed, based on the 2D-NMR experiments COSY, HSQC, HMBC and in some cases NOESY (see Supporting Information for details). The molecular structures of amides

Scheme 1. Synthesis of Adubangoamide (2)



https://doi.org/10.1021/acs.jnatprod.4c01377
J. Nat. Prod. 2025, 88, 530−536

Scheme 2. Synthesis of Fagaramide Analogues 11a−h



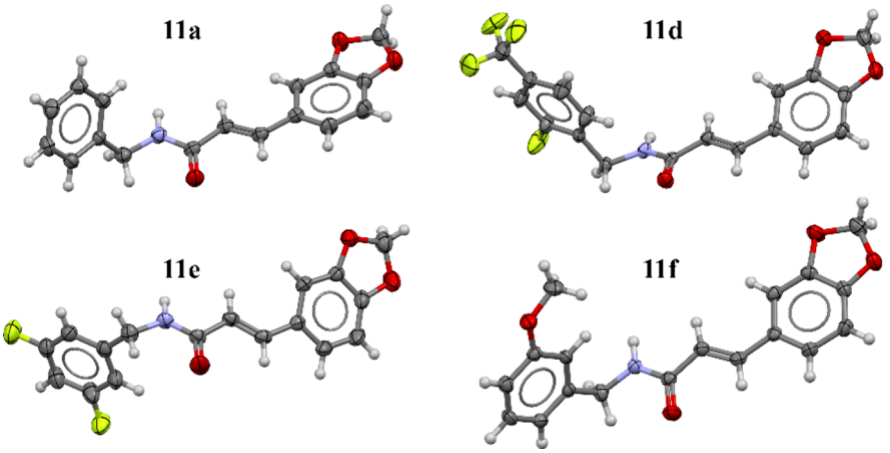


Figure 1. Single crystal X-ray structure of **11a**, **11d**, **11e**, and **11f**. Displacement ellipsoids are shown at the 50% probability level.

11a, **11d**, **11e** and **11f** were unambiguously corroborated by single crystal X-ray structure analysis (see Figure 1 and Supporting Information for details).

Antimycobacterial Activity Screening. We examined the *in vitro* antimycobacterial activity of the fagaramide analogues **11a-h** and synthetic adubangoamide (**2**) against a drug-susceptible ($H_{37}Rv$) and a multidrug-resistant (MDR TB (375)) strain of *Mycobacterium tuberculosis*. The results are shown in Table 1, together with the positive control rifampicin and literature values for *trans*-fagaramide (**1**), for comparison.

While the natural products, *trans*-fagaramide (**1**) and adubangoamide (**2**), and all *trans*-fagaramide analogues **11** investigated in this study were found to be inactive against the multidrug-resistant strain, four out of the nine compounds tested herein showed a notable activity against the drug-susceptible strain $H_{37}Rv$, with MIC values less than or equal to 10 μM. This includes the recently discovered natural product adubangoamide (**2**), which is 3-fold more active than *trans*-fagaramide (**1**). Out of the eight *trans*-fagaramide analogues **11** only three are significantly less active than *trans*-fagaramide (**1**)

Table 1. Mean MIC values of adubangoamide (2) and synthetic cinnamide analogues 11a-h against susceptible ($H_{37}Rv$) and MDR-TB strains

	mean MIC[a]	
compounds	$H_{37}Rv$	MDR
11a	46.9 (167.0)	187.5 (667.0)
11b	2.0 (6.0)	1000.0 (3555.0)
11c	31.5 (100.0)	250.0 (792.0)
11d	7.8 (21.0)	375.0 (1021.0)
11e	2.0 (6.1)	250.0 (788.0)
11f	62.5 (200.0)	250.0 (803.0)
11g	7.8 (17.0)	250.0 (545.0)
11h	2.0 (4.5)	1000.0 (2312.0)
adubangoamide (**2**)	2.9 (10.0)	375.0 (1200.0)
fagaramide (**1**)[b]	7.8 (32.0)	250.0 (1011.0)
rifampicin[c]	0.3 (0.3)	N/A

[a] $\mu g \cdot mL^{-1}$ (μM). [b] These data were previously reported by us[14] and are shown for comparison. [c] Positive control.

https://doi.org/10.1021/acs.jnatprod.4c01377
J. Nat. Prod. 2025, 88, 530−536

itself: for the unsubstituted benzyl amide **11a**, and the 2-chloro (**11c**) and 3-methoxy-substituted (**11f**) benzylamides MIC values above 100 μM were determined. Analogues **11d** and **11g** show MIC-values between 10 μM and 20 μM, and **11b**, **11e**, and **11h** possess MIC values between 4.5 and 6.1 μM, and are thus six- to 7-fold more active than *trans*-fagaramide (**1**). Notably, out of the five derivatives with increased activity, three share a tertiary amine group in para-position to the aminomethylene substituent, i.e. **11b** with a dimethylamino substituent, and **11g** and **11h** with a piperidine group.

In summary, the natural product adubangoamide, a secondary cinnamic acid amide with a *para*-prenyloxy substituent, that was recently isolated from *Zanthoxylum leprieurii* in quantities too small to allow any biotesting, was synthesized in four steps and 63% overall yield. Evaluation of the antimycobacterial activity was accomplished using synthetic material, and it was found that adubangoamide (MIC = 10 μM against H_{37}Rv strain) is 3-fold more active against this drug-susceptible *M. tuberculosis* strain than *trans*-fagaramide. We synthesized eight non-natural analogues of *trans*-fagaramide, in which the *sec*-butylamide was replaced by a benzylamide. Five of the non-natural analogues are notably more active than the parent natural product, and three of these possess MIC values lower than 10 μM against the susceptible H_{37}Rv strain. Our work provides further scientific evidence for the efficacy of the traditional use of *Z. leprieurii* against tuberculosis in Uganda, and shows that the basic cinnamic acid amide skeleton holds opportunities for obtaining more active analogues by structure variation. Further investigations in this regard are currently underway.

EXPERIMENTAL SECTION

General Experimental Procedures. All syntheses were conducted in dry reaction vessels under an atmosphere of dry nitrogen. Solvents were purified by standard procedures. Unless otherwise stated, reaction mixtures were heated with silicon oil baths. All NMR spectra were recorded with an AVANCE NEO 400 MHz spectrometer from Bruker Biospin GmbH, Ettlingen, Germany. ^{1}H NMR spectra were obtained at 400 MHz in $CDCl_3$ with residual $CHCl_3$ (δ = 7.26 ppm) as an internal reference. 13C{^{1}H} NMR spectra were recorded at 100 MHz in $CDCl_3$ with $CDCl_3$ (δ = 77.1 ppm) as an internal reference. Whenever the solubility of the sample was insuffient in $CDCl_3$, it was replaced by either methanol-d_4 (CD_2HOD as a calibrant for ^{1}H NMR spectroscopy, δ = 3.31; CD_3OD as a calibrant for ^{13}C{^{1}H} NMR spectroscopy, δ = 49.0) or DMSO-d_6 (DMSO-d_5 as a calibrant for ^{1}H NMR spectroscopy, δ = 2.50; DMSO-d_6 as a calibrant for ^{13}C{^{1}H} NMR spectroscopy, δ = 39.5). All signal assignments are based on 2D-NMR experiments COSY, HSQC, HMBC or NOESY. The numbering scheme used for signal assignments is shown for structure **1** and **2**; for the benzodioxole core of fagaramide derivatives the benzodioxole numbering scheme is used. IR spectra were recorded as ATR-FTIR spectra using a PerkinElmer UART TWO FT-IR spectrometer. Wavenumbers (ν) are given in cm^{-1}. The peak intensities are defined as strong (s), medium (m) or weak (w). Low- and high-resolution mass spectra were obtained by ESI-TOF using a Waters Micromass (Manchester, UK) instrument. For the chromatographic purification of compounds, the dry column vacuum chromatography (DCVC) method was used as described in the literature.[34] Benzyl amines **10g**,**h**[30] were synthesized based on previously published general procedures.

*Methyl (2E)-3-(4-Hydroxyphenyl)prop-2-enoate (**4**).*[27] To a solution of *p*-hydroxycinnamic acid (**3**, 3.30 g, 20.0 mmol) in dry and degassed MeOH (100 mL) was added conc. H_2SO_4 (0.50 mL, 9.3 mmol) at ambient temperature. The solution was heated at 65 °C for 24 h, cooled to ambient temperature, and all volatiles were evaporated in *vacuo*. The residue was dissolved in EtOAc (300 mL), the solution was washed with a saturated aq. sol. of $NaHCO_3$ and brine, dried with $MgSO_4$, filtered and evaporated to furnish ester **4** (3.05 g, 17.1 mmol, 85%): off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 16.0 Hz, 1H), 7.42 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.30 (d, J = 16.0 Hz, 1H), 5.76 (br s, 1H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.3, 158.0, 144.9, 130.1, 127.3, 116.0, 115.2, 51.9.

*Methyl (2E)-3-{4-[(3-Methylbut-2-en-1-yl)oxy]phenyl}prop-2-enoate (**6**).*[22] To a solution of methyl ester **4** (1.00 g, 5.6 mmol) in dry and degassed acetone (30 mL) was added K_2CO_3 (1.20 g, 8.4 mmol), followed by prenyl bromide (**5**, 0.97 mL, 8.4 mmol). The mixture was heated at 56 °C for 12 h, cooled to ambient temperature, filtered and evaporated. Water (40 mL) and EtOAc (40 mL) were added to the residue. The aqueous phase was separated, and extracted twice with EtOAc. The combined organic extracts were dried with $MgSO_4$, filtered and evaporated in vacuo to furnish compound **6** (1.35 g, 5.5 mmol, 98%): colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 15.9 Hz, 1H), 7.46 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.30 (d, J = 15.9 Hz, 1H), 5.48 (tm, J = 6.7 Hz, 1H), 4.54 (d, J = 6.7 Hz, 2H), 3.79 (s, 3H), 1.80 (s, 3H), 1.75 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.9, 160.9, 144.7, 138.8, 129.8, 127.1, 119.3, 115.3, 115.1, 65.0, 51.7, 26.0, 18.4.

*(2E)-3-{4-[(3-Methylbut-2-en-1-yl)oxy]phenyl}prop-2-enoic Acid (**7**).*[22] To a solution of methyl ester **6** (1.00 g, 4.1 mmol) in methanol (20 mL) was added a solution of K_2CO_3 (2.80 g, 20.2 mmol) in water (20 mL). The mixture was heated at 65 °C for 3 h. It was then cooled to ambient temperature, and methanol was evaporated in *vacuo*. The remaining aq. solution was cooled to 0 °C and then acidified to pH = 2 by addition of aq. HCl (1 M). The mixture was extracted with diethyl ether, the combined organic extracts were washed with brine, dried with $MgSO_4$, filtered and evaporated to furnish acid **7** (863 mg, 3.7 mmol, 92%), that was used in the next step without further purification: colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 15.9 Hz, 1H), 7.50 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 6.31 (d, J = 15.9 Hz, 1H), 5.48 (tm, J = 6.7 Hz, 1H), 4.54 (d, J = 6.7 Hz, 2H), 1.81 (s, 3H), 1.76 (s, 3H).

General Procedure for the Synthesis of Cinnamic Acid Amides 2 and 11. Cinnamic acid **7** (1.00 mmol, 232 mg) or **9** (1.00 mmol, 192 mg) was dissolved in DCM (10 mL). To this solution was added $NEt(i\text{-}Pr)_2$ (2.55 mmol, 0.43 mL), isobutylamine **8** (1.7 mmol) (for the synthesis of adubangoamide **2**) or the corresponding benzyl amine **10** (1.7 mmol) (for the synthesis of amides **11**), and PyBOP (1.02 mmol, 531 mg). The mixture was stirred under an atmosphere of dry nitrogen for 24 h. Progress of the reaction was checked by TLC (hexanes/EtOAc 1:1 (v/v)). The mixture was filtered through a short pad of silica, which was washed with MeOH. The filtrate was evaporated *in vacuo* and the residue was purified by DCVC using hexanes-EtOAc mixtures of increasing polarity (starting with 15% EtOAc and increasing to 50% EtOAc) to furnish the respective carboxamides **2** or **11**, respectively.

*(2E)-3-{4-[(3-Methylbut-2-en-1-yl)oxy]phenyl}-N-(2-methylpropyl)prop-2-enamide (Adubangoamide, **2**).* Following the general procedure for the synthesis of cinnamic acid amides, acid **7** (1.00 mmol, 232 mg) and isobuylamine (**8**, 1.70 mmol, 0.20 mL) were converted to **2** (236 mg, 0.82 mmol, 82%): colorless solid; IR (ATR) ν 3286 (m), 2959 (m), 2930 (m), 2869 (m), 1651 (m), 1602 (s), 1546 (s), 1508 (s), 1384 (m), 1334 (m), 1301 (m), 1200 (s), 1219 (s), 1173 (s), 980 (s), 825 (s), 517 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 15.5 Hz, 1H, -*H*C=CHC(O)), 7.43 (d, J = 8.7 Hz, 2H, H2), 6.88 (d, J = 8.7 Hz, 2H, H3), 6.28 (d, J = 15.5 Hz, 1H, -HC=C*H*C(O)), 5.76−5.68 (m, 1H, -N*H*-), 5.48 (tm, J = 6.8 Hz, 1H, -OCH$_2$C*H*=), 4.52 (d, J = 6.8 Hz, 2H, -OC*H*$_2$CH=), 3.21 (t, J = 6.5 Hz, 2H, -NHC*H*$_2$CH(CH$_3$)$_2$), 1.91−1.76 (m, 1H, -NHCH$_2$C*H*(CH$_3$)$_2$), 1.79 (s, 3H, *cis*-CH=C(C*H*$_3$)$_2$), 1.74 (s, 3H, *trans*-CH=C(C*H*$_3$)$_2$), 0.95 (d, J = 6.7 Hz, 6H, -NHCH$_2$CH(C*H*$_3$)$_2$); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.4 (C=O), 160.3 (C-4), 140.6 (-*H*C=CHC(O)), 138.7 (CH=*C*(CH$_3$)$_2$), 129.4 (C-2), 127.6 (C-1), 119.4 (−OCH$_2$*C*H=), 118.5 (-HC=*C*HC(O)), 115.0 (C-3), 65.0 (-O*C*H$_2$CH=), 47.2 (−NH*C*H$_2$CH(CH$_3$)$_2$), 28.8

https://doi.org/10.1021/acs.jnatprod.4c01377
J. Nat. Prod. 2025, 88, 530−536

(−$NHCH_2CH(CH_3)_2$), 25.9 (*cis*-CH=$C(CH_3)_2$), 20.3 -$NHCH_2CH(CH_3)_2$), 18.3 (*trans*-CH=$C(CH_3)_2$); HRESIMS *m/z* 288.1968 $[M + H]^+$ (calcd for $C_{18}H_{26}NO_2$, 288.1964). Analytical data match those previously reported for the natural product.[14]

*(2E)-3-(1,3-Benzodioxol-5-yl)-N-benzylprop-2-enamide (**11a**).*[35] Following the general procedure, acid **9** (1.00 mmol, 192 mg) and benzylamine (**10a**, 1.70 mmol, 0.19 mL) were converted to **11a** (159 mg, 0.57 mmol, 57%): colorless crystals, mp 150−154 °C; IR (ATR) ν 3283 (w), 3083 (w), 2898 (w), 1655 (m), 1619 (m), 1559 (m), 1488 (s), 1445 (s), 1249 (s), 1037 (s); ^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (d, *J* = 15.7 Hz, 1H), 7.30−7.35 (m, 4H), 7.28−7.22 (m, 1H), 7.10 (d, *J* = 1.5 Hz, 1H), 7.03 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.47 (d, *J* = 15.7 Hz, 1H), 5.98 (s, 2H), 4.48 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 168.8, 150.7, 149.9, 141.9, 140.0, 130.7, 129.6, 128.7, 128.3, 125.1, 119.7, 109.4, 107.1, 102.9, 44.3; HRESIMS *m/z* 282.1137 $[M + H]^+$ (calcd for $C_{17}H_{16}NO_3$, 282.1125).

*(2E)-3-(1,3-Benzodioxol-5-yl)-N-[4-(dimethylamino)benzyl]prop-2-enamide (**11b**).* Following the general procedure, acid **9** (1.00 mmol, 192 mg) and benzylamine **10b** (1.70 mmol, 379 mg) were converted to **11b** (308 mg, 0.95 mmol, 95%): yellow solid, mp 122−126 °C; IR (ATR) ν 3286 (w), 2907 (w), 1647 (m), 1615 (s), 1549 (s), 1525 (m), 1501 (s), 1488 (m), 1448 (s), 1355 (m), 1324 (m), 1251 (s), 1189 (m), 1103 (m), 1040 (s), 969 (s), 934 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 15.5 Hz, 1H, -*H*C=CHC(O)), 7.19 (d, *J* = 8.6 Hz, 2H, H-2-(−$C_6H_4(NCH_3)_2$), 6.96 (s, 1H, H-4), 6.95 (d, *J* = 8.0 Hz, 1H, H-6), 6.78 (d, *J* = 8.0 Hz, 1H, H-7), 6.70 (d, *J* = 8.6 Hz, 2H, H-3-(−$C_6H_4(NCH_3)_2$), 6.19 (d, *J* = 15.5, 1H, -HC=C*H*C(O)), 5.97 (s, 2H, H-2), 5.89−5.82 (m, 1H, -N*H*-), 4.44 (d, *J* = 5.4 Hz, 2H, -NHCH_2-), 2.93 (s, 6H, -N(CH_3)$_2$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9 (C=O), 150.3 (C-4-(−$C_6H_4(NCH_3)_2$), 149.1 (C-7a), 148.3 (C-3a), 140.9 (-H*C*=CHC(O)), 129.4 (C-5), 129.3 (C-2-(−$C_6H_4(NCH_3)_2$), 125.9 (C-1-(−$C_6H_4(NCH_3)_2$), 123.9 (C-6), 118.8 (-HC=C*H*C(O)), 112.9 (C-3-(−$C_6H_4(NCH_3)_2$), 108.6 (C-7), 106.4 (C-4), 101.5 (C-2), 43.6 (−$NHCH_2$-), 40.8 (-N(CH_3)$_2$); HRESIMS *m/z* 325.1559 $[M + H]^+$ (calcd for $C_{19}H_{21}N_2O_3$, 325.1547).

*(2E)-3-(1,3-Benzodioxol-5-yl)-N-(2-chlorobenzyl)prop-2-enamide (**11c**).* Following the general procedure, acid **9** (1.00 mmol, 192 mg) and benzylamine **10c** (1.70 mmol, 241 mg) were converted to **11c** (251 mg, 0.79 mmol, 79%): colorless solid, mp 155−157 °C; IR (ATR) ν 3268 (w), 3059 (w), 2905 (w), 1650 (m), 1617, 1548 (m), 1501 (s), 1443 (s), 1247 (s), 1037 (s); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (t, *J* = 5.9 Hz, 1H, -N*H*-), 7.45 (dd, *J* = 7.1, 1.8 Hz, 1H, H-3-(2-ClC_6H_4)), 7.40 (d, *J* = 15.7 Hz, 1H, -*H*C=CHC(O)), 7.37−7.27 (m, 3H, H-4,5,6-(2−Cl-C_6H_4)), 7.16 (d, *J* = 1.2 Hz, 1H, H-4), 7.09 (dd, *J* = 8.1, 1.2 Hz, 1H, H-6), 6.95 (d, *J* = 8.0 Hz, 1H, H-7), 6.58 (d, *J* = 15.7 Hz, 1H, -HC=C*H*C(O)), 6.07 (s, 2H, H-2), 4.46 (d, *J* = 5.8 Hz, 2H, -NHCH_2-); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.4 (C=O), 148.6 (C-7a), 148.0 (C-3a), 139.1 (-H*C*=CHC(O)), 136.3 (C-1,2-(2−Cl-C_6H_4)), 132.2 (C-1,2-(2−Cl-C_6H_4)), 129.2, 129.2, 129.1, 128.7, 127.2 (C-5; C-3,4,5,6-(2−Cl-C_6H_4)), 123.4 (C-6), 119.8 (-HC=CHC(O)), 108.6 (C-7), 106.3 (C-4), 101.5 (C-2), 40.3 (−$NHCH_2$-); HRESIMS *m/z* 316.0718 $[M + H]^+$ (calcd for $C_{17}H_{15}ClNO_3$, 316.0735).

*(2E)-3-(1,3-Benzodioxol-5-yl)-N-[2-fluoro-4-(trifluoromethyl)-benzyl]prop-2-enamide (**11d**).* Following the general procedure, acid **9** (1.00 mmol, 192 mg) and benzylamine **10d** (1.70 mmol, 328 mg) were converted to **11d** (245 mg, 0.67 mmol, 67%): colorless crystals, mp 169−172 °C; IR (ATR) ν 3295 (w), 2892 (w), 1648 (m), 1614 (m), 1501 (s), 1334 (s), 1254 (s), 1116 (s); ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (t, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 15.6, 1H), 7.50−7.42 (m, 2H), 7.11 (d, *J* = 1.6 Hz, 1H), 7.04 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 15.7 Hz, 1H), 5.99 (s, 2H), 4.59 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 169.0, 161.8 (d, $^1J(^{13}C-^{19}F$ = 248.6 Hz), 150.8, 149.9, 142.3, 131.8 (d, $^4J(^{13}C-^{19}F$ = 4.6 Hz), 130.6, 125.2, 122.2, 119.2, 113.8, 113.5, 109.4, 107.1, 102.9, 37.8 (d, $J(^{13}C-^{19}F$ = 4.5 Hz), two signals are not observed due to low intensity caused by $^{13}C-^{19}F$-coupling; HRESIMS *m/z* 368.0896 $[M + H]^+$ (calcd for $C_{18}H_{14}F_4NO_3$, 368.0904).

*(2E)-3-(1,3-Benzodioxol-5-yl)-N-(3,5-difluorobenzyl)prop-2-enamide (**11e**).* Following the general procedure, acid **9** (1.00 mmol, 192 mg) and benzylamine **10e** (1.70 mmol, 243 mg) were converted to **11e** (287 mg, 0.90 mmol, 90%): colorless crystals, mp 112−116 °C; IR (ATR) ν 3275 (w), 2930 (w), 1650 (m), 1621 (m), 1599 (m), 1539 (m), 1504 (m), 1446 (s), 1306 (m), 1254 (s), 1117 (s), 1038 (s), 932 (s), 855 (s); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (t, *J* = 5.9 Hz, 1H, -N*H*-), 7.40 (d, *J* = 15.7 Hz, 1H, -*H*C=CHC(O)), 7.17 (d, *J* = 1.3 Hz, 1H, H-4), 7.13−7.06 (m, 2H, H-6, H-4-(3,5-$F_2C_6H_4$)), 7.03−6.95 (m, 2H, H-2,6-(3,5-$F_2C_6H_4$)), 6.95 (d, *J* = 8.0 Hz, 1H), 6.53 (d, *J* = 15.7 Hz, 1H, -HC=C*H*C(O)), 6.06 (s, 2H, H-2), 4.41 (d, *J* = 6.0, 2H, -NHCH_2-); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.5 (C=O), 162.4 (dd, $^1J(^{13}C-^{19}F$) = 246.1 Hz, $^2J(^{13}C-^{19}F$) = 13.4 Hz, C-3,5-(3,5-$F_2C_6H_4$)), 148.6 (C-7a), 148.0 (C-3a), 144.5 (t, $J(^{13}C-^{19}F$) = 9.0 Hz, C-4-(3,5-$F_2C_6H_4$)), 139.2 -HC=CHC(O)), 129.2 (C-5), 123.4 (C-6), 119.7 (-HC=CHC(O)), 110.4−110.0 (m, C-2,6-(3,5-$F_2C_6H_4$)), 108.6 (C-7), 106.3 (C-4), 102.2 (t, $^2J(^{13}C-^{19}F$) = 26.0 Hz, C-4-(3,5-$F_2C_6H_4$)), 101.5 (C-2), 41.6 (−$NHCH_2$-); HREIMS *m/z* 317.0873 $[M]^+$ (calcd for $C_{17}H_{13}F_2NO_3$, 317.0858).

*(2E)-3-(1,3-Benzodioxol-5-yl)-N-(3-methoxybenzyl)prop-2-enamide (**11f**).* Following the general procedure, acid **9** (1.00 mmol, 192 mg) and benzylamine **10f** (1.70 mmol, 233 mg) were converted to **11f** (245 mg, 0.79 mmol, 79%): colorless crystals, mp 168−172 °C; IR (ATR) ν 3313 (w), 2894 (w), 1655 (m), 1615 (m), 1600 (m), 1547 (m), 1547 (m), 1499 (m), 1448 (m), 1435 (m), 1418 (m), 1325 (m), 1251 (s), 1034 (s), 781 (s); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (t, *J* = 5.9, 1H), 7.40 (d, *J* = 15.7 Hz, 1H), 7.25 (t, *J* = 8.1 Hz, 1H), 7.16 (d, *J* = 1.4, 1H), 7.08 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.81−6.87 (m, 3H), 6.54 (d, *J* = 15.7 Hz, 1H), 6.07 (s, 2H), 4.37 (d, *J* = 5.9 Hz, 2H), 3.74 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.2, 159.3, 148.5, 147.9, 141.1, 138.8, 129.4, 129.3, 123.3, 120.1, 119.5, 113.1, 112.2, 108.6, 106.2, 101.4, 55.0, 42.2; HRESIMS *m/z* 312.1227 $[M + H]^+$ (calcd for $C_{18}H_{18}NO_4$, 312.1230).

*(2E)-3-(1,3-Benzodioxol-5-yl)-N-{4-[4-(4-fluorophenyl)piperidin-1-yl]benzyl}prop-2-enamide (**11g**).* Following the general procedure, acid **9** (1.00 mmol, 192 mg) and benzylamine **10g** (1.70 mmol, 483 mg) were converted to **11g** (260 mg, 0.57 mmol, 57%): orange-colored solid; IR (ATR) ν 3280 (w), 2925 (w), 1653 (m), 1611 (m), 1557 (m)1506 (m), 1491 (m), 1446 (m), 1250 (s), 831 (s), 816 (s), 561 (s); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (t, *J* = 5.8 Hz, 1H), 7.38 (d, *J* = 15.7 Hz, 1H), 7.26−7.34 (m, 2H), 7.00−7.20 (m, 6H), 6.92−6.98 (m, 3H), 6.52 (d, *J* = 15.7 Hz, 1H), 6.07 (s, 2H), 4.29 (d, *J* = 5.8 Hz, 2H), 3.77 (dm, *J* = 12.4 Hz, 2H), 2.72 (td, *J* = 12.6, 2.9 Hz, 2H), 2.67 (tt, *J* = 12.2, 3.8 Hz, 1H), 1.84 (dm, *J* = 12.6 Hz, 2H), 1.73 (qd, *J* = 12.6, 3.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.0, 160.7 (d, $^1J(^{13}C-^{19}F$) = 243.5 Hz), 150.4, 148.4, 147.9, 142.2 (d, $^3J(^{13}C-^{19}F$) = 3.0 Hz), 138.5, 129.5, 129.3, 128.4 (d, $^1J(^{13}C-^{19}F$) = 8.0 Hz), 128.3, 123.1, 120.3, 115.9, 115.0 (d, $^3J(^{13}C-^{19}F$) = 20.9 Hz), 108.6, 106.2, 101.4, 49.6, 41.8, 40.8, 32.8; HRESIMS *m/z* 459.2068 $[M + H]^+$ (calcd for $C_{28}H_{28}FN_2O_3$, 459.2078).

*(2E)-3-(1,3-Benzodioxol-5-yl)-N-{4-[4-(trifluoromethyl)piperidin-1-yl]benzyl}prop-2-enamide (**11h**).* Following the general procedure, acid **9** (1.00 mmol, 192 mg) and benzylamine **10h** (1.70 mmol, 296 mg) were converted to **11h** (250 mg, 0.85 mmol, 85%): off-white solid, mp 165−170 °C; IR (ATR) ν 3299 (w), 2923 (w), 1653 (m), 1610 (s), 1539 (m), 1520 (m), 1508 (m), 1491 (s), 1448 (s), 1388 (m), 1324 (m), 1250 (s), 1190 (m), 1140 (s), 1078 (s); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (t, *J* = 5.8 Hz, 1H), 7.37 (d, *J* = 15.7 Hz, 1H), 7.17−7.11 (m, 3H), 7.07 (dd, *J* = 8.1, 1.5, 1H), 6.96−6.88 (m, 3H), 6.52 (d, *J* = 15.7 Hz, 1H), 6.07 (s, 2H), 4.28 (d, *J* = 5.8 Hz, 2H), 3.75 (dm, *J* = 12.6 Hz, 2H), 2.68 (td, *J* = 12.4, 1.9 Hz, 2H), 2.54−2.40 (m, 1H), 1.86 (dm, *J* = 12.4 Hz, 2H), 1.54 (qd, *J* = 12.5, 3.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 164.9, 149.8, 148.4, 147.9, 138.6, 129.8, 129.3, 128.4, 123.2, 120.3, 121.7 (q, $^1J(^{13}C-^{19}F$) = 287.1 Hz), 116.0, 108.6, 106.2, 101.4, 47.7, 41.8, 39.8 (q, $J(^{13}C-^{19}F$) = 21.7 Hz), 23.6 (q, $J(^{13}C-^{19}F$) = 2.5 Hz), signal for CF_3 group was not observed due to low intensity caused by $^{13}C-^{19}F$-coupling; HRESIMS *m/z* 433.1719 $[M + H]^+$ (calcd for $C_{23}H_{24}F_3N_2O_3$, 433.1734).

https://doi.org/10.1021/acs.jnatprod.4c01377
J. Nat. Prod. 2025, 88, 530−536

X-ray Crystallographic Data. Compounds **11a,d,e,f** crystallized from hexanes-ethyl acetate solutions as colorless blocks (**11a**), needles (**11d**, **11f**), or plates (**11e**). For all compounds, crystallographic data were collected at 210 K on a Stoe Imaging Plate Diffraction System Stadivari, using Mo-$K\alpha$ radiation (λ = 0.71073 Å). Afterward, a spherical absorption correction (STOE LANA)[36] and an extinction correction were performed. The structures were solved with SHELXS-2013/1[37] using direct methods and refined against F^2 by full-matrix least-squares procedures with SHELXL-2014/7.[38] The non-hydrogen atoms were refined anisotropically. For the visualization of the structure, the graphic program Mercury was used.[39]

The crystallographic data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/ or from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax (+44) 1223−336−033; or via e-mail: deposit@ccdc.cam.ac; deposit numbers: CCDC 2257759 (**11a**); CCDC 2257760 (**11d**); CCDC 2257761 (**11e**); CCDC 2257762 (**11f**).

Data for Compound ***11a***. $C_{17}H_{15}NO_3$, M = 281.30 g/mol, 0.600 × 0.433 × 0.300 mm^3, monoclinic, space group $P2_1/c$ (no. 14), a = 12.0479(7) Å, b = 9.8040(4) Å, c = 11.8974(8) Å, α = 90°, β = 94.777(5)°, γ = 90°, V = 1400.41(14) Å^3, Z = 4, D_c = 1.334 g/cm^3, 41446 reflections measured (6.5° ≤ 2θ ≤ 60.0°), 4081 unique (R_{int} = 0.0446, R_{sigma} = 0.0269), which were used in all calculations. The final R_1 was 0.0360 ($I > 2\sigma(I)$) and wR_2 was 0.0949 (all data).

Data for Compound ***11d***. $C_{18}H_{13}F_4NO_3$, M = 367.29 g/mol, 0.300 × 0.100 × 0.100 mm^3, triclinic, space group $P\bar{1}$ (no. 2), a = 5.0783(10) Å, b = 10.231(2) Å, c = 15.521(3) Å, α = 96.49(3)°, β = 93.66(3)°, γ = 101.72(3)°, V = 781.4(3) Å^3, Z = 2, D_c = 1.561 g/cm^3, 17927 reflections measured (6.3° ≤ 2θ ≤ 55.0°), 3588 unique (R_{int} = 0.0520, R_{sigma} = 0.0380), which were used in all calculations. The final R_1 was 0.0531 ($I > 2\sigma(I)$) and wR_2 was 0.1553 (all data).

Data for Compound ***11e***. $C_{17}H_{13}F_2NO_3$, M = 317.28 g/mol, 0.500 × 0.300 × 0.100 mm^3, triclinic, space group $P\bar{1}$ (no. 2), a = 4.9614(6) Å, b = 16.4845(18) Å, c = 17.8656(19) Å, α = 94.570(9)°, β = 93.940(9)°, γ = 90.844(9)°, V = 1452.8(3) Å^3, Z = 4, D_c = 1.451 g/cm^3, 29297 reflections measured (5.3° ≤ 2θ ≤ 57.0°), 7306 unique (R_{int} = 0.0491, R_{sigma} = 0.0522), which were used in all calculations. The final R_1 was 0.0481 ($I > 2\sigma(I)$) and wR_2 was 0.1239 (all data).

Data for Compound ***11f***. $C_{18}H_{17}NO_4$, M = 311.32 g/mol, 0.700 × 0.100 × 0.100 mm^3, monoclinic, space group $P2_1/n$ (no. 14), a = 8.2457(16) Å, b = 9.850(2) Å, c = 18.925(4) Å, α = 90°, β = 101.97(3)°, γ = 90°, V = 1503.6(5) Å^3, Z = 4, D_c = 1.375 g/cm^3, 28020 reflections measured (6.0° ≤ 2θ ≤ 50.0°), 2652 unique (R_{int} = 0.0515, R_{sigma} = 0.0308), which were used in all calculations. The final R_1 was 0.0316 ($I > 2\sigma(I)$) and wR_2 was 0.0802 (all data).

Antimycobacterial Assay. *Mycobacterium tuberculosis Strains and Preparation of Inoculums.* As mycobacterial strains for this study a fully susceptible (H37Rv) and a multidrug resistant (MDR TB 375) were used from a WHO Proficiency Testing panel. Both were obtained from the Mycobacteriology Laboratory (BSL-3), College of Health Sciences, Makerere University, Kampala, Uganda, which is accredited by the College of American Pathologists (CAP: ISO 15189). The preparation of the inoculums was done as previously reported.[13,14]

Determination of MIC for the Isolated Compounds. The microplate Alamar blue assay (MABA) was used to determine the MIC, with minor modifications as previously described.[40] A color change from blue to pink confirmed the growth of the bacteria.[41] The lowest concentration of the sample that prevented a color change to pink was defined as the MIC. Rifampicin, a standard drug was used as the positive control, while the negative control was sterile distilled water.[41,42]

■ ASSOCIATED CONTENT

Data Availability Statement

Primary NMR FID files for compounds **2**, **4**, **6**, **7**, and **11a**−**11h** via the Zenodo data repository at https://doi.org/10.5281/zenodo.14198152.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.4c01377.

Copies of ^{1}H and ^{13}C{^{1}H} NMR spectra of all compounds; crystallographic details and refinement data for **11a**, **11d**, **11e**, and **11f** (PDF)
X-ray crystallographic data for **11a** (CIF)
X-ray crystallographic data for **11d** (CIF)
X-ray crystallographic data for **11e** (CIF)
X-ray crystallographic data for **11f** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

Benson Oloya − *Department of Chemistry, Muni University, Arua, Uganda; Department of Chemistry, Makerere University, Kampala, Uganda; University of Potsdam, Institut für Chemie, D-14476 Potsdam-Golm, Germany*; Email: b.oloya@muni.ac.ug

Bernd Schmidt − *University of Potsdam, Institut für Chemie, D-14476 Potsdam-Golm, Germany*; orcid.org/0000-0002-0224-6069; Email: bernd.schmidt@uni-potsdam.de

Authors

Jane Namukobe − *Department of Chemistry, Makerere University, Kampala, Uganda*

Mandy Krüger − *University of Potsdam, Institut für Chemie, D-14476 Potsdam-Golm, Germany*

Willy Ssengooba − *Department of Medical Microbiology, and Makerere University Lung Institute, Makerere University, Kampala, Uganda*

Eric Sperlich − *University of Potsdam, Institut für Chemie, D-14476 Potsdam-Golm, Germany*

George Kwesiga − *Department of Chemistry, Kabale University, Kabale, Uganda*

Kevin Komakech − *Department of Medical Microbiology, and Makerere University Lung Institute, Makerere University, Kampala, Uganda*

Matthias Heydenreich − *University of Potsdam, Institut für Chemie, D-14476 Potsdam-Golm, Germany*

Robert Byamukama − *Department of Chemistry, Makerere University, Kampala, Uganda*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jnatprod.4c01377

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Organization for the Prohibition of Chemical Weapons (OPCW) for financially supporting Benson Oloya's research stay at the University of Potsdam through a short-term Fellowship. Also, the authors thank the Institute of Chemistry, University of Potsdam, for hosting Benson Oloya during the Fellowship.

■ REFERENCES

(1) Global Tuberculosis Programme, Tuberculosis Vaccine Accelerator Council. *Global Tuberculosis Report 2022*; World Health Organization: Geneva, Switzerland, 2022.
(2) Global Tuberculosis Programme. *Global Tuberculosis Report 2021*; World Health Organization: Geneva, Switzerland, 2021.
(3) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*, 311−335.
(4) Chen, J.; Li, W.; Yao, H.; Xu, J. *Fitoterapia* **2015**, *103*, 231−241.

(5) Zhang, L.; Song, J.; Kong, L.; Yuan, T.; Li, W.; Zhang, W.; Hou, B.; Lu, Y.; Du, G. *Pharmacol. Ther.* **2020**, *216*, No. 107686.
(6) Woo, S.; Marquez, L.; Crandall, W. J.; Risener, C. J.; Quave, C. L. *Nat. Prod. Rep.* **2023**, *40*, 1271−1290.
(7) Igarashi, M.; Ishizaki, Y.; Takahashi, Y. *J. Antibiot.* **2018**, *71*, 15−25.
(8) Pauli, G. F.; Case, R. J.; Inui, T.; Wang, Y.; Cho, S.; Fischer, N. H.; Franzblau, S. G. *Life Sci.* **2005**, *78*, 485−494.
(9) Verma, A.; Naik, B.; Kumar, V.; Mishra, S.; Choudhary, M.; Khan, J. M.; Gupta, A. K.; Pandey, P.; Rustagi, S.; Kakati, B.; Gupta, S. *ACS Infectious Diseases* **2023**, *9*, 2369−2385.
(10) Sathiya, M.; Muthuchelian, K. *Ethnobotanical Leaflets* **2008**, *12*, 891−895.
(11) Bunalema, L.; Fotso, G. W.; Waako, P.; Tabuti, J.; Yeboah, S. O. *BMC Complement. Altern. Med.* **2017**, *17*, 89.
(12) Oloya, B.; Namukobe, J.; Ssengooba, W.; Afayoa, M.; Byamukama, R. *Trop. Med. Health* **2022**, *50*, 16.
(13) Oloya, B.; Namukobe, J.; Heydenreich, M.; Ssengooba, W.; Schmidt, B.; Byamukama, R. *Nat. Prod. Commun.* **2021**, *16*, 1−8.
(14) Oloya, B.; Namukobe, J.; Heydenreich, M.; Ssengooba, W.; Martin, J.; Möller, H. M.; Schmidt, B.; Byamukama, R. *Phytochemistry Lett.* **2023**, *54*, 107−113.
(15) Okagu, I. U.; Ndefo, J. C.; Aham, E. C.; Udenigwe, C. C. *Molecules* **2021**, *26*, 4023.
(16) Tomas, M. B.; Shiao, T. C.; Nguyen, P. T.; Bourgault, S.; Roy, R. *Pharm. Chem. J.* **2018**, *51*, 995−1004.
(17) Richter, P. *Archiv f. Pathol. Anat. Phys. klin. Med.* **1893**, *133*, 376−386.
(18) Warbasse, J. P. I. *Ann. Surg.* **1894**, *19*, 102−111.
(19) Rastogi, N.; Goh, K. S.; Horgen, L.; Barrow, W. W. *FEMS Immunol. Med. Microbiol.* **1998**, *21*, 149−157.
(20) Chen, Y.-L.; Huang, S.-T.; Sun, F.-M.; Chiang, Y.-L.; Chiang, C.-J.; Tsai, C.-M.; Weng, C.-J. *Eur. J. Pharm. Sci.* **2011**, *43*, 188−194.
(21) Guzman, J. D. *Molecules* **2014**, *19*, 19292−19349.
(22) De, P.; Koumba Yoya, G.; Constant, P.; Bedos-Belval, F.; Duran, H.; Saffon, N.; Daffé, M.; Baltas, M. *J. Med. Chem.* **2011**, *54*, 1449−1461.
(23) De, P.; Bedos-Belval, F.; Vanucci-Bacque, C.; Baltas, M. *Curr. Org. Chem.* **2012**, *16*, 747−768.
(24) Pospisilova, S.; Kos, J.; Michnova, H.; Kapustikova, I.; Strharsky, T.; Oravec, M.; Moricz, A. M.; Bakonyi, J.; Kauerova, T.; Kollar, P.; Cizek, A.; Jampilek, J. *Int. J. Mol. Sci.* **2018**, *19*, 2318.
(25) Teixeira, C.; Ventura, C.; Gomes, J. R. B.; Gomes, P.; Martins, F. *Molecules* **2020**, *25*, 456.
(26) Fu, J.; Fu, H.; Xia, Y.; N'Go, I.; Cao, J.; Pan, W.; Vincent, S. P. *Org. Biomol. Chem.* **2021**, *19*, 1818−1826.
(27) Nguyen, S. T.; Murray, P. R. D.; Knowles, R. R. *ACS Catal.* **2020**, *10*, 800−805.
(28) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557−6602.
(29) Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205−208.
(30) Kang, S.; Kim, R. Y.; Seo, M. J.; Lee, S.; Kim, Y. M.; Seo, M.; Seo, J. J.; Ko, Y.; Choi, I.; Jang, J.; Nam, J.; Park, S.; Kang, H.; Kim, H. J.; Kim, J.; Ahn, S.; Pethe, K.; Nam, K.; No, Z.; Kim, J. *J. Med. Chem.* **2014**, *57*, 5293−5305.
(31) Tang, J.; Wang, B.; Wu, T.; Wan, J.; Tu, Z.; Njire, M.; Wan, B.; Franzblauc, S. G.; Zhang, T.; Lu, X.; Ding, K. *ACS Med. Chem. Lett.* **2015**, *6*, 814−818.
(32) Li, L.; Lv, K.; Yang, Y.; Sun, J.; Tao, Z.; Wang, A.; Wang, B.; Wang, H.; Geng, Y.; Liu, M.; Guo, H.; Lu, Y. *ACS Med. Chem. Lett.* **2018**, *9*, 741−745.
(33) Wang, H.; Lv, K.; Li, X.; Wang, B.; Wang, A.; Tao, Z.; Geng, Y.; Wang, B.; Huang, M.; Liu, M.; Guo, H.; Lu, Y. *Chin. Chem. Lett.* **2019**, *30*, 413−416.
(34) Pedersen, D. S.; Rosenbohm, C. *Synthesis* **2001**, *2001*, 2431−2434.
(35) Krause, T.; Baader, S.; Erb, B.; Gooßen, L. J. *Nat. Commun.* **2016**, *7*, 11732.
(36) Koziskova, J.; Hahn, F.; Richter, J.; Kožíšek, J. *Acta Chim. Slovaca* **2016**, *9*, 136.
(37) Sheldrick, G. M. *SHELXS-2013/2, Program for the Crystal Structure Solution*; University of Göttingen: Göttingen, Germany, 1997.
(38) Sheldrick, G. M. *SHELXL-2014/7, Program for the Crystal Solution Refinement*; University of Göttingen: Göttingen, Germany, 2013.
(39) Macrae, C. F.; Sovago, I.; Cottrell, S. J.; Galek, P. T. A.; McCabe, P.; Pidcock, E.; Platings, M.; Shields, G. P.; Stevens, J. S.; Towler, M.; Wood, P. A. *J. Appl. Crystallogr.* **2020**, *53*, 226−235.
(40) Lawal, T. O.; Adeniyi, B. A.; Wan, B.; Franzblau, S. G.; Mahady, G. B. *Afr. J. Biomed. Res.* **2011**, *14*, 17−21.
(41) Kaur, R.; Kaur, H. *Orient. J. Chem.* **2015**, *31*, 597−600.
(42) Bhatnagar, M.; Ghosal, S. *Int. J. Pharm. Sci. Res.* **2018**, *9*, 712−717.

https://doi.org/10.1021/acs.jnatprod.4c01377
J. Nat. Prod. 2025, 88, 530−536