



Cite this: *Green Chem.*, 2025, **27**, 7506

Received 25th February 2025,
Accepted 16th May 2025

DOI: 10.1039/d5gc01003a

rsc.li/greenchem

Modular synthetic routes to biologically active indoles from lignin†

Antonio A. Castillo-Garcia, ^{a,b} Jörg Haupenthal, ^{c,d} Anna K. Hirsch ^{c,d,e} and Katalin Barta *^a

Diol-assisted fractionation has emerged as an important 'lignin-first' processing method that delivers aromatic C2-acetals with high selectivity. This contribution describes the development of an unexpectedly straightforward synthetic route to biologically active indoles from this aromatic platform chemical, boosting the scope of this unique biorefinery approach. The novel method utilizes the functionalization of C2-acetal via phenol alkylation and mild

halogenation reactions, enabling catalytic C–N coupling with anilines and benzylamines and forging *ortho*-aminoacetal intermediates. Such derivatives are suitable for *in situ* Schiff base formation/intramolecular cyclization by acetal deprotection in a mixture of MeOH/H₂O and PTSA as the catalyst, resulting in a novel library of lignin-based indoles. Evaluation of the biological activity in terms of anticancer activity using human Hep G2 cells shows promising early results.

Green foundation

The ubiquity of indoles as building blocks in a plethora of pharmaceuticals demands much greener and more sustainable synthetic strategies incorporating two fundamental aspects:

1. The valorization of renewable aromatic platform chemicals such as lignin with the full incorporation of intrinsic functionalities in the final products ensures high-atom economical processes and, at the same time, alleviates the high dependence on fossil-based resources.
2. The use of catalytic strategies and mild reaction conditions in combination with more environmentally friendly solvents and reagents is highly desired, perfectly in line with the principles of Green Chemistry, and addresses the UN SDGs-2030, **GOAL-3** (Good Health and Well-being) and **GOAL-12** (Responsible Consumption and Production).

Introduction

Naturally occurring in tryptophan and several alkaloids, indole motifs^{1,2} are privileged moieties given their omnipresence in multiple biologically active compounds^{3–6} and versatility towards further transformations.^{7,8} Throughout the years, traditional strategies such as the Fischer, Bischler and Baeyer–Emmerling indole syntheses, among others, have been

explored in depth, enriching the diversity of these derivatives,^{9–11} however, the design of greener pathways in combination with the use of renewable building blocks would still be highly advantageous.^{12,13} In that sense, several approaches for the sustainable synthesis of indoles have been recently described in the literature, including the use of benign solvents, such as mixtures of water and ethanol, deep eutectic solvents (DESS), bio-based ethyl lactate or biodegradable polyethylene glycol, and the use of green techniques such as microwave/UV-visible light irradiation or ultrasound-assisted synthesis,¹⁴ however, the use of renewable starting materials in this arena remains scarcely explored.¹⁵ We have previously described the utilization of lignin-derived building blocks for the synthesis of N-heterocycles providing green access to a handful of pharmaceutically relevant scaffolds¹⁶ conventionally obtained from petrochemicals, paving the way for the diversification of high-value chemicals from biomass streams.^{17,18} To the best of our knowledge, however, only one example has been reported employing lignin model compounds for the synthesis of indoles. In that

^aInstitute of Chemistry, University of Graz, Heinrichstrasse 28, A-8010 Graz, Austria.
E-mail: katalin.barta@uni-graz.at

^bStratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

^cHelmholtz Institute for Pharmaceutical Research Saarland (HIPS) – Helmholtz Centre for Infection Research (HZI), Campus Building E8.1, 66123 Saarbrücken, Germany

^dPharmScienceHub, Campus Building A2.3, 66123 Saarbrücken, Germany

^eSaarland University, Department of Pharmacy, Campus Building E8.1, 66123 Saarbrücken, Germany

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d5gc01003a>



work, lignin models bearing α -hydroxyacetophenones were reacted with pyrroles *via* [4 + 2] annulation.¹⁹ Furthermore, the valorization of lignin-derived mono-aromatics as platform chemicals^{20,21} has emerged as a sustainable alternative where the intrinsic moieties from parent lignin can be conveniently modified towards the production of nitrogen-containing compounds.^{22–24} Following this principle, our group has recently reported the atom-efficient valorisation of the lignin-derived acetal **C2-G**, selectively obtained *via* acidolysis of softwood lignin in conjunction with ethylene glycol (EG) stabilization,^{25–28} into a novel series of biologically active N-chemicals such as dopamine derivatives, tetrahydroisoquinolines, and quinazolinones as well as the natural product tetrahydropapaveroline in clean synthetic pathways, principally relying on the amination of the aliphatic alcohol side chain (Fig. 1A).²⁹

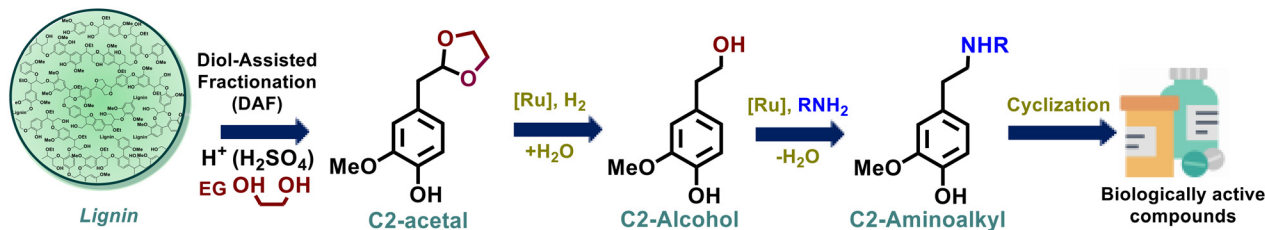
Herein, we aimed to develop a different methodology, aligning with the inherent structural features of **C2-G**, but manipulating the aromatic core first to target the formation of a new series of lignin-based N-heterocycles, whereby ring formation is promoted by the presence of the ‘masked’ aldehyde, inherently present in the **C2-G** platform chemical.

In this regard, the formation of indoles, employing acetal derivatives, has previously been attempted. For instance, the

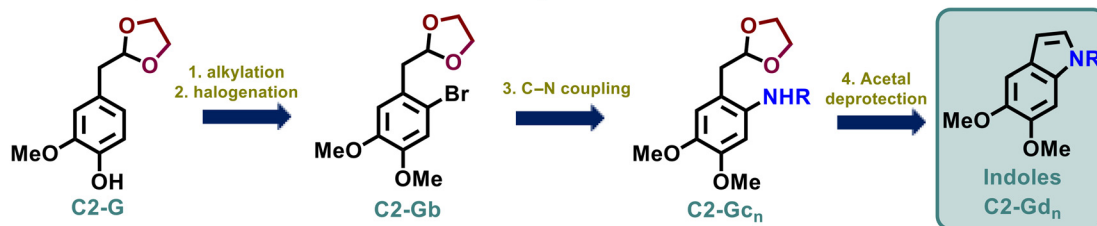
commonly named Nordlander synthesis³⁰ involves the use of acetals in an intramolecular cyclization with anilines and sulfonamides.^{31,32} Moreover, we expected that the inherent acetal moiety might facilitate the direct aromatic halogenation of **C2-G** and the subsequent nitrogen incorporation by C–N coupling, avoiding undesired side reactions.

A similar approach has indeed been reported for the synthesis of petrol-based isoquinolines, employing aryl halides containing acetal moieties in the *ortho*-position as convenient starting building blocks.³³ Based on these antecedents, our new methodology for the synthesis of a series of lignin-based indoles contemplates (a) the efficient functionalization of **C2-G** by phenol alkylation/SEAr reactions, followed by (b) the Pd-mediated C–N coupling of **C2-Gb** with anilines and benzylamines and (c) acid-catalyzed acetal deprotection leading to *in situ* Schiff base formation and intramolecular cyclization towards the formation of indoles (**C2-Gd_n**) (Fig. 1B). Interestingly, numerous indoles containing intrinsic lignin-like functionalities have shown promising biological activity, for instance as anticancer^{34,35} or antidepressive³⁶ agents (Fig. 1C); therefore, the pharmaceutical relevance of the new lignin-derived indoles **C2-Gd_n** was evaluated in terms of their anticancer activity on human Hep G2 cells, displaying promising activity for several of these derivatives.

A) Access to Biologically active N-Heterocycles from C2-Acetal by acetal deprotection/hydrogenation (Ref. 29)



B) From C2-Acetal (**C2-G**) to Lignin-based Indoles (**C2-Gd_n**) via formation of *ortho*-aminoacetal intermediates (This work)



C) Representative biologically active compounds containing both indole and lignin-derived motifs

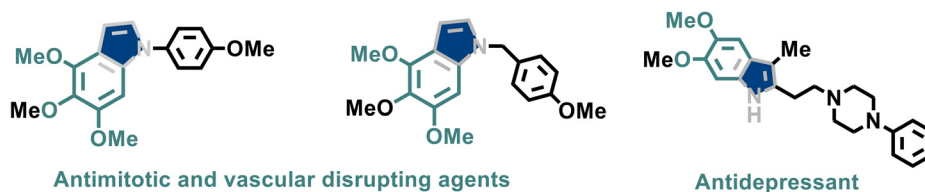


Fig. 1 General strategy for the synthesis of bio-active indoles from lignin and relevant biologically active compounds bearing lignin-derived functionalities.



Results and discussion

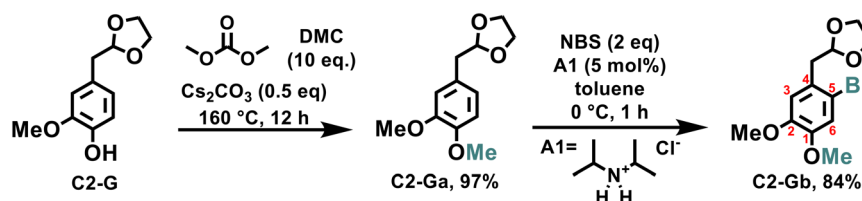
Establishing a catalytic strategy for the construction of lignin-based indoles (C2-Gd_n)

We began our study with the synthesis of **C2-Gb** through a convenient two-step method. First, the reaction of **C2-G** with dimethyl carbonate (DMC) as a non-toxic alkylating agent³⁷ led to the formation of **C2-Ga** in an almost quantitative yield (97%). Then, the formation of **C2-Ga** allowed selective bromination in the *ortho* position (C5) to the aliphatic chain, employing NBS and di-isopropyl ammonium chloride (**A1**) as additives under mild conditions, affording an isolated yield of 84% (Scheme 1). Next, the catalytic C–N coupling of **C2-Gb** with aniline was investigated.

For this purpose, well-established Pd-protocols³⁸ were tested, observing that the combination of Pd₂dba₃ (1 mol%) with Xantphos³⁹ (2 mol%) as the ligand and Cs₂CO₃ as the base provided the best results, affording full conversion and good isolated yield (80%) of the target product (Table 1, entry 1). Similar results were obtained when Pd(dba)₃⁴⁰ or Pd(MeCN)Cl₂ was employed as the catalyst; however, a significant loss of

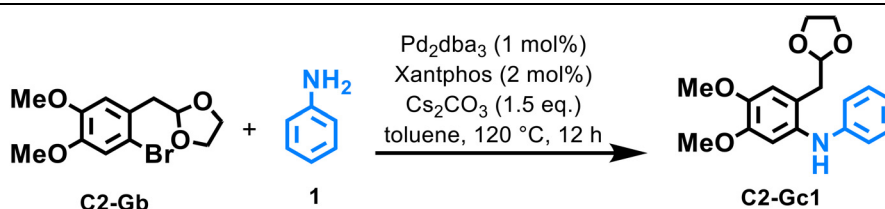
activity was observed when different phosphines were utilized instead of Xantphos (Table 1, entries 4–6). Additionally, Ni-catalysts Ni(cod)₂ and Ni(dme)Cl₂ were also tested under the same reaction conditions without achieving conversion; therefore, we decided to continue our study using the aforementioned Pd₂dba₃/Xantphos system. The influence of temperature and reaction time was evaluated when the reaction was performed either at 100 °C or for 8 h (Table 1, entries 11 and 13), observing lower conversion in both cases. Finally, we found that the use of a small excess of aniline was beneficial since a loss of yield was detected when the reaction was performed using a stoichiometric ratio (1 eq.) of aniline (entry 9).

With the optimized conditions in hand, we turned our attention to evaluate the scope of the C–N coupling between **C2-Gb** with diverse aromatic amines. A host of differently substituted anilines were tested obtaining moderate to good yields in most of the cases, including those anilines bearing electron-donating groups such as –OMe (**C2-Gc3**) and –SMe (**C2-Gc7**), as well as those featuring electron-withdrawing groups like –CN (**C2-Gc2**), –CF₃ (**C2-Gc5** and **C2-Gc6**), –F (**C2-Gc9** and **C2-Gc10**) and –NO₂ (**C2-Gc11**). Moreover, anilines bearing car-



Scheme 1 Synthesis of intermediate **C2-Gb** (for experimental details, see the ESI†).

Table 1 Pd-catalyzed C–N coupling of **C2-Gb** with anilines and benzylamines^a



Entry	Deviation from standard conditions	C2-Gc1 ^b (%)
1	—	91 (80) ^c
2	Pd(dba) ₃ as precatalyst	86
3	Pd(MeCN)Cl ₂ as precatalyst	89
4	Dppp as ligand	0
5	Dppf as ligand	23
6	DPEPhos as ligand	35
7	Ni(cod) ₂ as precatalyst	0
8	Ni(dme)Cl ₂ as precatalyst	0
9	1 eq. of 1	76
10	T = 100 °C	56
11	NaOtBu instead of Cs ₂ CO ₃	86
12	t = 8 h	64

^a General reaction conditions: **C2-Gb** (0.28 mmol), **1** (0.30 mmol), Pd₂dba₃ (2.8 × 10^{−3} mmol), Xantphos (5.6 × 10^{−3} mmol), Cs₂CO₃ (0.42 mmol), 120 °C, 12 h. ^b Yields were determined by GC-FID. ^c Isolated yield.

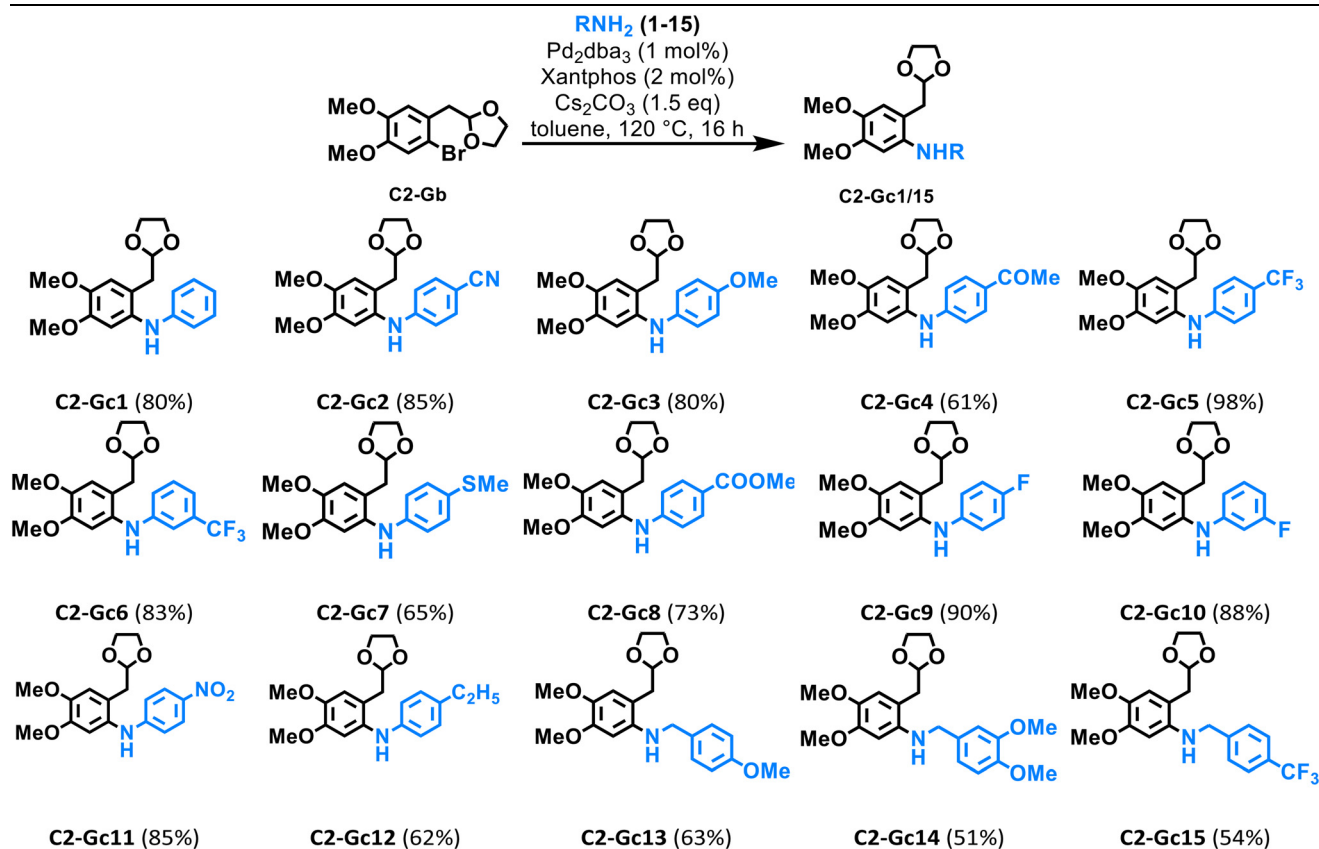


bonyl groups such as $-\text{COMe}$ (**C2-Gc4**) and $-\text{COOMe}$ (**C2-Gc8**) were also subjected to C–N coupling with **C2-Gb** affording good yields in both cases (Table 2). In addition, the coupling with potentially lignin-based benzylamines⁴¹ was efficiently performed achieving acceptable yields in the cases of **C2-Gc13** and **C2-Gc14**. Interestingly, the influence of the steric hindrance from different functional groups was noted especially in the case of those derivatives containing benzylamines or anilines containing substituents such as $-\text{COMe}$ and $-\text{SMe}$. Although the deprotection of acetals mediated by Pd-catalysis has been previously reported,^{42,43} the reaction nonetheless has to be performed in aqueous media and preferably under acidic conditions; therefore, the C–N coupling of **C2-Gb** was smoothly achieved under the above-mentioned anhydrous conditions without acetal deprotection being observed; therefore, the C–N coupling of **C2-Gb** was smoothly achieved under the abovementioned anhydrous conditions.

In order to establish the reaction conditions for the acetal deprotection of **C2-Gc1** and *in situ* Schiff-base formation, a mixture of MeOH/H₂O was employed as the reaction medium given the low solubility of these derivatives in water, which was imperative to perform this reaction (Table S2†). Previously, the deprotection of 1,3-dioxolanes containing sensitive functional groups has been carried out using aqueous methanol under

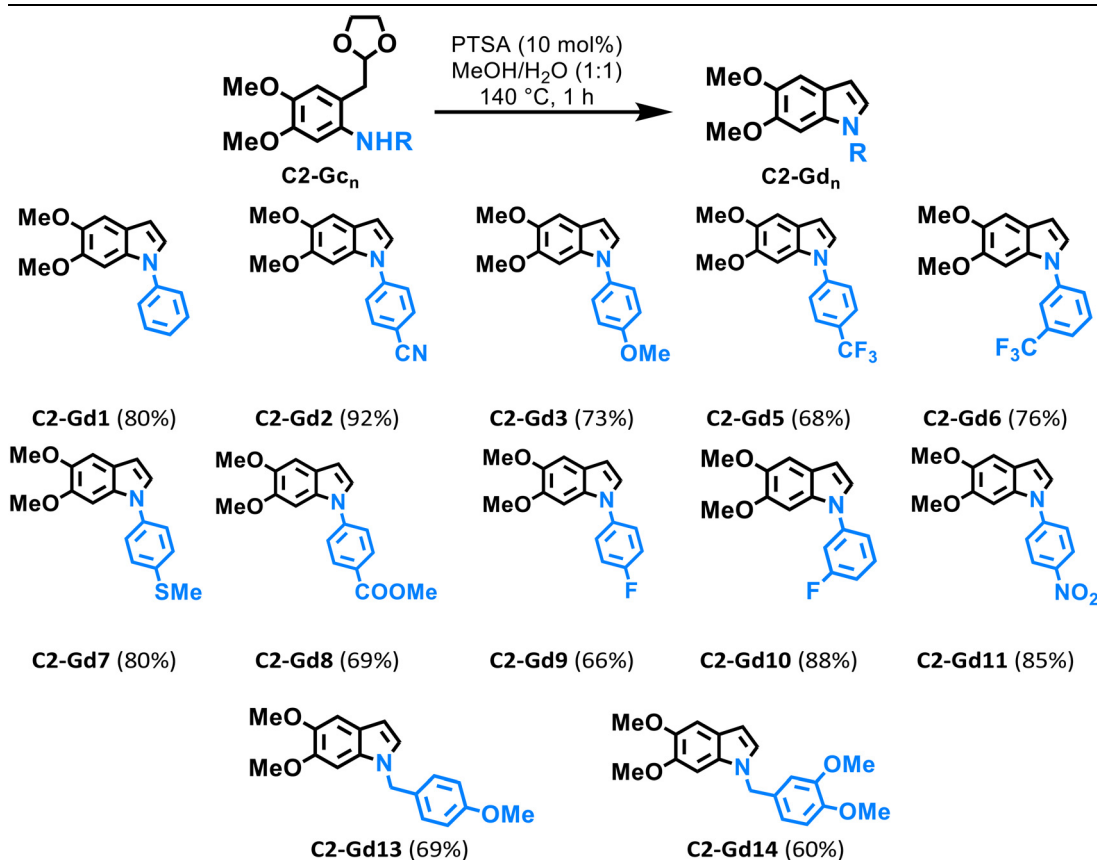
reflux and InCl₃ as the Lewis acid catalyst.⁴⁴ Indeed, the use of an acidic additive is crucial for both acetal deprotection and indole formation, where Brønsted acids such as HCl or *p*-toluene sulfonic acid (PTSA) are commonly applied;⁴⁵ therefore, we decided to use PTSA as the additive for our study. As expected, the formation of the indole **C2-Gd1** was achieved almost quantitatively when the reaction was performed in MeOH/H₂O (1:1) at 140 °C for 1 h using 0.1 eq. of PTSA, affording an isolated yield of 80% (Table S2,† entry 1). A significant loss of conversion was observed when only MeOH or H₂O was used as the solvent (Table S2,† entries 2 and 3). Moreover, the acetal deprotection was found to be temperature dependent, since only 69% conversion was observed when performing the reaction at 120 °C (Table S2,† entry 5). The effect of the additive was also tested by using oxalic acid instead of PTSA (entry 6), albeit leading to diminished conversion. After establishing the reaction conditions for the synthesis of **C2-Gd1**, the scope of this method was evaluated for several *ortho*-aminoacetal derivatives **C2-Gc_n** (Table 3). Overall, compounds bearing aniline scaffolds delivered good to excellent yields in comparison with substrates containing benzylamines, which can be attributed to the higher basicity of benzylamines and to the plausible Nordlander-indole synthesis mechanism for intramolecular cyclization that requires strong acidic con-

Table 2 Pd-catalyzed C–N coupling of **C2-Gb** with anilines and benzylamines^a



^a General reaction conditions: **C2-Gb** (0.28 mmol), **1-15** (0.3 mmol), Pd₂dba₃ (2.8×10^{-3} mmol), Xantphos (5.6×10^{-3} mmol), Cs₂CO₃ (0.42 mmol), 120 °C, 16 h. Isolated yields are shown.



Table 3 Lignin-based indoles **C2-Gd_n** via *ortho*-aminoacetal deprotection: scope of the reaction^a

^a General reaction conditions: **C2-Gc_n** (0.15 mmol), PTSA (0.015 mmol), MeOH/H₂O (1 : 1, 2 mL) 140 °C, 1 h. Isolated yields are shown.

ditions.⁹ In fact, the formation of indoles starting from α -anilinoacetal intermediates typically requires the use of harsh chemicals such as trifluoroacetic acid and halogenated solvents; therefore, our method provides a more sustainable pathway for the synthesis of these moieties by using a greener reaction medium such as MeOH/H₂O in combination with catalytic amounts of acid.

Evaluation of biological activity of indoles **C2-Gd_n**

The intrinsic functionalities of the lignin-derived **C2**-acetal **C2-G** not only allow sustainable access to indoles but might also increase the biological activity given their occurrence in multiple natural products. In fact, the impact of methoxy substituents on the structural rigidity of indoles and their antiproliferative activity in various human cancer cell lines has been previously identified.⁴⁶ In order to determine the bioactivity of the new series of lignin-based indoles, the effects on a human hepatoma cell line (Hep G2) as an early indication of anticancer activity of selected **C2-Gd_n** derivatives was explored (Fig. 2).

Overall, a common structure–activity trend was observed. Indoles with electron-donating substituents such as –OMe (**C2-Gd3** and **C2-Gd13**), –SMe (**C2-Gd7**) or electron-withdrawing –COOMe (**C2-Gd8**) displayed higher inhibition in comparison with those with strongly deactivating substituents such as –CF₃

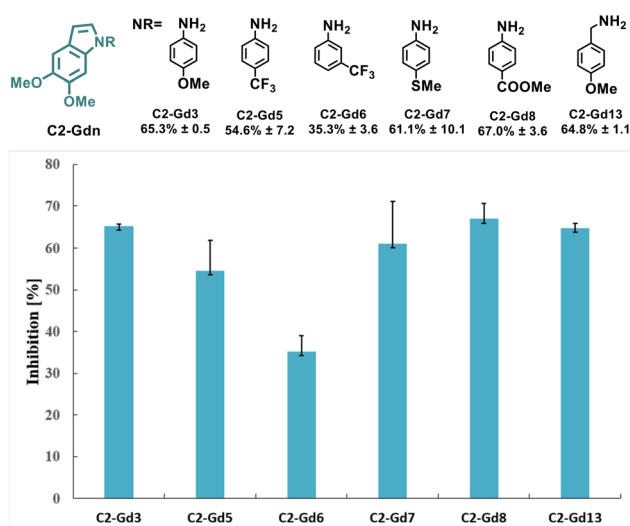


Fig. 2 Inhibitory effects of selected examples of lignin-based indoles **C2-Gd_n** on the viability of HepG2 cells treated with the indicated compounds at 100 μ M. Percentage (%) inhibition values and standard deviations from at least two independent experiments are indicated.



Table 4 Qualitative assessment of solvent use, inherent hazards of used chemicals, catalyst or reagent use, energy and workup methods for the synthesis of indoles **C2-Gd_n**^a

Step Metric	Alkylation	Halogenation	C–N coupling	Indole formation
Solvent	Neat	Toluene	Toluene	MeOH/H ₂ O
Critical element	—	—	Pd	—
Health/safety	—	NBS (H400)	—	—
Catalyst	✓	✓	✓	✓
Energy	160 °C	0 °C	120 °C	140 °C
Work-up	Filtration	Flash Chrom.	Flash chrom.	Flash Chrom.
AE ^b	74.9	75.0	45.9	80.1
RME ^c	72.3	44.1	32.0	61.0
OE ^d	96.5	58.8	69.7	76.1
PMI ^e	4.9	48.7	30.8	60.1

^a Values calculated for the synthesis of 5,6-dimethoxy-1-(4-methoxyphenyl)-1*H*-indole (**C2-Gd3**) from **C2-G**. ^b AE (atom economy) = (molecular weight of product/total molecular weight of reactants) × 100. ^c RME (reaction mass efficiency) = (mass of isolated products/total mass of reactants) × 100. ^d OE (overall economy) = RME/AE × 100. ^e PMI (process mass intensity) = total mass process step (reagents + reactants + catalyst + solvent)/total mass product.

(**C2-Gd5** and **C2-Gd6**) or –F (**C2-Gd9**), and led to a lower activity. These results reveal the potential application of these novel scaffolds as anticancer agents. However, further optimization and more rigorous drug design are nonetheless required in order to enhance the biological activity of these molecules.

Qualitative assessment of green credentials for the synthesis of **C2-Gd_n**

Evaluation of the synthetic methodology was performed in terms of the CHEM21⁴⁷ green metrics toolkit at the first pass level, and the results are summarized in Table 4. The first enhancement of the greenness of this method is observed during the phenol alkylation with dimethyl carbonate, allowing the formation of **C2-G** under neat conditions with a practical work-up procedure and displaying high atom-economy (AE) and remarkable overall economy (OE). Nonetheless, the halogenation step underperforms in terms of process mass intensity due to the usage of stoichiometric amounts of brominating agent (NBS) and solvent, as well as in health/safety aspects and work-up procedures where flash chromatography is required to isolate the desired product. The amination step towards the formation of *ortho*-aminoacetals **C2-Gc_n** proceeds under catalytic conditions employing 1 mol% of Pd₂(dba)₃, which displays a significantly higher activity compared to earth-abundant Ni catalysts, although the stoichiometric use of Cs₂CO₃ is nonetheless required, increasing the process mass intensity (PMI) of this step.⁴⁸ Finally, a successful acetal deprotection/cyclization step can be afforded by using environmentally benign solvent mixtures such as MeOH/H₂O with the use of catalytic amounts of PTSA, affording satisfactory values in terms of atom economy (AE) and overall economy (OE).

Conclusions

The efficient incorporation of intrinsic functionalities of the lignin-derived mono-aromatic **C2-acetal** (**C2-G**) for the construction of bio-derived indoles has been successfully accom-

plished following a modular procedure involving the use of mild reaction conditions, safe solvents and catalytic methods. Since we have previously identified **C2-acetal** as a central lignin-derived platform chemical, this work represents a unique and meaningful pathway towards N-chemicals *via* 'lignin-first' biorefining, with particular relevance for the pharmaceutical industry. Evaluation of the biological activity as anticancer agents has shown the potential of the novel lignin-derived indoles; nevertheless, further structural modification, likely *via* the indole moiety, could enhance the activity of these derivatives, leading to the design and optimization of promising pharmaceuticals from renewable resources.

Author contributions

AC: conceptualization, investigation, original draft writing and editing; JH: investigation and writing; AKHH: supervision, review, editing and funding acquisition; KB: conceptualization, writing, review and editing, funding acquisition and supervision.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There authors declare no conflict of interest.

Acknowledgements

A. K. H. H. is thankful for financial support from Helmholtz Association's Initiative and Networking Fund and an ERC starting grant 757913. K. B. is grateful for the financial support by the Austrian Science Fund (FWF) PAT5229224 "WoodValue".



References

- 1 E. R. Radwanski and R. L. Last', *Plant Cell*, 1995, **7**, 921–934.
- 2 A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489–4497.
- 3 N. Chadha and O. Silakari, *Eur. J. Med. Chem.*, 2017, **134**, 159–184.
- 4 N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma and E. H. Choi, *Molecules*, 2013, **18**, 6620–6662.
- 5 V. Sharma, P. Kumar and D. Pathaka, *J. Heterocycl. Chem.*, 2010, **47**, 491–502.
- 6 A. Kumari and R. K. Singh, *Bioorg. Chem.*, 2019, **89**, 103021.
- 7 P. Oeser, J. Koudelka, A. Petrenko and T. Tobrman, *Molecules*, 2021, **26**, 5079.
- 8 J. A. Leitch, Y. Bhonoah and C. G. Frost, *ACS Catal.*, 2017, **7**, 5618–5627.
- 9 M. Inman and C. J. Moody, *Chem. Sci.*, 2012, **4**, 29–41.
- 10 G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**(7), 2875–2911.
- 11 G. Jenner, *Organometallics*, 2002, **4**, 8881–8885.
- 12 N. R. Candeias, L. C. Branco, P. M. P. Gois, C. A. M. Afonso and A. F. Trindade, *Chem. Rev.*, 2009, **109**, 2703–2802.
- 13 R. P. Bhusal and J. Sperry, *Green Chem.*, 2016, **18**, 2453.
- 14 S. Nasri, M. Bayat, F. R. Miankooshki and N. H. Samet, *Mol. Divers.*, 2022, **26**, 3411–3445.
- 15 H. Li, H. Guo, Z. Fang, T. M. Aida and R. L. Smith, *Green Chem.*, 2020, **22**, 582–611.
- 16 S. Elangovan, A. Afanasenko, J. Hauptenthal, Z. Sun, Y. Liu, A. K. H. Hirsch and K. Barta, *ACS Cent. Sci.*, 2019, **5**, 1707–1716.
- 17 A. Afanasenko and K. Barta, *iScience*, 2021, **24**, 102211.
- 18 W. Lan and J. S. Luterbacher, *ACS Cent. Sci.*, 2019, **5**, 1642–1644.
- 19 Z. Chen, W. Huang, L. Yi, X. Dong, K. Sheng, M. Li, R. Bai, A. Y. Sidorenko, J. Huang and Y. Gu, *Green Chem.*, 2022, **24**, 2919–2926.
- 20 Z. Sun, B. Fridrich, A. De Santi, S. Elangovan and K. Barta, *Chem. Rev.*, 2018, **118**(2), 614–678.
- 21 W. Schutyser, T. Renders, S. Van den Bosch, S.-F. Koelewijn, G. T. Beckham and B. F. Sels, *Chem. Soc. Rev.*, 2018, **47**, 852–908.
- 22 X. Chen, Y. Liu and J. Wang, *Ind. Eng. Chem. Res.*, 2020, **59**, 17008–17025.
- 23 X. Chen, S. Song, H. Li, G. Gözaydın and N. Yan, *Acc. Chem. Res.*, 2021, **54**, 1711–1722.
- 24 K. Natte, A. Narani, V. Goyal, N. Sarki and R. V. Jagadeesh, *Adv. Synth. Catal.*, 2020, **362**, 5143–5169.
- 25 Y. M. Questell-Santiago, M. V. Galkin, K. Barta and J. S. Luterbacher, *Nat. Rev. Chem.*, 2020, **4**, 311–330.
- 26 P. J. Deuss, C. W. Lahive, C. S. Lancefield, N. J. Westwood, P. C. J. Kamer, K. Barta and J. G. de Vries, *ChemSusChem*, 2016, **9**, 2974–2981.
- 27 A. De Santi, M. V. Galkin, C. W. Lahive, P. J. Deuss and K. Barta, *ChemSusChem*, 2020, **13**, 4468–4477.
- 28 P. J. Deuss, M. Scott, F. Tran, N. J. Westwood, J. G. De Vries and K. Barta, *J. Am. Chem. Soc.*, 2015, **137**, 7456–7467.
- 29 A. M. Afanasenko, X. Wu, A. De Santi, W. A. M. Elgaher, A. M. Kany, R. Shafiei, M.-S. Schulze, T. Schulz, J. Hauptenthal, A. K. H. Hirsch and K. Barta, *Angew. Chem., Int. Ed.*, 2023, e202308131.
- 30 G. W. Gribble, *Indole Ring Synthesis*, 2016, pp. 260–263.
- 31 M. J. Forbes, E. J. Naik, N. N. Uff, B. C. Jackson, A. H. Jenkins and P. R. Shannon, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1698.
- 32 J. E. Nordlander, D. B. Catalane, K. D. Kotian, R. M. Stevens and J. E. Haky, *J. Org. Chem.*, 1981, **46**(4), 778–782.
- 33 T. J. Donohoe, B. S. Pilgrim, G. R. Jones and J. A. Bassuto, *Proc. Natl. Acad. Sci. U. S. A.*, 2012, **109**(29), 11605–11608.
- 34 S. Dadashpour and S. Emami, *Eur. J. Med. Chem.*, 2018, **150**, 9–29.
- 35 H. Y. Lee, J. Y. Chang, L. Y. Chang, W. Y. Lai, M. J. Lai, K. H. Shih, C. C. Kuo, C. Y. Chang and J. P. Liou, *Org. Biomol. Chem.*, 2011, **9**, 3154–3157.
- 36 M. S. Estevão, L. C. Carvalho, D. Ribeiro, D. Couto, M. Freitas, A. Gomes, L. M. Ferreira, E. Fernandes and M. M. B. Marques, *Eur. J. Med. Chem.*, 2010, **45**, 4869–4878.
- 37 G. Fiorani, A. Perosa and M. Selva, *Green Chem.*, 2018, **20**, 288–322.
- 38 P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev.*, 2016, **116**(19), 12564–12649.
- 39 S. Wagaw, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 10251–10263.
- 40 M. Cong, Y. Fan, J. M. Raimundo, J. Tang and L. Peng, *Org. Lett.*, 2014, **16**, 4074–4077.
- 41 Y. Liu, A. Afanasenko, S. Elangovan, Z. Sun and K. Barta, *ACS Sustainable Chem. Eng.*, 2019, **7**, 11267–11274.
- 42 B. H. Lipshutz, D. Pollart, J. Monforte and H. Kotsuki, *Tetrahedron Lett.*, 1985, **26**, 705–708.
- 43 F. Juliá-Hernández, A. Arcas and J. Vicente, *Tetrahedron Lett.*, 2014, **55**, 1141–1144.
- 44 B. C. Ranu, R. Jana and S. Samanta, *Adv. Synth. Catal.*, 2004, **346**, 446–450.
- 45 J. Park, S. Y. Kim, J. E. Kim and C. G. Cho, *Org. Lett.*, 2014, **16**, 178–181.
- 46 M. J. Lai, J. Y. Chang, H. Y. Lee, C. C. Kuo, M. H. Lin, H. P. Hsieh, C. Y. Chang, J. S. Wu, S. Y. Wu, K. S. Shey and J. P. Liou, *Eur. J. Med. Chem.*, 2011, **46**, 3623–3629.
- 47 C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton and J. H. Clark, *Green Chem.*, 2015, **17**, 3111.
- 48 E. Monteith, P. Mampuy, L. Summerton, J. Clark, B. U. W. Maes and C. R. McElroy, *Green Chem.*, 2020, **22**, 123–135.

