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Biosourced Vanillin-Based Building Blocks for Organic Electronic Materials

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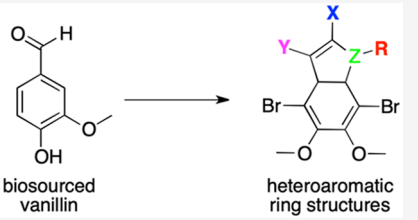
ABSTRACT: Forest biomass is viewed as a significant source of organic carbon and thus the ideal replacement of petroleum products. From the resources derived from biomass, lignocellulose is the most abundant biobased material on earth. One of the aromatic added value compounds obtained from the depolymerization of lignin is vanillin. Here, we report the preparation of new compounds having benzothiophene, indole, isatin, benzofuroxan, benzofurazan, benzothiadiazole, and phthalimide heteroaromatic ring structures. More precisely, our results show that vanillin can be used as a biosourced starting material for the preparation of a variety of aromatic dibrominated monomers. X-ray crystallography on single crystals was also performed to obtain meaningful information on their solid-state ordering. This work opens the way to new, sustainable, biosourced aromatic materials (small molecules or polymers) for organic electronics.



INTRODUCTION

We live in a world where consumer electronics (tablets, laptops, and cellphones) are so well integrated into our lives that they have become an essential part of our daily routine. However, their lifespan is limited, and the resources used in their fabrication are derived from petroleum-based materials. Furthermore, the global demands for these electronic products lead to two major consequences: (1) the production of an enormous quantity of waste (50 MTons yearly) and (2) the decrease of limited resources such as gallium and indium.[1] Thus, extensive efforts are being made to improve the way to exploit resources and to handle electronic waste in order to reduce its negative impact on our environment. In this regard, organic electronic materials (small molecules and polymers) represent a promising alternative to inorganic electronics as they possess unique advantages such as flexibility, mechanical robustness and ionic or electronic conductivity. However, only a few organic semiconductors have been prepared from renewable sources.[2] In this context, it would be valuable to seek starting materials from renewable and sustainable sources.

Naturally abundant lignocellulosic biomass is highly considered as it has the potential to replace fossil fuels and is principally composed of carbohydrates (cellulose and hemicellulose) as well as aromatics (lignin and tannin).[3] More specifically, one structure of interest can be obtained from the depolymerization of lignin: which is vanillin.[4] Due to its chemical structure, vanillin can be readily modified to several conjugated heterostructures to be used as monomers for the preparation of semiconducting polymers. As a matter of fact, naturally derived biobased vanillin is produced from Borregaard from the Norway spruce at the rate of 250 tons/annually.[5] Only a few studies have reported the use of vanillin as a starting compound for the preparation of semiconducting polymers.[2,6] The first polymerization of the vanillin dimer was carried out by Amarasekara and co-workers using an electrochemical reductive polymerization approach.[7] Later, Selvaraju et al. reported the preparation of a copolymer incorporating an eumelamin core obtained from vanillin in seven steps. In another approach, Kayser et al. describe catechyl-substituted phosphonite mediated polymerization to convert vanillin-derived diimines together with diacid chloride and alkyne into a polypyrrole-based polymer.[8] Recently, Garbay and co-workers reported the preparation of divanillin-based polyazomethine derivatives.[9]

Herein, we report the synthesis of a series of biosourced vanillin derivatives having different heteroaromatic structures such as benzothiophene, indole, isatin, benzofuroxan, benzofurazan, benzothiadiazole, and phthalimide rings (Figure 1). It is worth mentioning that most structures were developed, keeping in mind their use as monomers to be later polymerized using direct (hetero)arylation polymerization (DHAP).[10] To do so, we focused our efforts on the preparation of the dibromo derivatives that we intend to polymerize with different comonomers bearing reactive hydrogen atoms. Such dibromo derivatives can also undergo Stille or Suzuki cross-coupling reactions.[11,12] Furthermore, we grew a single crystal for several compounds in order to obtain complementary information on their solid-state ordering. At last, we

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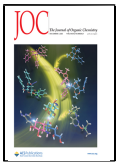


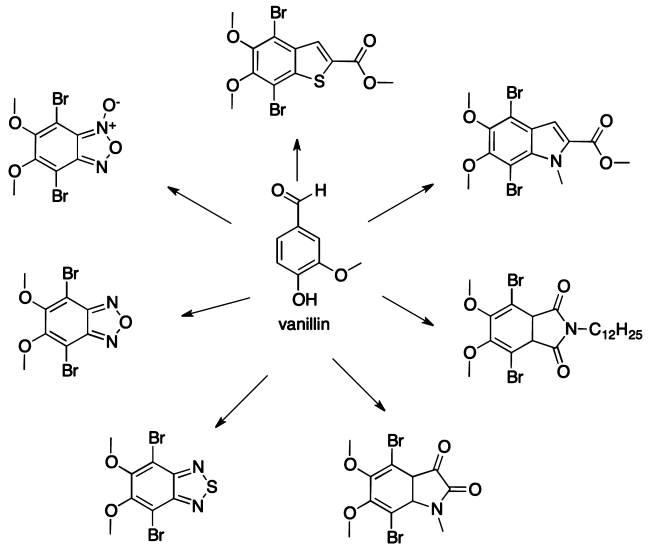


Figure 1. Vanillin and its derivatives (present work).

demonstrate that biosourced vanillin can be employed as a starting product for the synthesis of a variety of structures offering a convenient alternative to the use of petroleum-based compounds.

RESULTS AND DISCUSSION

Synthesis. The synthetic pathway to compounds **6** and **7** is illustrated in Scheme 1. The first step is the preparation of compound **1**, obtained by methylation of vanillin using dimethyl sulfate.[13] Then, 3,4-dimethoxybenzaldehyde is subjected to nitration with concentrated HNO_3 to give compound **2**.[13] After recrystallization in EtOH, compound **2** is dibrominated with *n*-bromosuccinimide (NBS) in H_2SO_4 affording compound **3** with 60% overall yield when starting from vanillin.[14] Using compound **3**, a Wittig reaction was carried out with methyl bromoacetate and PPh_3, which, in the presence of $NaHCO_3$, formed *in situ* the ylide intermediate to afford compound **4** in 73% yield.[6,14] In order to obtain compound **5**, we probed two approaches; 1) using microwaves (MW)[15] and 2) a conventional batch heating (heating mantle) while reacting compound **4** with $MoO_2Cl_2(dmf)_2$ in the presence of PPh_3.[6,16] We found that for the Cadogan reaction, both approaches led to similar yields either (1) 82% using MW heating or (2) 88% yield using conventional heating. The methylation of compound **5** was done using dimethyl sulfate as a methylating agent to afford compound **6** in 87% yield.

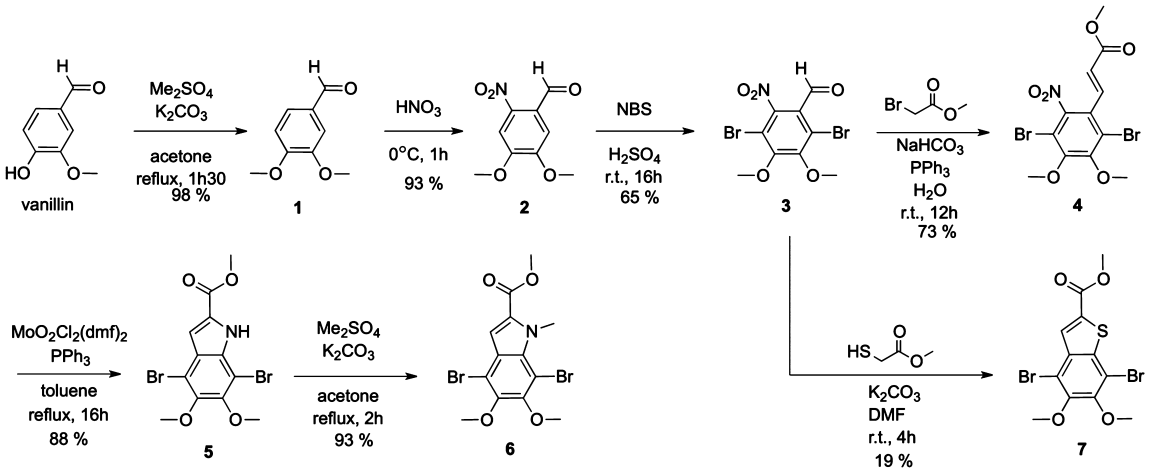
The reaction of **3** with methyl thioglycolate gave compound **7** in a yield of 19% by using a modified procedure from Romero-Parra et al.[17] This low yield could be partially explained by the presence of the methoxy groups that enrich the benzene ring, thus decreasing its electrophilic character for the nucleophilic attack of the methyl thioglycolate. Likewise, due to the presence of bromine atoms (good leaving groups) on the benzene ring, we observed the generation of a substitution product (methyl 6-bromo-4,5-dimethoxy-7-nitrobenzo[*b*]thiophene-2-carboxylate) in 19% yield.

Scheme 2 details the synthesis of compound **11**. Compound **5** was saponified with NaOH to give compound **8** in quantitative yield. The decarboxylation was carried out in diphenyl ether at 260 °C to afford intermediate **9** in 87% yield.[18] Compound **9** was then methylated using dimethyl sulfate to afford compound **10a** in 87% yield. At last, the formation of the isatin derivative **11** was done using I_2O_5 as the oxidative reagent to generate the target compound with a yield of 92%.[19] We found that performing the oxidation with I_2O_5 before the methylation step led to a lower yield (31%) for compound **10b**. Finally, compound **10b** was converted in 97% yield to compound **11** using dimethyl sulfate as the methylation reagent.

The synthesis of compounds **15**, **17**, and **20** is described in Scheme 3. The formation of the nitrile intermediate **12** was done from the reaction of compound **2** with NH_4OH and I_2 in 85% yield.[20] The nitrile **12** was converted to the amide **13** with KOH and H_2O_2 as reagents in 88% yield.[21,22] The reaction of **13** with Br_2 and NaOH afforded the benzofuroxan derivative **14** with 84% yield.[23] More specifically, this novel one-pot transformation of the amide and nitro groups into the furoxan moiety could first go through a Hofmann rearrangement in order to transform the amide into an amine.[22,24] Then, the conditions just described are used again with the nitro group. Bromination of **14** with Br_2 in a mixture of CH_2Cl_2/AcOH gave compound **15** in 32% yield.[25]

Compounds **17** and **20** have previously been synthesized from catechol in a multistep synthesis.[26] Here, we report their preparation from vanillin using a unique approach. Thus, in

Scheme 1. Synthesis of Compounds 6 and 7



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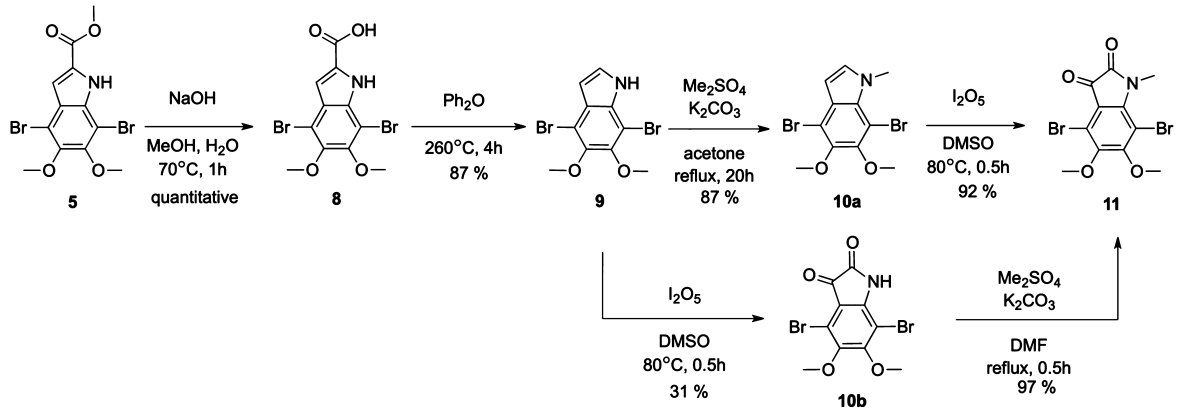
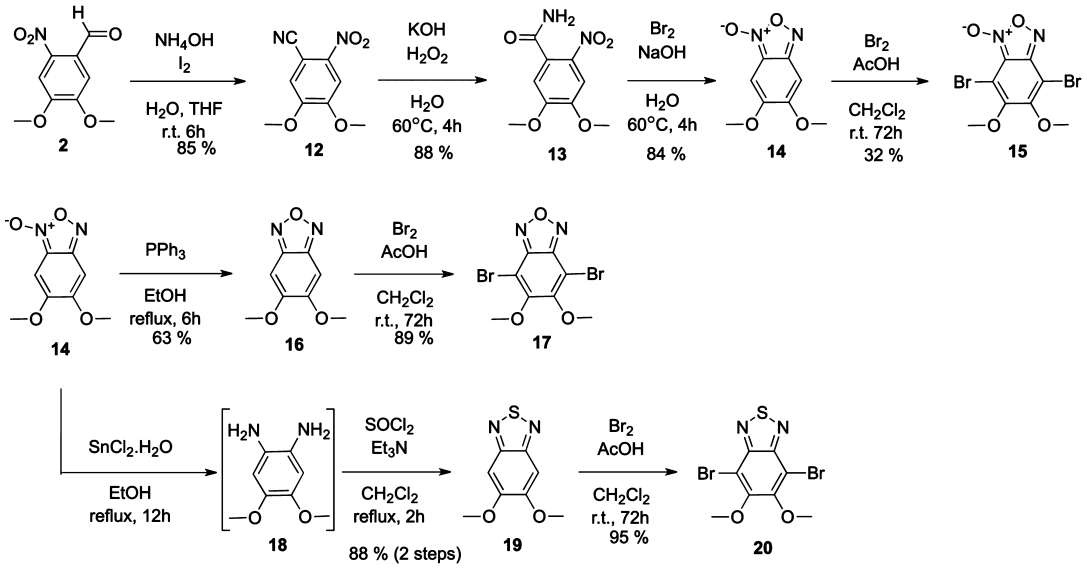
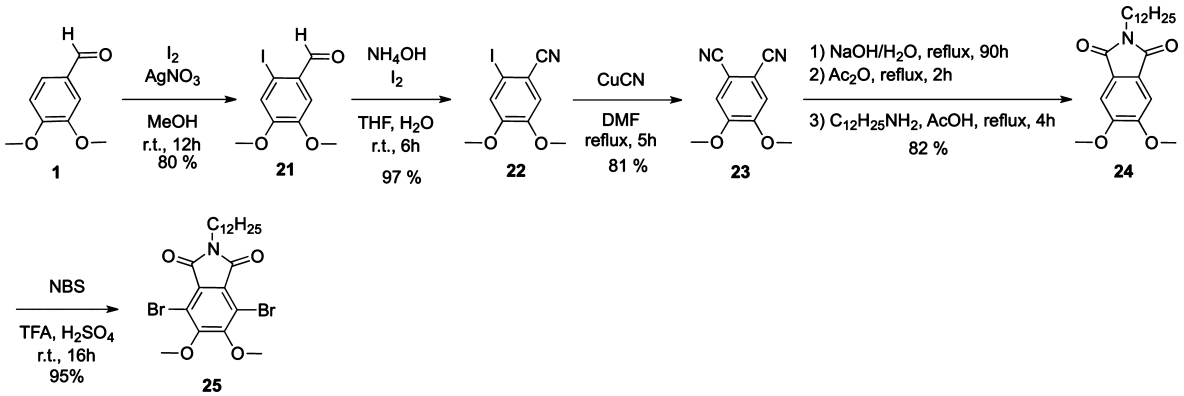
Scheme 2. Synthesis of Compound 11



Scheme 3. Synthesis of Compounds 15, 17, and 20



Scheme 4. Synthesis of Compound 25



order to obtain compound **17**, we first reacted compound **14** with PPh_3 to afford intermediate **16** in 63% yield.[23] Then, a bromination reaction with Br_2 in a mixture of CH_2Cl_2/AcOH gave the oxadiazole derivative **17** in 89% yield.[25] Compound **14** was converted to 4,5-dimethoxybenzene-1,2-diamine **18** using $SnCl_2{\cdot}H_2O$ as the reducing agent and due to its instability was quickly converted into the benzothiadiazole intermediate **19** by a ring closure using $SOCl_2$ with 88% yield over two steps.[27] Bromination of **19** with Br_2 in a mixture of CH_2Cl_2/AcOH gave compound **20** in 95% yield.[25]

The synthetic pathway to compound **25** is illustrated in Scheme 4. The reaction of compound **1** with I_2 and $AgNO_3$ affords compound **21** in 80% yield.[28] Compound **22** was obtained in 97% yield upon reacting compound **21** with NH_4OH and I_2.[20] Conversion of iodine intermediate **22** to the dinitrile **23** was carried out with CuCN in 81% yield.[29] Then,

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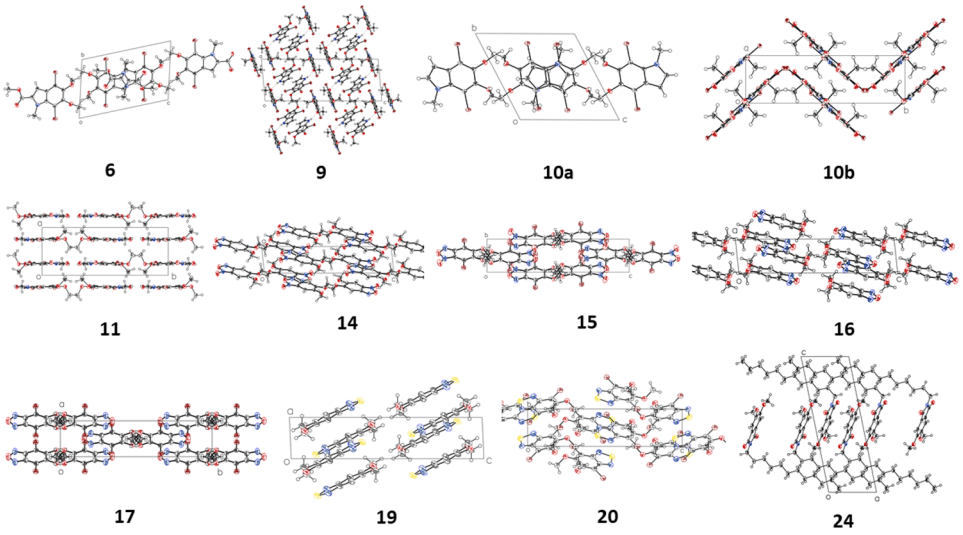

Figure 2. Molecular packing observed in single crystals for **6** (unit cell viewed along *a* axis), **9** (unit cell viewed along *b* axis), **10a** (unit cell viewed along *a* axis), **10b** (unit cell viewed along *c* axis), **11** (unit cell viewed along *c* axis), **14** (unit cell viewed along *b* axis), **15** (unit cell viewed along *c* axis), **16** (unit cell viewed along *b* axis), **17** (unit cell viewed along *c* axis), **19** (unit cell viewed along *b* axis), **20** (unit cell viewed along *a* axis), and **24** (unit cell viewed along *b* axis). Atoms of C, O, S, N, and Br are shown in gray, red, yellow, blue, and purple, respectively.

the reaction of compound **23** with NaOH affords the 4,5-dimethoxyphthalic acid intermediate,[30] which after workup, was reacted directly with acetic anhydride[31] to generate the 5,6-dimethoxyisobenzofuran-1,3-dione intermediate. The latter was then reacted with dodecylamine in acetic acid at reflux, affording compound **24** in 82% yield.[31] At last, compound **24** was brominated with *N*-bromosuccinimde (NBS) in a mixture of trifluoroacetic acid (TFA) and H_2SO_4, giving compound **25** in 95% yield.[32]

Crystallography. The molecular ordering can provide useful insights on the three-dimensional arrangement of the monomers and, potentially, the corresponding polymeric structures. Therefore, in order to understand the solid-state ordering and packing of molecules **6**, **9**, **10a**, **10b**, **11**, **14**, **15**, **16**, **17**, **19**, **20**, and **24**, single crystals were grown. For these compounds, single crystals were successfully grown from the slow evaporation of chloroform. Figure 2 shows their molecular packing, and Table 1 summarizes the crystallographic data of these 12 compounds. As shown in Table 1, we note that compounds **9**, **10b**, **11**, **14**, **15**, **16**, **19**, and **20** have the same monoclinic crystal system. We found that compounds **6**, **10a**, and **26** possess a triclinic crystal system, whereas compound **17** is orthorhombic. Moreover, compounds **9**, **10b**, **11**, **15**, and **20** possess a $P2_1/c$ space group, whereas compounds **14**, **16**, and **19** have the $P2_1/n$ space group. Compounds **6**, **10a**, and **24** possess a $P\bar{1}$ space group. Lastly, compound **17** has a *Pbcn* space group.

From the crystal structure, we observe that some C−N, N−S, and C−O bond lengths vary depending on the presence of an additional oxygen, carbon or bromine atom (Figure 3). First, we compared the indole derivatives, **6**, **9**, **10a**, **10b**, and **11**. Compound **6** possesses three N−C bonds, namely, N1−C1 (1.374(3) Å), N1−C7 (1.399(3) Å), and N1−C9 (1.4674(3) Å). Concerning compound **9**, we note the presence of two crystallographic isomers having C1−N1(A/B) bond lengths of 1.372(3) Å and 1.378(3) Å. Besides, we also observed N1−C4A and N1−C4B bond lengths of 1.378(2) Å and 1.370(2) Å. Compound **10a** possesses three N−C bonds that are N1−C1 (1.379(3) Å), N1−C9 (1.457(3) Å), and N1−C8 (1.378(3) Å). Interestingly, the addition of the methyl group does not affect the length of the N1−C8 and N1−C1(A/B) bonds (compounds **9** and **10a**). Concerning compound **10b**, we note that the N1−C1 bond length has a value of 1.3567 (10) Å and that the carbonyl (C1−O1) adjacent to the N−H possesses a longer bond length (1.2188(19) Å) than the carbonyl (C2−O2) near to the benzene ring (1.2087(19) Å). At last, for compound **11**, we notice the following bond lengths: N1−C1 (1.419(3) Å), N1−C9 (1.464(3) Å), N1−C8 (1.374(3) Å), C8−O1 (1.202(3) Å), and C7−O2 (1.201(3) Å). Upon comparing compounds **9** and **10b**, we observed that the presence of the carbonyl groups decreases the N1−C1 bond length in compound **10b**. Moreover, the addition of a methyl group to compound **10b** decreases the carbonyl C1−O1 bond length while increasing the N1−C1 bond length.

When comparing benzofuroxan compounds **14** and **15**, we observe that the addition of the bromine atoms decreased the N1−O4 bond length from 1.2427(13) Å to 1.195(8) Å, respectively. Also, we note that the N1−C1 bond length increases from 1.3257(14) (compound **14**) Å to 1.354(8) Å (compound **15**) with the presence of the bromine atoms. However, the N1−O1 bond length remains similar (1.4463(13) Å and 1.450(9) Å). The benzofurazan derivatives **16** and **17** possess similar N1−C1 bond lengths, 1.3142(15) Å and 1.3185(19) Å, respectively. However, the N1−O1 bond length decrease upon the addition of the bromine atoms, passing from 1.3913(14) Å to 1.3806(17) Å for compounds **16** and **17**, respectively. Concerning the benzothiadiazole compounds **19** and **20**, we first note a very similar N1−C1 bond length 1.363(3) Å for **19** and 1.353(11) Å for **20** with the presence of bromine atoms on the aromatic ring. Likewise, their S1−N1 bond lengths are comparable, noticing only a slight decrease from 1.635(3) Å for **19** and to 1.627(7) Å for **20**, respectively. Interestingly, it was observed that crystals of compound **20** possess a unique attribute. They can be easily bent, which is rather uncommon for crystals. Still, this phenomenon has been previously discussed by Reddy et al.[33] The bending observed from crystals of compound **20** shows

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Table 1. Crystallographic Data for Compounds 6, 9, 10a, 10b, 11, 14, 15, 16, 17, 19, 20, and 24

crystal	6	9	10a	10b	11	14	15	16	17	19	20	24
empirical formula	$C_{13}H_{13}Br_2NO_4$	$C_{10}H_9Br_2NO_2$	$C_{11}H_{11}Br_2NO_2$	$C_{10}H_7Br_2NO_4$	$C_{11}H_9Br_2NO_4$	$C_8H_8N_2O_4$	$C_8H_6Br_2N_2O_4$	$C_8H_8N_2O_3$	$C_8H_6Br_2N_2O_3$	$C_8H_8N_2O_2S$	$C_8H_6Br_2N_2O_2S$	$C_{22}H_{33}NO_4$
molecular weight (g mol^{-1})	407.06	335.00	349.03	364.99	379.01	196.16	353.97	180.16	337.97	196.22	354.03	375.49
crystal habit, color	block, colorless	block, colorless	block, colorless	plate, light red	block, light red	needle, colorless	needle, light yellow	needle, colorless	plate, colorless	needle, colorless	needle, colorless	block, colorless
crystal system	triclinic	monoclinic	triclinic	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic	orthorhombic	monoclinic	monoclinic	triclinic
space group	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P2_1/c$	$P2_1/c$	$P2_1/n$	$P2_1/c$	$P2_1/n$	$Pbcn$	$P2_1/n$	$P2_1/c$	$P\bar{1}$
a (Å)	7.4414(2)	9.4880(2)	7.8454(4)	4.5365(2)	7.4617(3)	3.8279(1)	13.8817(3)	3.8877(2)	4.21660(10)	3.8723(3)	13.7538(17)	7.0791(3)
b (Å)	8.4353(3)	9.0504(2)	9.1260(4)	15.1952(7)	18.6085(7)	11.9914(3)	4.22940(10)	11.5943(5)	17.6642(5)	12.2407(14)	4.3334(6)	8.1707(4)
c (Å)	12.9257(4)	26.2439(6)	9.4297(5)	16.8720(8)	9.1111(3)	18.3829(5)	18.0916(4)	18.0265(7)	13.7270(4)	18.1270(18)	17.987(2)	19.4361(8)
α (Å)	71.738(1)	90	115.583(2)	90	90	90	90	90	90	90	90	94.303(2)
β (Å)	73.844(1)	95.0740(10)	101.521(2)	94.521(2)	109.381(2)	95.810(2)	90.0860(10)	95.881(2)	90	92.458(7)	90.916(5)	99.485(2)
γ (Å)	72.611(1)	90	95.928(2)	90	90	90	90	90	90	90	90	109.081(2)
V (Å^3)	719.86(4)	2244.74(9)	582.80(5)	1159.42(9)	1193.40(8)	839.48(4)	1062.18(4)	808.27(6)	102.43(5)	858.42(15)	1071.9(2)	1037.85(8)
Z	2	8	2	4	4	4	4	4	4	4	4	2
μ (mm^{-1})	7.270	5.971	8.709	5.913	8.709	0.693	6.452	0.624	6.628	3.098	11.287	0.653
density (g cm^{-3})	1.878	1.983	1.989	2.091	2.109	1.552	2.213	1.481	2.196	1.518	2.194	1.202

that the interactions of the molecules in the crystal packing are anisotropic in perpendicular directions. In other words, the interactions in one axis are notably stronger than the interactions in a perpendicular axis.

Finally, for the phthalimide derivative **24**, we note a N1−C1 bond length of 1.398(2) Å, a N1−C11 bond length of 1.4634(19) Å, and a C1−O1 bond length of 1.2143(19) Å. As we could not obtain satisfactory single crystals of compound **25**, it was not possible to evaluate the effect of the presence of the bromine atoms on the N1−C1 and C1−O1 bond length.

CONCLUSIONS

In summary, we have synthesized a series of novel vanillin-based derivatives **6**, **7**, **10a**, **11**, **15**, **17**, **20**, and **25** having different heterocycles such as benzothiophene, indole, isatin, benzofuroxan, benzofurazan, benzothiadiazole, and phthalimide. The synthetic pathways show the versatility of the vanillin moiety, specifically its initial functional groups (aldehyde, hydroxyl, and methoxy) to undergo a variety of chemical transformations. Moreover, the present work shows that vanillin is a viable and flexible substitute to petroleum-based compounds for the preparation of many aromatic molecules. Crystallographic data demonstrate three-dimensional structures of several compounds and the effect of their chemical transformation on their bond lengths and solid-state ordering. Further studies on the polymerization of these molecules to obtain conjugated polymers are currently underway. At last, this work could also be of interest in the field of medicinal chemistry, as heteroaromatic moieties are associated with a wide range of pharmacological activities.[34−36]

EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR spectra were recorded using an Agilent DD2 500 MHz and a Varian Innova 400 MHz spectrometer in the appropriate deuterated solvents at 228 K (compounds **14** and **15** only) and 293 K. Chemical shifts were reported as δ values (ppm) relative to the residual solvent signals ($CDCl_3$ = 7.26 ppm (^{1}H NMR), 77.00 ppm (^{13}C NMR); C_6D_6 = 7.16 ppm (^{1}H NMR), 128.06 ppm (^{13}C NMR); DMSO-d_6 = 2.50 ppm (^{1}H NMR), 39.52 ppm (^{13}C NMR)), and coupling constant are given to the nearest 0.5 Hz. FT-IR spectroscopy was performed on solid samples using a Thermo Scientific Nicolet IS50 FT-IR with an ATR attachment. The melting point (mp) was measured in a glass capillary using an electrothermal MEL-TEMP melting point apparatus and is uncorrected (Thermo Scientific Flash 2000 organic elemental analyzer). Electrospray ionization (ESI) high-resolution mass spectrometry (HRMS) was carried out using an Agilent 6210 LC time-of-flight mass spectrometer. Column chromatography was performed with 230−400 mesh silica purchased from Silicycle. Thin-layer chromatography (TLC) was performed on aluminum-backed plates coated with silica gel (thickness = 200 μm). All chemicals were used as supplied from Sigma-Aldrich. Tetrahydrofuran (THF) was first distilled from potassium carbonate and then from sodium and benzophenone under an argon atmosphere before use. The biosourced vanillin was provided by Borregaard. 3,4-Dimethoxybenzaldehyde **1**,[13] 4,5-dimethoxy-2-nitrobenzaldehyde **2**,[13] 2,5-dibromo-3,4−6-nitrobenzaldehyde **3**,[14] (*E*)-methyl 3-(2,5-dibromo-3,4-dimethoxy-6-nitrophenyl)acrylate **4**,[6,14] methyl 4,7-dibromo-5,6-dimethoxy-1*H*-indole-2-carboxylate **5**,[6] and 2-iodo-4,5-dimethoxybenzaldehyde **21**[28] were synthesized according to previously reported literature.

X-ray Crystallographic Data for Single-Crystalline Products. The data were collected from a shock-cooled single crystal, crystallized from chloroform, at 150 K on a Bruker Venture Metaljet k-geometry diffractometer with a Metal Jet using Helios MX Mirror Optics as monochromator and a Bruker CMOS Photon III detector. The diffractometer was equipped with an Oxford Cryostream 700

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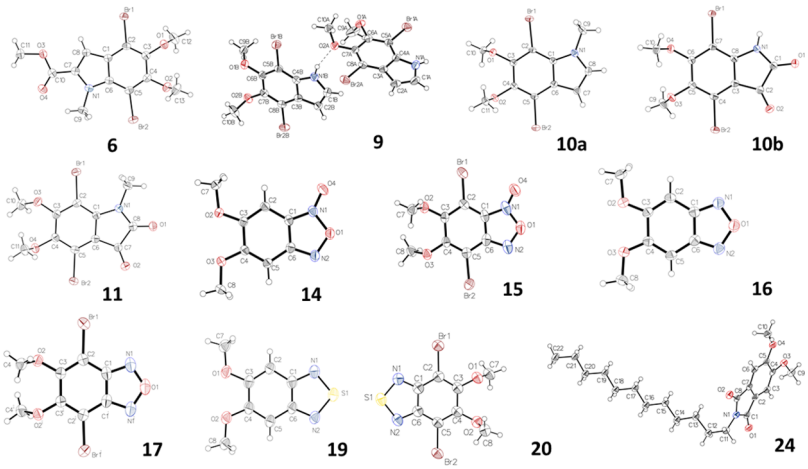

Figure 3. ORTEP representations of compounds **6**, **9**, **10a**, **10b**, **11**, **14**, **15**, **16**, **17**, **19**, **20**, and **24**. Ellipsoids are drawn at the 50% probability level, and hydrogen atoms are shown as spheres of arbitrary sizes.

low-temperature device and used Ga Kα radiation (λ = 1.34139 Å). All data were integrated with SAINT, and a multiscan absorption correction using SADABS was applied.[37,38] The structures were solved by dual methods using XT and refined by full-matrix least-squares methods against F^2 by XL.[39,40] Structure solution and refinement cycles were performed within the graphical user interface of OLEX2.[41] For compounds **10b**, **14**, **16**, **17**, and **19**, all non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were refined isotropically on calculated positions using a riding model with their U_{iso} values constrained to 1.5 times the U_{eq} of their pivot atoms for terminal sp^3 carbon atoms. Concerning compound **9**, the hydrogen atoms were located from the Fourier difference map and fully refined isotropically. In the case of compound **15**, the sample was found to be a two-component twin. Final refinement involved both components applied to the reflections file as generated using the TWINROTMAT routine from PLATON.[42]

*Synthesis of Methyl 4,7-Dibromo-5,6-dimethoxy-1-methyl-1H-indole-2-carboxylate (**6**).* Methyl 4,7-dibromo-5,6-dimethoxy-1*H*-indole-2-carboxylate **5** (289 mg, 0.74 mmol, 1 equiv), anhydrous potassium carbonate (152 mg, 1.10 mmol, 1.2 equiv), and dry acetone (11.5 mL) were added into a dry vessel under an argon atmosphere. Dimethyl sulfate (111 mg, 0.88, 1.5 equiv) was added dropwise, and the reaction was refluxed and monitored using TLC and allowed to react for 2 h until the total disappearance of the starting product. The solvent was then removed under reduced pressure, and the crude solid was purified using silica gel chromatography (ethyl acetate/hexanes, 1:4) to give the final product as a white crystalline solid (278 mg, 93%): mp 136−140 °C; IR ν_{max} (solid)/cm^{-1} 3153 (w, N−H), 2951 (b, C−H), 1721 (s, C═O), 1221 (s, C-OMe); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (s, 1H), 4.45 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 3.91 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 161.7, 150.3, 146.6, 133.0, 129.9, 125.1, 111.5, 109.3, 99.9, 61.2, 61.2, 51.9, 34.8; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{13}Br_2NO_4H$ 405.9290, found 405.9317. Anal. Calcd for $C_{13}H_{13}Br_2NO_4$: C, 38.36; H, 3.22; N, 3.44. Found: C, 38.30; H, 3.36; N, 3.34.

*Synthesis of 4,7-Dibromo-5,6-dimethoxybenzo[b]thiophene-2-methylcarboxylate (**7**).* A mixture of 2,5-dibromo-3,4-dimethoxy-6-nitrobenzaldehyde **3** (1 g, 2.72 mmol, 1 equiv), methyl thioglycolate (0.25 mL, 2.74 mmol, 1.1 equiv), and anhydrous potassium carbonate (452 mg, 3.27 mmol, 1.2 equiv) in anhydrous *N*,*N*-dimethylformamide (5 mL) was mixed under an argon atmosphere. The mixture was refluxed, monitored by TLC, and allowed to react overnight. The reacting mixture was then allowed to cool to room temperature. After cooling, the mixture was extracted three times with diethyl ether (3 × 20 mL). The combined organic layers were then washed with water (50 mL) and brine (50 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The product was then purified using silica gel chromatography (ethyl acetate/hexanes, 1:5) to give the final product as a white powder (196 mg, 19%): mp 155−162 °C; IR ν_{max} (solid)/cm^{-1} 2948 (b, C−H), 1709 (s, C═O), 1205 (s, C-OMe); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 3.99 (s, 3H), 3.95 (s, 3H), 3.95 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 162.4, 151.3, 149.8, 140.1, 135.0, 134.4, 131.3, 112.8, 109.3, 61.5, 61.2, 52.7; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{10}Br_2SO_4H$ 408.8745, found 408.8736. Anal. Calcd for $C_{12}H_{10}Br_2SO_4$: C, 35.15; H, 2.46; S, 7.82. Found: C, 35.30; H, 2.44; S, 7.73.

*Synthesis of 4,7-Dibromo-5,6-dimethoxy-1H-indole-2-carboxylic Acid (**8**).* Methyl 4,7-dibromo-5,6-dimethoxy-1*H*-indole-2-carboxylate **5** (1.27g, 3.24 mmol, 1 equiv), a solution of 2 M sodium hydroxide (16.25 mL, 32.4 mmol, 10 equiv), and methanol (108 mL) were added into a 250 mL flask. The mixture was stirred at 70 °C, and the reaction was monitored using TLC and allowed to react for 1 h until total disappearance of the starting product. The reaction mixture was then allowed to cool to room temperature, acidified with a solution of 2 M HCl until complete precipitation of the product, and extracted three times with ethyl acetate (3 × 30 mL). The combined organic layers were then washed with water (50 mL) and brine (50 mL). The organic phase was then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a white crystalline solid (1.22g, quantitative): mp 199−202 °C; IR ν_{max} (solid)/cm^{-1} 3441 (m, N−H), 2931 (b, COOH), 1675 (s, C═O), 1258 (s, C-OMe); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.44 (d, J = 2.4 Hz, 1H), 3.99 (s, 3H), 3.93 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz; $CDCl_3$) δ 165.6, 150.8, 147.1, 132.9, 127.1, 124.7, 112.1, 109.6, 98.8, 61.6, 61.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{11}H_9Br_2NO_4H$ 377.8977, found 377.8971.

*Synthesis of 4,7-Dibromo-5,6-dimethoxy-1H-indole (**9**).* 4,7-Dibromo-5,6-dimethoxy-1*H*-indole-2-carboxylic acid **8** (604 mg, 1.6 mmol, 1 equiv) and diphenyl ether (8.6 g, 50.5 mmol, 32 equiv) were put in a 50 mL flask under an argon atmosphere. The reaction mixture was stirred at 250 °C (sand bath temperature) for 4 h. The reaction was allowed to cool to room temperature and then purified by flash column chromatography using ethyl acetate and hexanes as the eluent (5:95) to give an off-white solid which was kept at 0°C (496 mg, 87%): mp 129−133 °C; IR ν_{max} (solid)/cm^{-1} 3437 (m, N−H), 2938 (b, C−H), 1291 (s, C-OMe); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.27 (dd, J = 3.2, 2.4 Hz, 1H), 6.62 (dd, J = 3.2, 2.4 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 147.3, 145.8, 131.0, 125.3, 125.0, 107.8, 104.3, 98.4, 61.6, 61.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_9Br_2NO_2H$ 333.9078, found 333.9066. Anal. Calcd for $C_{10}H_9Br_2NO_2$: C, 35.85; H, 2.71; N, 4.18. Found: C, 36.1; H, 2.86; N, 4.14.

*Synthesis of 4,7-Dibromo-5,6-dimethoxy-1-methyl-1H-indole (**10a**).* 4,7-Dibromo-5,6-dimethoxy-1*H*-indole **9** (350 mg, 1.0 mmol,

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1 equiv) and potassium carbonate (231 mg, 1.7 mmol, 1.6 equiv) were added to a 50 mL reaction vessel under an argon atmosphere. Then, dry acetone was added (17 mL), and the mixture was stirred at 40 °C for 30 min. Dimethyl sulfate (171 mg, 1.4 mmol, 1.3 equiv) was then added. After the addition, the reaction mixture was heated up to 55 °C and allowed to react for 20 h. The reaction was allowed to cool to room temperature, and the solid residues were removed by vacuum filtration. The resulting mixture was concentrated under reduced pressure. Then, the product is purified by flash silica gel chromatography (ethyl acetate/hexanes, 1:9) to afford the title compound as a yellow crystalline solid (317 mg, 87%): mp 71−74 °C; IR ν_{max} (solid)/cm^{-1} 2940 (b, C−H), 1271 (s, C-OMe); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, J = 3.2 Hz, 1H), 6.48 (d, J = 3.2 Hz, 1H), 4.14 (s, 3H), 3.93 (s, 3H), 3.92 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 165.6, 150.8, 147.2, 132.9, 127.1, 124.7, 112.1, 109.6, 98.9, 61.6, 61.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{11}H_{11}Br_2NO_2H$ 347.9235, found 347.9228. Anal. Calcd for $C_{11}H_{11}Br_2NO_2$: C, 37.85; H, 3.18; N, 4.01. Found: C, 38.00; H, 3.40; N, 3.96.

*Synthesis of 4,7-Dibromo-5,6-dimethoxyindoline-2,3-dione (**10b**).* To a solution of 4,7-dibromo-5,6-dimethoxy-1*H*-indole **9** (1 g, 2.99 mmol, 1 equiv) in dimethyl sulfoxide (18 mL) under an inert atmosphere was added I_2O_5 (2 g, 5.99 mmol, 2 equiv) The reaction mixture was stirred at 80 °C for 1 h. Then, the mixture was cooled to room temperature, and a saturated solution of $Na_2S_2O_5$ (120 mL) was added. The mixture was extracted three times with ethyl acetate (3 × 40 mL). The combined organic layers were then washed with water and brine and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The product was then purified by a silica gel chromatography (ethyl acetate/hexanes, 2:3), followed by recrystallization in ethanol, to afford a bright orange crystalline solid (404 mg, 31%): mp 229−233 °C; IR ν_{max} (solid)/cm^{-1} 3173 (b, N−H and C−H), 1755 (s, C═O), 1732 (s, C═O), 1323 (s, C-OMe); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 4.10 (s, 3H), 3.85 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 178.9, 158.9, 158.0, 147.3, 146.7, 117.9, 100.0, 61.7, 61.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_7Br_2NO_4H$ 363.8820, found 363.8805. Anal. Calcd for $C_{10}H_7Br_2NO_4$: C, 32.91; H, 1.93; N, 3.84. Found: C, 32.60; H, 1.91; N, 3.88.

*Synthesis of 4,7-Dibromo-5,6-dimethoxy-1-methylindoline-2,3-dione (**11**).* To a solution of 4,7-dibromo-5,6-dimethoxy-1-methyl-1*H*-indole **10**a (100 mg, 0.29 mmol, 1 equiv) in dimethyl sulfoxide (2 mL) under an ambient atmosphere was added I_2O_5 (191 mg, 0.57 mmol, 2 equiv). The reaction mixture was stirred at 80 °C for 20 min. Then, the mixture was cooled to room temperature, and a saturated solution of $Na_2S_2O_5$ (20 mL) was added. The mixture was extracted three times with ethyl acetate (3 × 30 mL). The combined organic layers were then washed with water and brine and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The product was then purified by flash silica gel chromatography (ethyl acetate/hexanes, 6:4) to afford a deep red crystalline solid (100 mg, 92%): mp 193−197 °C; IR ν_{max} (solid)/cm^{-1} 2949 (b, C−H), 1738 (s, C═O), 1352 (C-OMe); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05 (s, 3H), 3.85 (s, 3H), 3.66 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 179.1, 159.1, 158.5, 147.5, 147.3, 118.3, 113.7, 100.8, 61.5, 61.2, 30.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{11}H_9Br_2NO_4H$ 377.8977, found 377.8953.

*Synthesis of 4,5-Dimethoxy-2-nitrobenzonitrile (**12**).* A mixture of 4,5-dimethoxy-2-nitrobenzaldehyde **2** (5 g, 23.7 mmol, 1 equiv), aqueous ammonia (58 mL, 0.86 mol, 36 equiv), and iodine (6.61 g, 26.0 mmol, 1.1 equiv) was added into a 250 mL flask. Then, 70 mL of tetrahydrofuran was added. The reaction was monitored using TLC and allowed to react at room temperature for 6 h until total disappearance of the starting product. Then, a saturated solution of sodium thiosulfate (150 mL) was added, and the reaction was extracted three times with diethyl ether (3 × 50 mL). The combined organic layers were then washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The reaction crude was purified by a silica gel chromatography with ethyl acetate/hexanes (35:65) to give a light yellow solid (4.17 g, 85%): mp 160−167 °C; IR ν_{max} (solid)/cm^{-1} 2988 (w, C−H), 2225 (w, C≡N), 1517, (s, N═O_2), 1227 (s, C-OMe); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, s), 7.21 (1H, s), 4.03 (3H, s), 4.02 (3H, s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.4, 152.2, 142.7, 115.5, 115.4, 107.9, 100.8, 57.0, 56.8; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_9H_8N_2O_4H$ 209.0563, found 209.0574. Anal. Calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.90; H, 3.92; N, 13.20.

*Synthesis of 4,5-Dimethoxy-2-nitrobenzamide (**13**).* 4,5-Dimethoxy-2-nitrobenzonitrile **12** (3.78 g, 18.2 mmol, 1 equiv) was stirred at room temperature in ethanol (80 mL). Sodium hydroxide (871 mg, 21.8 mmol, 1.2 equiv) was then added followed by a slow addition of 30% hydrogen peroxide (8.4 mL, 82 mmol, 4.5 equiv). After the addition, the reaction mixture was heated up to 60 °C, and the reaction was monitored using TLC and allowed to react for 5 h until total disappearance of the starting product. The mixture was then cooled to 0 °C with an ice bath, and a solution of 2 M HCl was added until complete precipitation of the product (2 h). The precipitate was isolated by vacuum filtration, giving a yellow solid (3.41 g, 88%): mp 187−191 °C; IR ν_{max} (solid)/cm^{-1} 3286 (b, C−H), 1652 (s, C═O), 1511 (N−O), 1224 (C-OMe); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.59 (s, 1H), 7.56 (s, 1H), 7.10 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 167.6, 152.6, 149.1, 139.9, 127.4, 111.2, 107.7, 56.8, 56.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_9H_{10}N_2O_5H$ 227.0668, found 227.0662. Anal. Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.39. Found: C, 47.90; H, 4.51; N, 12.00.

*Synthesis of 5,6-Dimethoxybenzo[c][1,2,5]oxadiazole-1-oxide (**14**).* A mixture of sodium hydroxide (884 mg, 22.1 mmol, 10 equiv) and bromine (0.28 mL, 5.57 mmol, 2.5 equiv) in water (9.2 mL) was stirred at room temperature for 10 min. Then, the mixture was added at 0 °C onto 4,5-dimethoxy-2-nitrobenzamide **13** (504 mg, 2,23 mmol, 1 equiv). The reaction mixture was then heated at 40 °C and monitored using TLC for 6 h until complete disappearance of the starting product. After completion of the reaction, water (100 mL) was added to the reaction mixture and extracted three times with ethyl acetate (3 × 50 mL). The combined organic layers were then washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford a yellow solid (369 mg, 84%): mp 212−215 °C; IR ν_{max} (solid)/cm^{-1} 3075 (w, C−H), 1633 (s, C═N), 1485 (s, N−O), 1225 (s, O-Me); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.46 (s, 1H), 4.00 (s, 3H), 3.96 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 155.7, 153.3, 150.3, 111.8, 92.3, 87.5, 57.0, 56.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_8H_8N_2O_4H$ 197.0563, found 197.0581. Anal. Calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.30; H, 4.11; N, 14.20.

*Synthesis of 4,7-Dibromo-5,6-dimethoxybenzo[c][1,2,5]-oxadiazole-1-oxide (**15**).* 5,6-Dimethoxybenzo[*c*][1,2,5]oxadiazole-1-oxide **14** (144 mg, 0.73 mmol, 1 equiv), dichloromethane (5.6 mL), and acetic acid (5.6 mL) were added to a reacting vessel under an argon atmosphere. The solution was then degassed for 20 min using argon while cooling down to 0 °C in an ice bath. *N*-Bromosuccinimide (287 mg, 1.61 mmol, 2.2 equiv) was added portion wise, and the mixture was allowed to react at room temperature. The reaction was monitored using TLC and allowed to react for 3 days until total disappearance of the starting product. Water (30 mL) was added, and the reaction mixture was extracted three times with ethyl acetate (3 × 40 mL). The combined organic layers were then washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (1:9 ethyl acetate/hexanes) to give a bright yellow crystalline product (85 mg, 32%): mp 153−157 °C; IR ν_{max} (solid)/cm^{-1} 2954 (w, C−H), 1605 (s, C═N), 1485 (s, N−O), 1295 (s, C-OMe); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (s, 3H), 3.95 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.0, 153.2, 150.1, 111.3, 101.7, 97.8, 61.8, 61.6, 29.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_8H_6N_2Br_2O_4H$ 352.8773, found 352.8805.

*Synthesis of 5,6-Dimethoxybenzo[c][1,2,5]oxadiazole (**16**).* To a solution of 5,6-dimethoxybenzo[*c*][1,2,5]oxadiazole 1-oxide **14** (900

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mg, 4.6 mmol, 1 equiv) in ethanol (352 mL) was added triphenyl phosphine (1.26 g, 4.8 mmol, 1.09 equiv), and the mixture was refluxed for 6 h. The solvent was evaporated under reduced pressure, and the crude product was purified by silica gel chromatography (ethyl acetate/hexanes, 1:3) to give 5,6-dimethoxybenzo[*c*][1,2,5]-oxadiazole as a white crystalline solid (524 mg, 63%): mp 193−195 °C; IR ν_{max} (solid)/cm^{-1} 3094 (b, C−H), 1515 (s, C═N), 1222 (C-OMe); ^{1}H NMR (500 MHz, $CDCl_3$) 6.89 (s, 2H), 4.00 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.3, 146.7, 90.6, 56.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_8H_8N_2O_3H$ 181.0613, found 181.0627.

*Synthesis of 4,7-Dibromo-5,6-dimethoxybenzo[c][1,2,5]-oxadiazole (**17**).* 5,6-Dimethoxybenzo[*c*][1,2,5]oxadiazole **16** (480 mg, 2.7 mmol, 1 equiv) was dissolved in dichloromethane (54 mL) and put under an argon atmosphere. Acetic acid (6.66 mL, 2.7 mmol, 1 equiv) was then added followed by a slow addition of bromine (0.55 mL, 10.7 mmol, 4 equiv). The reaction mixture was stirred at room temperature for 72 h. A solution of 2 M NaOH (50 mL) was added, and the reaction mixture was extracted three times with dichloromethane (3 × 30 mL). The combined organic layers were then washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (ethyl acetate/hexanes, 1:5) to give a white crystalline product (802 mg, 89%): mp 132−134 °C; IR ν_{max} (solid)/cm^{-1} 2952 (w, C−H), 1474 (s, C═N), 1301 (s, O-Me); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 155.9, 147.2, 99.5, 61.7; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_8H_6Br_2N_2O_3H$ 336.8824, found 336.8813. Anal. Calcd for $C_8H_6Br_2N_2O_3$: C, 28.43; H, 1.79; N, 8.29. Found: C, 28.30; H, 1.77; N, 8.14.

*Synthesis of 4,5-Dimethoxybenzene-1,2-diamine (**18**).* 5,6-Dimethoxybenzo[*c*][1,2,5]oxadiazole 1-oxide **14** (480 mg, 2.4 mmol, 1 equiv) and $SnCl_2{\cdot}2H_2O$ (4.42 g, 19.6 mmol, 8 equiv) were added in a round-bottom flask and put under an argon atmosphere. Then, ethanol (35 mL) and concentrated HCl (14.5 mL) were added to the flask, and the reaction mixture was refluxed for 2 h. The reaction mixture was quickly basified with a solution of 2 M NaOH until pH 10 and extracted 4 times with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give 4,5-dimethoxybenzene-1,2-diamine **18** as a gray solid. The product being unstable was quickly used without further purification in the next step.

*Synthesis of 5,6-Dimethoxybenzo[c][1,2,5]thiadiazole (**19**).* 4,5-Dimethoxybenzene-1,2-diamine **18** (480 mg, 2.4 mmol, 1 equiv) was put under an argon atmosphere, and anhydrous dichloromethane (35 mL) was added. Thionyl chloride (0.35 mL, 4.8 mmol, 2 equiv) was slowly added to the reaction mixture at 0 °C, and the mixture was allowed to react for 10 min. Then, triethylamine (2.73 mL, 19.6 mmol, 8.2 equiv) was slowly added at 0 °C. The reaction mixture was refluxed overnight. After cooling back to room temperature, water was added (50 mL), and the reaction mixture was extracted three times with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was then purified by flash silica gel chromatography (CH_2Cl_2) to give 5,6-dimethoxybenzo[*c*][1,2,5]thiadiazole as a white solid (421 mg, 88%): mp 157−160 °C; IR ν_{max} (solid)/cm^{-1} 2994 (b, C−H), 1493 (m, C═N), 1215 (s, C-OMe); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 2H), 4.01 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.2, 151.2, 97.9, 56.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_8H_8N_2O_2SH$ 197.0385, found 197.0398.

*Synthesis of 4,7-Dibromo-5,6-dimethoxybenzo[c][1,2,5]-thiadiazole (**20**).* 5,6-Dimethoxybenzo[*c*][1,2,5]thiadiazole **19** (309 mg, 1.6 mmol, 1 equiv) was dissolved in dichloromethane (31 mL) and put under an argon atmosphere. Acetic acid (4 mL, 1.6 mmol, 1 equiv) was then added followed by a slow addition of bromine (0.32 mL, 6.4 mmol, 4 equiv). The reaction mixture was stirred at room temperature for 72h. A solution of NaOH 2 M was added until pH 10 and the reaction mixture was extracted 3 times with dichloromethane (3 × 35 mL). The combined organic layers were then washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (ethyl acetate/hexanes, 1:5) to give a white crystalline product (527 mg, 95%): mp 133−135 °C; IR ν_{max} (solid)/cm^{-1} 2945 (w, C−H), 1449 (m, C═N), 1263 (s, O-Me); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.7, 150.2, 106.0, 61.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_8H_6Br_2N_2O_2SH$ 352.8595, found 352.8595. Anal. Calcd for $C_8H_6Br_2N_2O_2S$: C, 27.14; H, 1.71; N, 7.91; S, 9.06. Found: C, 27.40; H, 1.64; N, 7.97; S, 8.95.

*Synthesis of 2-Iodo-4,5-dimethoxybenzonitrile (**22**).* 2-Iodo-4,5-dimethoxybenzaldehyde **21** (1.0 g, 3.4 mmol, 1 equiv), aqueous ammonia (11.5 mL, 122 mmol, 36 equiv), and iodine (956 mg, 3.7, 1.1 equiv) were added into a 100 mL flask. Then, tetrahydrofuran (15 mL) was added, and the mixture was stirred at room temperature for 6 h. After completion of the reaction, sodium thiosulfate was added, and the reaction was extracted three times with diethyl ether (3 × 50 mL). The combined organic layers were then washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a white solid (964 mg, 97%): mp 123−126 °C; IR ν_{max} (solid)/cm^{-1} 2937 (b, C−H), 2224 (m, C≡N), 1262 (s, O-Me); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.02 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz; $CDCl_3$) δ 152.8, 149.2, 121.5, 121.3, 119.7, 115.7, 115.5, 112.0, 88.6, 56.4, 56.3, 56.1, 56.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_9H_8INO_2H$ 289.9678, found 289.9678. Anal. Calcd for $C_9H_8INO_2$: C, 37.39; H, 2.79; N, 4.85. Found: C, 37.40; H, 2.65; N, 4.74.

*Synthesis of 4,5-Dimethoxyphthalonitrile (**23**).* 2-Iodo-4,5-dimethoxybenzonitrile **22** (964 mg, 3.3 mmol, 1 equiv) and copper(I) cyanide (388 mg, 4.3 mmol, 1.3 equiv) were added in a round-bottom flask and put under an argon atmosphere. Anhydrous *N*,*N*-dimethylformamide (67 mL) was then added, and the reaction mixture was refluxed for 5 h. After cooling to room temperature, the reaction mixture was filtered to remove residual copper compounds, and water was added on the filtrate. The formed precipitate was filtered using vacuum filtration and was further purified by silica gel chromatography (ethyl acetate/hexanes, 7:13) to afford a white solid (508 mg, 81%): mp 183−187 °C; IR ν_{max} (solid)/cm^{-1} 3069 (b, C−H), 2225 (s, C≡N), 1222 (s, C-OMe); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 2H), 3.96 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.6, 115.7, 114.8, 108.8, 56.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_8N_2O_2H$ 189.0664, found 189.0657.

*Synthesis of 2-Dodecyl-5,6-dimethoxyisoindoline-1,3-dione (**24**).* 4,5-Dimethoxyphthalonitrile **23** (1 g, 5.3 mmol, 1 equiv), potassium hydroxide (2.98 g, 53 mmol, 10 equiv), and water (10 mL) were added in a round-bottom flask and refluxed for 90 h. The reaction mixture was acidified with 2 M HCl until pH 1, and then the formed precipitate was filtered. A fraction of the off-white solid (4,5-dimethoxyphthalic acid intermediate) (0.258g, 1.14 mmol, 1 equiv) was taken up and added in a round-bottom flask followed by acetic anhydride (5 mL, 0.22 mol/L). The mixture was stirred at refluxed for 2 h, and the solvent was evaporated under reduced pressure. The resulting yellow powder (5,6-dimethoxyisobenzofuran-1,3-dione intermediate) (0.237g, 1.14 mmol, 1 equiv) was added in a round-bottom flask followed by the addition of dodecylamine (0.223g, 1.2 mmol, 1.05 equiv) and acetic acid (23 mL, 0.05 mol/L). The mixture was stirred at reflux for 4 h. Water (50 mL) was then added to the mixture to precipitate the crude product as an off-white powder after filtration. The crude product was further purified silica gel chromatography (ethyl acetate/hexanes, 1:10) to give the pure product as a white powder (0.351 g, 82% overall yield): mp 140−146 °C; IR ν_{max} (solid)/cm^{-1} 2919 (b, C−H), 1687 (s, C═O), 1222 (s, C-OMe); ^{1}H NMR (400 MHz, C_6D_6) δ 6.99 (s, 2H), 3.61 (t, J = 7.3 Hz, 2H), 3.06 (s, 6H), 1.65 (t, J = 7.3 Hz, 2H), 1.29−1.15 (m, 18H), 0.85 (t, J = 5.7 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.6, 153.6, 125.5, 105.2, 56.5, 38.0, 31.8, 29.6, 29.6, 29.5, 29.5, 29.3, 29.2, 28.7, 26.8, 22.6, 14.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{33}NO_4H$ 376.2488, found 376.2472. Anal. Calcd for $C_{22}H_{33}NO_4$: C, 70.37; H, 8.86; N, 3.73. Found: C, 70.5; H, 9.08; N, 3.77.

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*Synthesis of 4,7-Dibromo-2-dodecyl-5,6-dimethoxyisoindoline-1,3-dione (**25**).* 2-Dodecyl-5,6-dimethoxyisoindoline-1,3-dione **26** (81 mg, 0.22 mmol, 1 equiv) was added in a round-bottom flask followed by H_2SO_4 (0.4 mL, 0.64 mol/L) and trifluoroacetic acid (1.1 mL, 0.2 mol/L). Then, freshly recrystallized *N*-bromosuccinimide (0.115 g, 0.66 mmol, 3 equiv) was slowly added over a period of 30 min at room temperature. The flask was covered with aluminum foil to block the light, and then the mixture was stirred at room temperature overnight. The next morning, the brown mixture was added to a beaker with 25 mL of ice. An off-white precipitate appeared and was filtered. The crude product was further purified by a silica gel plug (ethyl acetate/hexanes, 1:4) to give a white solid (0.109 g, 95%): mp 109−112 °C; IR ν_{max} (solid)/cm^{-1} 2865 (b, C−H), 1697 (s, C═O), 1245 (s, C-OMe); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (s, 6H), 3.64 (t, J = 7.0 Hz, 2H), 1.67−1.59 (m, 2H), 1.30−1.21 (m, 18H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.7, 156.0, 127.0, 114.3, 61.4, 38.6, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 29.1, 28.3, 26.8, 22.6, 14.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{31}Br_2NO_4H$ 532.0698, found 532.0678.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01869.

NMR spectra (^{1}H NMR and ^{13}C{^{1}H} NMR) of all compounds and thermal ellipsoid plots for each crystal structure (PDF)

Accession Codes

CCDC 2101231−2101242 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033.

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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