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Solid-Supported [2+2+2] Cyclotrimerizations

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Dedicated to Professor Stephen F. Martin on the occasion of his 60th birthday

Abstract: The transition-metal-catalyzed [2+2+2] cyclotrimerization of a diyne and an alkyne provides a convergent route to highly-substituted aromatic rings. This reaction possesses distinct drawbacks, especially low chemo- and regioselectivities, which hamper its application in combinatorial synthesis. These problems have been solved by the development of solid-supported [2+2+2]-cycloaddition reactions. If conducted on a solid-support, this reaction enables rapid combinatorial access to diverse sets of carbo- and heterocyclic small-molecule arrays. The scope of this methodology has been investigated by examining different immobilization strategies, different diyne precursors, and a variety of functionalized alkyne reaction partners. Overall, isoindoline, phthalan, and indan libraries were assembled in good to excellent yields and with high purities.

Keywords: combinatorial chemistry · cyclotrimerization · homogeneous catalysis · solid-phase synthesis

Introduction

Due to our interest in applying solid-supported multicomponent reactions in library synthesis,[1–5] we explored transition-metal-catalyzed solid-supported [2+2+2]-cycloaddition reactions. These reactions represent a facile route for the preparation of highly-substituted benzene and pyridine rings in a single operation.[6–10] Because of its atom economy and convergent nature, the cycloaddition approach is advantageous in the construction of highly-substituted benzene rings in comparison with conventional strategies (for example, sequential reactions of aromatic rings in electrophilic aromatic substitutions or *ortho*-metalations). Since the discovery of the first transition-metal-mediated cyclotrimerizations in 1949, further accomplishments have increased the broad utility of this reaction in the assembly of polycyclic aromatic frameworks from simple acyclic precursors.[11] The development of several catalyst systems based on Ni, Co, Ru, and Rh have led to mild reaction conditions applicable to organic synthesis.[12–19] However, various problems are still associated with these reactions, including chemo- and regioselectivity issues.[20] The crossed solution-phase reaction of diynes and alkynes often results in only moderate yields and contamination with side products, due to the participation of the diyne in competing cycloadditions.[21] Scheme 1 shows a general [2+2+2] cycloaddition between an unsymmetrically substituted diyne **1** and an unsymmetrical alkyne **2**. Besides forming the desired product **3** (as two possible regioisomers, only one is shown), this reaction can potentially lead to the formation of dimer **4** (as four isomers) and, depending on the catalyst system, the benzene **5** (as four isomers), and the trimer **6** (as three isomers). The potential formation of products resulting from trimolecular cyclotrimerizations of **1** are omitted in this scheme due to their low probability. To resolve these issues we conducted this reaction on a solid support by immobilizing the diyne **1** on a polystyrene resin. Moreover, solid-phase organic synthesis allows for easy automation, parallelization, and purification—important for the rapid generation of compound libraries.[22–26] Due to the commercial availability of a wide range of alkyne precursors and several catalyst systems, [2+2+2] cycloadditions represent ideal tools for the facile assembly of diverse arrays of aromatic compounds. Additionally, the highly convergent and efficient nature of cyclotrimerization reactions makes them ideal candidates for solid-phase combinatorial chemistry.[27]

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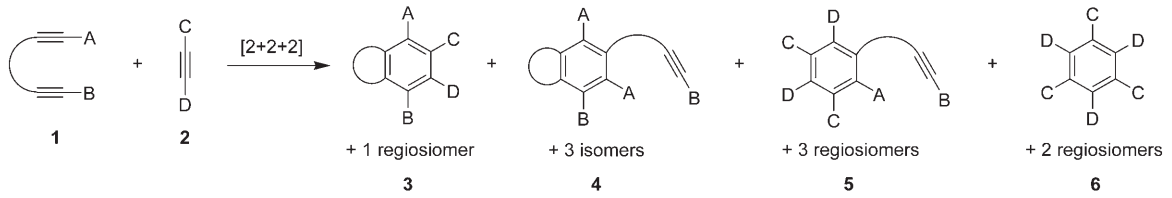


1 2 3 4 5 6

Scheme 1. Potential products formed in the solution-phase [2+2+2] cycloaddition of **1** and **2**.

Results and Discussion

1,6-Diyne substrates **7**, **8**, and **9** (Figure 1a) have either been purchased or prepared according to literature procedures.[28,29] The diynes were immobilized on polystyrene

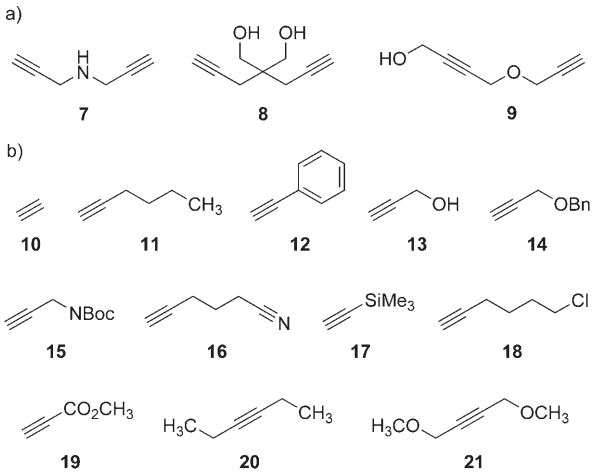
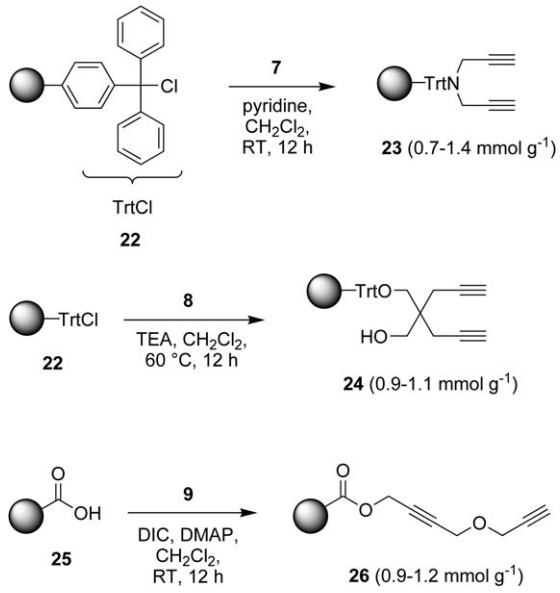


Figure 1. Diynes (a) and alkynes (b) employed in solid-supported cyclotrimerizations.

resins (100–200 mesh, 1% cross-linked) with excellent loadings. Common trityl (for **7** and **8**) and carboxy linkers (for **9**) were employed and the couplings occurred under standard conditions (Scheme 2).[30] The loading of the diyne precursors was 1 mmol g^{-1} on average, as determined by GCMS analysis. The trityl linker was chosen for substrates **7** and **8** as its mild cleavage conditions (1% HCl in CH_2Cl_2/MeOH for 1 h at room temperature) provided the cyclotrimerization products with highest purity. To our surprise, **9** immobilized via a trityl linker only yielded trace amounts of cyclotrimerization products. Switching to the carboxy resin **26**, however, delivered cyclotrimerization products in good yields. This is probably due to the steric constraints imposed by the trityl linker which are lowered by using the sterically less demanding carboxy-functionalized resin.

Solid-supported cyclotrimerizations were conducted with a set of alkynes **10**–**21** (Figure 1b). We employed alkyne substrates with a limited range of functionalities, probing the versatility of this methodology. Most of the substrates shown in Figure 1 were commercially available. Acetylene **10** was the most reactive substrate and the cycloadditions proceeded smoothly at room temperature with excellent



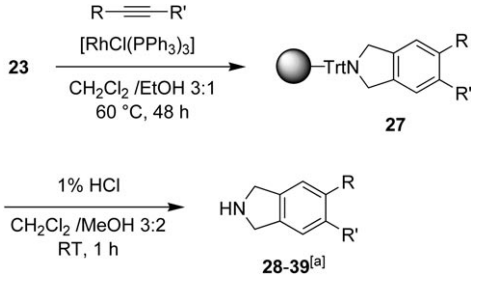
Scheme 2. Immobilization of diynes **7**–**9**. DIC = diisopropylcarbodiimide; DMAP = 4-dimethylaminopyridine; TEA = triethylamine.

yields. Monosubstituted alkynes appeared to be less reactive and required elevated reaction temperatures. However, the mild reaction conditions tolerated a wide range of functionalities including alkyl chains (in **11** and **20**), hydroxy and alkoxy groups (in **13**, **14**, and **21**), aromatic rings (in **12** and **14**), carbamates (in **15**) cyano groups (in **16**), silyl groups (in **17**), chlorines (in **18**), and esters (in **19**). The disubstituted alkynes **20** and **21** lead to the formation of up to pentasubstituted benzenes **64**–**65**, however, the yields were lower, probably due to increased steric repulsion in the cycloaddition. Catalyst efficiency appears to be reduced in the presence of hydroxyl functionalities (in **13**); however, by benzyl protection of the alcohol (in **14**), activity was restored resulting in excellent yields. A similar trend was observed for amine functionalities as propargylamine failed to undergo cyclotrimerization. Simple installation of a Boc protecting group (in **15**) facilitated the cyclotrimerization and conveniently yielded the desired amine product as the protecting group was removed under the acidic conditions utilized for cleavage of **33** and **46** from the resin.

In initial experiments immobilized dipropargylamine **23** was treated with the soluble alkyne reaction partner (10 equiv) in presence of 10 mol% Wilkinson's catalyst [$RhCl(PPh_3)_3$] at 30 to 60 °C for 12 to 48 h. Various solvents were employed including toluene, CH_2Cl_2, THF, and etha-

nol; however, a 3:1 ratio of CH_2Cl_2 to ethanol at 60 °C was found to be optimal. The cyclotrimerized products **27** were cleaved from the resin by treatment with 1 % anhydrous hydrochloric acid in CH_2Cl_2 for one hour and analyzed by ^{1}H NMR and LCMS spectroscopy. Under these conditions yields ranged from 30–60 % and incomplete conversion of the diyne **7** was observed in most cases. Optimized conditions were found by addition of the catalyst in two portions (10 mol % each, the second aliquot was added after 24 h). Moreover, it was found that yields could be substantially increased by degassing the solvents prior to catalyst addition. After 48 h the resins were filtered and washed following standard protocols (alternating rinses with CH_2Cl_2 and methanol). Release from the resin indicated complete consumption of diyne **7**, and the isoindolines **28–39** were obtained in 70–95 % yields (Table 1). The compounds were isolated as the HCl salts and purities were determined to be > 90 % (^{1}H NMR spectroscopic analysis), obviating the need for further purification.

Table 1. Solid-supported formation of isoindolines.



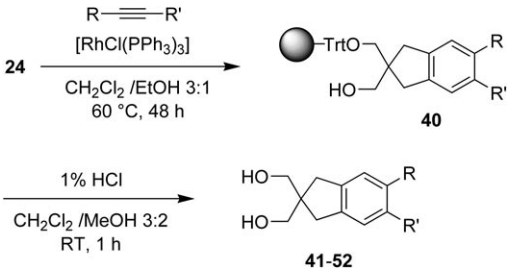
	R	R′	Yield [%]
28	H	H	95
29	$(CH_2)_3CH_3$	H	90
30	Ph	H	84
31	CH_2OH	H	82
32	CH_2OBn	H	93
33	CH_2NH_2	H	69
34	$(CH_2)_3CN$	H	81
35	$SiMe_3$	H	75
36	$(CH_2)_4Cl$	H	71
37	COOMe	H	79
38	CH_2CH_3	CH_2CH_3	70
39	CH_2OCH_3	CH_2OCH_3	87

[a] Isolated as the HCl salt.

Cyclotrimerization reactions with the immobilized diyne **24** were performed under identical conditions; however, to achieve compound purities of > 90 % (^{1}H NMR spectroscopic analysis), the cleavage solutions were filtered through a plug of silica gel to remove unidentified polar impurities. In these cases yields were equally high, and the 2,3-dihydro-indenes (indans) **41–52** were obtained in 60–84 % yields (Table 2).

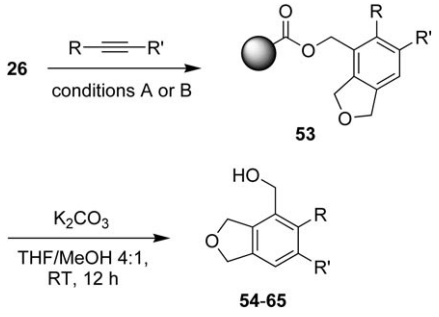
We also investigated the solid-supported formation of phthalans by employing the cyclotrimerization precursor **26** (Table 3). Due to the presence of an internal triple bond in **26** a higher reaction temperature (80 °C in dichloroethane)

Table 2. Solid-supported formation of indans.



	R	R′	Yield [%]
41	H	H	78
42	$(CH_2)_3CH_3$	H	81
43	Ph	H	84
44	CH_2OH	H	60
45	CH_2OBn	H	82
46	CH_2NH_2	H	67
47	$(CH_2)_3CN$	H	64
48	$SiMe_3$	H	70
49	$(CH_2)_4Cl$	H	65
50	COOMe	H	69
51	CH_2CH_3	CH_2CH_3	63
52	CH_2OCH_3	CH_2OCH_3	61

Table 3. Solid-supported formation of phtalans.[a]



	R	R′	Conditions A Yield [%]	**a/b**	Conditions B Yield [%]	**a/b**
54	H	H	82		94	
55a	$(CH_2)_3CH_3$	H	67	1:3	86	1:9
55b	H	$(CH_2)_3CH_3$				
56a	Ph	H	73	3:1	93	1:9
56b	H	Ph				
57a	CH_2OH	H	64	1:1	79	1:9
57b	H	CH_2OH				
58a	CH_2OBn	H	74	1:1	78	1:9
58b	H	CH_2OBn				
59a	CH_2NBoc	H	76	1:1	73	1:9
59b	H	CH_2NBoc				
60a	$(CH_2)_3CN$	H	71	1:3	90	1:9
60b	H	$(CH_2)_3CN$				
61a	$SiMe_3$	H	68	2:1	69	1:9
61b	H	$SiMe_3$				
62a	$(CH_2)_4Cl$	H	68	2:1	95	1:9
62b	H	$(CH_2)_4Cl$				
63a	COOMe	H	75	1:1	73	1:3
63b	H	COOMe				
64	CH_2CH_3	CH_2CH_3	57		68	
65	CH_2OCH_3	CH_2OCH_3	62		71	

[a] Conditions A: [$RhCl(Ph_3P)_3$], DCE, 80 °C, 48 h. Conditions B: [RuCl-(cod)Cp*], DCE, RT, 24 h. DCE = dichloroethane.

was required to achieve complete conversion of the starting material. The obtained yields (57–82%) were lower than in case of the other two diynes **23** and **24**. Cyclotrimerization products **54–65** were obtained in excellent purities (>90%) after filtration through a plug of silica gel to remove unidentified polar impurities. Cycloadditions of the unsymmetrical diyne **26** led to the formation of regioisomers, as determined by ^{1}H NMR spectroscopic analysis. Low or no regioselectivity was obtained by using Wilkinson's catalyst. However, a slight substrate dependency was observed, which is in accordance with published reports.[31] To obtain a higher degree of control over the regioisomeric ratio, we examined two ruthenium catalysts in the cyclotrimerization reaction. In the case of both, Grubbs catalyst [$Cl_2(Cy_3P)_2RuCHPh$][31–33] and [Cp*ClRu(cod)][17] (cod = 1,5-cyclooctadiene; Cp* = pentamethylcyclopentadiene) a high degree of regioselectivity was observed independent of the nature of the alkyne (>90% isomers **55b–63b**). Ultimately, the [Cp*ClRu(cod)] catalyst was utilized due to its favorable reaction conditions (24 h, room temperature, addition of 10 mol% catalyst in one aliquot) and high product yields (69%–95%). The observed regioselectivity is in agreement with the previously reported observation in which the bulky Cp* ligand on the metal center directs the alkyne approach on the metallacycle intermediate to reduce steric interactions.[17] Surprisingly, while all alkyne substrates displayed a high regioselectivity, cyclotrimerizations with the electron-deficient alkyne **19** led to dramatically reduced regioselectivity.

Conclusion

In summary, we demonstrated the application of solid-supported rhodium- and ruthenium-catalyzed [2+2+2]-cycloaddition reactions in combinatorial chemistry, enabling their use in the assembly of complex compound libraries. This methodology provides a rapid means for the generation of diverse carbo- and heterocyclic structures, including isoindolines, phthalans, and indans; compound classes which have already been validated as exhibiting important biological activities and are found in a variety of natural products.[34–37] The reaction conditions used for these solid-supported cyclotrimerization reactions are compatible with a variety of functional groups allowing for further diversification of the generated small molecule arrays. The compounds were obtained in good to excellent yields and with high purities. Initial regioselectivity issues were solved by switching from a rhodium to a ruthenium-catalyst system.

Experimental Section

General: Solvents and reagents were obtained from either Sigma Aldrich or Fisher Scientific and were used without further purification unless otherwise noted. Tritylchloride and carboxy resins, 100–200 mesh, 1% cross-linking, were purchased from Sigma Aldrich and Novabiochem. Diynes **8** and **9** were prepared according to literature procedures.[28,29] Reactions were conducted under a N_2 atmosphere by using dry solvents distilled from appropriate drying agents prior to use. NMR spectroscopic data were acquired on a Varian Gemini 300 MHz NMR spectrometer, GCMS data were obtained on an HP 5890 Series II G1800 A spectrometer, LCMS data were obtained on an HP 1100 MSD system with a ZorbaxSB C-18 3.5 μM pore size 4.5X100 mm column, and HRMS was conducted on a JEOL HX110HF mass spectrometer with a resolving power of 10000 and an accelerating voltage of 10 keV. Compound purity was assessed by gradient runs of 9:1–1:9 H_2O/acetonitrile at a flow rate of 0.75 mL min^{-1} for 15 minutes.

Immobilization of 7: Resin **22** (990 mg, 1.9 mmol) was left to swell for 15 minutes in CH_2Cl_2 (10 mL). Dipropargylamine (0.59 mL, 5.7 mmol, 3 equiv) was added, followed by pyridine (2.14 mL, 19.0 mmol, 10 equiv). The reaction was shaken at room temperature for 12 h. The resin was transferred to a syringe filter and washed with alternating rinses of CH_2Cl_2 and MeOH (4×7 mL). The resin was then dried under vacuum and 15 mg were removed, cleaved (1% HCl in CH_2Cl_2/MeOH, 1 h), and used to determine the loading by GC spectroscopic analysis.

Immobilization of 8: Resin **22** (500 mg, 0.95 mmol) was left to swell for 15 minutes in CH_2Cl_2 (5 mL). Diyne **8** (370 mg, 2.43 mmol, 3 equiv) was added, followed by TEA (1.26 mL, 9.5 mmol, 10 equiv) and the reaction was stirred at room temperature for 12 h. The resin was transferred to a syringe filter and washed with alternating rinses of CH_2Cl_2 and MeOH (4×5 mL). The resin was then dried under vacuum and 15 mg were removed, cleaved (1% HCl in CH_2Cl_2/MeOH, 1 h), and used to determine the loading by GC spectroscopic analysis.

Immobilization of 9: Resin **25** (1.0 g, 1.2 mmol) was left to swell for 15 minutes in CH_2Cl_2 (6 mL). Diyne **9** (750 mg, 6 mmol, 5 equiv) was added, followed by DMAP (29 mg, 0.24 mmol, 0.2 equiv), and diisopropylcarbodiimide (0.93 mL, 6 mmol, 5 equiv) and the reaction was shaken at room temperature for 12 h. The resin was transferred to a syringe filter and washed with alternating rinses of CH_2Cl_2 and MeOH (4×5 mL). The resin was then dried under vacuum and 15 mg were removed, cleaved (25 mg K_2CO_3, THF/MeOH 4:1, 12 h), and used to determine the loading by GC spectroscopic analysis.

Cyclotrimerization of 23: Derivatized resin **23** (50 mg, 0.07 mmol) was placed in a flame-dried vial with CH_2Cl_2/EtOH (3:1, 2 mL). The soluble alkyne (0.70 mmol, 10 equiv) was added and the solution was degassed with three freeze-pump-thaw cycles. Wilkinson's Catalyst (6 mg, 0.07 mmol, 0.1 equiv) was added and the reaction was heated to 60°C. After 24 h, additional catalyst was added (6 mg, 0.07 mmol, 0.1 equiv) and the reaction was left to progress for an additional 24 h. The resin was transferred to a syringe filter and washed with alternating rinses of CH_2Cl_2 and MeOH (4×5 mL). The resin was then treated with 1% HCl in CH_2Cl_2/MeOH for 1 h. The filtrate was concentrated to yield the cyclotrimerized product. Yields ranged from 69–95% and products were obtained in quantities of 7.2–3.4 mg.

Cyclotrimerization of 24: Derivatized resin **24** (50 mg, 0.05 mmol) was placed in a flame-dried vial with CH_2Cl_2/EtOH (3:1, 2 mL). The soluble alkyne (0.49 mmol, 10 equiv) was added and the solution was degassed with three freeze-pump-thaw cycles. Wilkinson's catalyst (5 mg, 0.05 mmol, 0.1 equiv) was added and the reaction was heated to 60°C. After 24 h, additional catalyst was added (5 mg, 0.05 mmol, 0.1 equiv) and the reaction was left to progress for another 24 h. The resin was then transferred to a syringe filter and washed with alternating rinses of CH_2Cl_2 and MeOH (4×5 mL). The resin was then treated with 1% HCl in CH_2Cl_2/MeOH for 1 h. The filtrate was removed, concentrated, dissolved in ether, and filtered through a plug of silica gel to yield the cyclotrimerized product. Yields ranged from 60–84% and products were obtained in quantities of 6.4–2.8 mg.

Cyclotrimerization of 26 by using Wilkinson's catalyst: Derivatized resin **26** (50 mg, 0.05 mmol) was placed in a flame-dried vial with dichloroethane (2 mL). The soluble alkyne (0.50 mmol, 10 equiv) was added and the solution was degassed with three freeze-pump-thaw cycles. Wilkinson's catalyst (4 mg, 0.005 mmol, 0.1 equiv) was added and the reaction was heated to 80°C. After 24 h, additional catalyst was added (4 mg, 0.005 mmol, 0.1eq) and the reaction was left to progress for another 24 h.

The resin was transferred to a syringe filter and washed with alternating rinses of CH_2Cl_2 and MeOH (4×3 mL). The resin was then treated with K_2CO_3 in THF/MeOH 4:1 for 12 h. The filtrate was removed, concentrated, dissolved in ether, and filtered through a plug of silica gel to yield the cyclotrimerized product. Yields ranged from 52–87% and products were obtained in quantities of 6.4–2.2 mg.

Cyclotrimerization of 26 by using [Cp*ClRu(cod)] as the catalyst: Derivatized resin **26** (50 mg, 0.05 mmol) was placed in a flame-dried vial with dichloroethane (2 mL). The soluble alkyne (0.50 mmol, 10 equiv) was added and the solution was degassed with three freeze-pump-thaw cycles. [Cp*ClRu(cod)] catalyst (2 mg, 0.01 mmol, 0.1 equiv) was added and the reaction was shaken at room temperature for 24 h. The resin was transferred to a syringe filter and washed with alternating rinses of CH_2Cl_2 and MeOH (4×3 mL). The resin was then treated with K_2CO_3 in THF/MeOH 4:1 for 12 h. The filtrate was removed and concentrated to yield the cyclotrimerized product. Yields ranged from 69–95% and products were obtained in quantities of 8.1–3.9 mg.

Compound 28:[38] ^{1}H NMR (300 MHz, CD_3OD): δ=10.46 (s, 2H), 7.28–7.24 (m, 4H), 4.50 ppm (s, 4H); LCMS: *m*/*z*: 119.1 $[M+H]^+$, t_R=4.04 min.

Compound 29: ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.40 (s, 2H), 7.12 (d, ^3J(H,H)=8.1 Hz, 1H), 7.14 (d, ^3J(H,H)=8.1 Hz, 1H), 7.08 (s, 1H), 4.62 (s, 4H), 2.61 (t, ^3J(H,H)=7.5 Hz, 2H), 1.58 (p, ^3J(H,H)=6.9 Hz, 2H), 1.35 (m, 2H), 0.93 ppm (t, ^3J(H,H)=7.2 Hz, 3H); LCMS: *m*/*z*: 176.1 $[M+H]^+$, t_R=5.93 min.

Compound 30: ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.49 (s, 2H), 7.56–7.33 (m, 8H), 4.73 ppm (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=142.6, 140.2, 134.8, 132.9, 129.1, 128.3, 128.0, 127.4, 123.4, 121.7, 50.9, 50.7 ppm; HRMS (FAB): *m*/*z*: calcd for $C_{14}H_{14}N$: 196.1126; found: 196.1114 $[M+H]^+$; LCMS: *m*/*z*: 196.1 $[M+H]^+$, t_R=5.75 min.

Compound 31: ^{1}H NMR (300 MHz, CD_3OD): δ=7.39 (d, ^3J(H,H)=7.6 Hz, 2H), 7.38 (s, 1H), 4.63 (s, 4H), 3.09 ppm (s, 2H); LCMS: *m*/*z*: 150.1 $[M+H]^+$, t_R=1.97 min.

Compound 32: ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.42 (s, 2H), 7.35–7.22 (m, 8H), 4.64 (s, 4H), 4.55 (s, 2H), 4.53 ppm (s, 2H); LCMS: *m*/*z*: 240.1 $[M+H]^+$, t_R=5.81 min.

Compound 33: ^{1}H NMR (300 MHz, CD_3OD): δ=7.52 (d, ^3J(H,H)=8.1 Hz, 2H), 7.50 (s, 1H), 4.67 (s, 4H), 4.17 ppm (s, 2H); LCMS: *m*/*z*: 149.1 $[M+H]^+$, t_R=1.34 min.

Compound 34: ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.52 (s, 2H), 7.23–7.12 (m, 3H), 4.67 (s, 4H), 2.35 (t, ^3J(H,H)=7.2 Hz, 2H), 2.18 (t, ^3J(H,H)=7.2 Hz, 2H), 2.00 ppm (quin, ^3J(H,H)=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=141.2, 134.7, 132.3, 129.5, 123.4, 123.1, 119.3, 50.7, 50.6, 34.4, 27.1, 16.8 ppm; HRMS (FAB): *m*/*z*: calcd for $C_{12}H_{15}N_2$: 187.1235; found: 187.1231 $[M+H]^+$; LCMS: *m*/*z*: 187.1 $[M+H]^+$, t_R=4.41 min.

Compound 35: ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.44 (s, 2H), 7.47 (d, ^3J(H,H)=7.5 Hz, 1H), 7.43 (s, 1H), 7.29 (s, 1H), 4.68 (s, 4H), 0.28 ppm (s, 9H); LCMS: *m*/*z*: 192.0 $[M+H]^+$, t_R=6.37 min.

Compound 36: ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.41 (s, 2H), 7.25–7.09 (m, 3H), 4.63 (s, 4H), 3.55 (t, ^3J(H,H)=6.3 Hz, 2H), 2.65 (t, ^3J(H,H)=6.6 Hz, 2H), 1.78–1.76 ppm (m, 4H); LCMS: *m*/*z*: 210.0 $[M+H]^+$, t_R=6.03 min.

Compound 37: ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.43 (s, 2H), 8.03 (m, 2H), 7.95 (s, 1H), 3.92 (s, 3H), 3.48 ppm (s, 4H); LCMS: *m*/*z*: 178.1 $[M+H]^+$, t_R=5.34 min.

Compound 38: ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.31 (s, 2H), 7.06 (s, 2H), 4.61 (s, 4H), 2.64 (q, ^3J(H,H)=7.2 Hz, 4H), 1.21 ppm (t, ^3J(H,H)=7.2 Hz, 6H); LCMS: *m*/*z*: 176.1 $[M+H]^+$, t_R=5.93 min.

Compound 39: ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.34 (s, 2H), 7.33 (s, 2H), 4.64 (s, 4H), 4.49 (s, 4H), 3.40 ppm (s, 6H); LCMS: *m*/*z*: 208.1 $[M+H]^+$, t_R=4.20 min.

Compound 41:[39] ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.18–7.13 (m, 4H), 3.78 (s, 4H), 2.86 (s, 4H), 2.39 ppm (s, 2H); LCMS: *m*/*z*: 179.0 $[M+Na]^+$, t_R=5.01 min.

Compound 42: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.08–6.95 (m, 3H), 3.77 (s, 4H), 2.81 (s, 4H), 2.57 (t, ^3J(H,H)=7.8 Hz, 2H), 2.12 (s, 2H), 1.61–1.55 (m, 2H), 1.40–1.32 (m, 2H), 0.93 ppm (t, ^3J(H,H)=7.5 Hz, 3H); LCMS: *m*/*z*: 257.1 ppm $[M+Na]^+$, t_R=6.73 min.

Compound 43: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.55 (d, ^3J(H,H)=6.9 Hz, 2H), 7.43–7.23 (m, 6H), 3.82 (s, 4H), 2.91 (s, 2H), 2.90 (s, 2H), 2.34 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=142.4, 141.6, 140.9, 140.1, 128.9, 127.3, 127.2, 125.9, 125.5, 124.0, 69.9, 49.5, 38.8, 38.6 ppm; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{19}O_2$: 255.1385; found: 255.1381 $[M+H]^+$; LCMS: *m*/*z*: 277.0 $[M+Na]^+$, t_R=6.16 min.

Compound 44: ^{1}H NMR (300 MHz, CD_3OD): δ=7.14–7.09 (m, 3H), 4.53 (s, 2H), 3.78 (s, 4H), 2.76 ppm (s, 4H); LCMS: *m*/*z*: 231.0 $[M+Na]^+$, t_R=3.89 min.

Compound 45: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.37–7.15 (m, 8H), 4.56 (s, 2H), 4.52 (s, 2H), 3.75 (s, 4H), 2.83 (s, 4H), 2.23 ppm (s, 2H); LCMS: *m*/*z*: 321.1 $[M+Na]^+$, t_R=6.07 min.

Compound 46: ^{1}H NMR (300 MHz, CD_3OD): δ=7.25–7.20 (m, 3H), 4.04 (s, 2H), 3.55 (s, 4H), 2.81 ppm (s, 4H); LCMS: *m*/*z*: 230.0 $[M+Na]^+$, t_R=1.97 min.

Compound 47: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.12–6.94 (m, 3H), 3.76 (s, 4H), 2.83 (s, 2H), 2.81 (s, 2H), 2.74 (t, ^3J(H,H)=7.5 Hz, 2H), 2.35–2.30 (m, 2H), 2.29 (s, 2H), 1.97 ppm (t, ^3J(H,H)=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=142.5, 140.1, 138.3, 127.0, 125.4, 125.3, 119.9, 69.7, 49.3, 38.6, 38.4, 34.5, 27.3, 16.6 ppm; HRMS (EI): *m*/*z*: calcd for $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1494; found: 246.1488; LCMS: *m*/*z*: 268.0 $[M+Na]^+$, t_R=5.12 min.

Compound 48: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.35–7.15 (m, 3H), 3.77 (s, 4H), 2.85 (s, 4H), 2.43 (s, 2H), 0.25 ppm (s, 9H); LCMS: *m*/*z*: 273.0 $[M+Na]^+$, t_R=6.77 min.

Compound 49: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.10–6.94 (m, 3H), 3.77 (s, 4H), 3.55 (t, ^3J(H,H)=6.3 Hz, 2H), 2.82 (s, 4H), 2.61 (t, ^3J(H,H)=7.5 Hz, 2H), 2.32–2.10 (brs, 2H), 1.84–1.75 ppm (m, 4H); LCMS: *m*/*z*: 291.0 $[M+Na]^+$, t_R=6.36 min.

Compound 50: ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.58 (s, 1H), 8.25–7.93 (m, 2H), 3.76 (s, 4H), 3.59 (s, 3H), 3.25 ppm (d, ^3J(H,H)=7.5 Hz, 4H); LCMS: *m*/*z*: 259.0 $[M+Na]^+$, t_R=5.57 min.

Compound 51: ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.99 (s, 2H), 3.78 (s, 4H), 2.81 (s, 4H), 2.62 (q, ^3J(H,H)=7.2 Hz, 4H), 1.91 (s, 2H), 1.21 ppm (t, ^3J(H,H)=7.2 Hz, 6H); LCMS: *m*/*z*: 257.1 $[M+Na]^+$, t_R=6.48 min.

Compound 52: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.20 (s, 2H), 4.74 (s, 4H), 3.74 (s, 4H), 3.93 (s, 6H), 2.82 (s, 4H), 2.34–2.22 ppm (brs, 2H); LCMS: *m*/*z*: 289.1 $[M+Na]^+$, t_R=4.72 min.

Compound 54: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.28–7.18 (m, 3H), 5.19 (s, 2H), 5.12 (s, 2H), 4.67 ppm (d, ^3J(H,H)=5.7 Hz, 2H); LCMS: *m*/*z*: 151.0 $[M+H]^+$, t_R=5.37 min.

Compound 55: **55a**/**55b** 1:3; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.11 (s, 0.5H), 7.06 (s, 0.75H), 7.00 (s, 0.75H), 5.24 (s, 1H), 5.15 (s, 1.5H), 5.09 (1.5H), 4.87 (s, 0.5H), 4.64 (s, 1.5H), 2.71 (t, ^3J(H,H)=7.8 Hz, 0.5H), 2.63 (t, ^3J(H,H)=7.8 Hz, 1.5H), 1.43–1.30 (m, 4H), 0.92 ppm (t, ^3J=7.2 Hz, 3H); LCMS: *m*/*z*: 207.1 $[M+H]^+$, t_R=8.25 min.

Compound 56: **56a**/**56b** 3:1; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.57 (d, ^3J(H,H)=6.9 Hz, 0.5H, 7.44–7.35 (m, 5H), 7.22 (s, 1.5H), 5.32 (s, 1.5H), 5.22 (s, 1H), 5.17 (s, 1.5H), 4.73 (d, ^3J(H,H)=5.4 Hz, 0.5H), 4.58 ppm (d, ^3J(H,H)=5.4 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=141.6, 141.1, 140.8, 136.7, 134.8, 129.0, 127.7, 127.4, 125.2, 119.2, 73.7, 72.7, 63.9 ppm; HRMS (FAB): *m*/*z* calcd for $C_{15}H_{15}NO_2$ $[M+H]^+$: 227.1072; found: 227.1069; LCMS: *m*/*z*: 227.0 $[M+H]^+$, t_R=7.64 min.

Compound 57: **57a**/**57b** 1:1; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.67–7.44 (m, 1H), 7.17 (s, 0.5H), 7.14 (s, 0.5H), 5.22–5.10 (m, 4H), 4.77–4.66 ppm (m, 4H); LCMS: *m*/*z*: 203.0 $[M+Na]^+$, t_R=4.50 min.

Compound 58: **58a**/**58b** 1:1; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.37–7.16 (m, 7H), 5.24 (s, 1H), 5.17 (s, 1H), 5.12 (d, ^3J(H,H)=4.5 Hz, 2H), 4.67 (s, 2H), 4.60–4.56 ppm (m, 4H); LCMS: *m*/*z*: 293.0 $[M+Na]^+$, t_R=7.83 min.

Compound 59: **59a**/**59b** 1:1; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.24–7.09 (m, 3H), 5.23–5.02 (m, 4H), 4.65 (d, ^3J(H,H)=5.4 Hz, 2H), 4.38 (d, ^3J(H,H)=6.0 Hz, 2H), 4.31 (d, ^3J(H,H)=5.4 Hz, 2H), 1.46 (s, 4.5H), 1.43 ppm (s, 4.5H); LCMS: *m*/*z*: 302.1 $[M+Na]^+$, t_R=5.37 min.

Compound 60: **60a**/**60b** 1:3; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.13$ (s, 0.5H), 7.07 (s, 0.75H), 7.00 (s, 0.75H), 5.23–5.09 (m, 4H), 4.69–4.64 (m, 2H), 2.90 (t, ^3J(H,H) = 7.8 Hz, 0.5H), 2.81 (t, ^3J (H,H) = 7.8 Hz, 1.5H), 2.42–2.32 (m, 2H), 2.04–1.95 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 140.6$, 139.8, 135.9, 134.6, 126.1, 120.4, 119.6, 73.6, 72.7, 63.7, 34.5, 27.4, 16.8 ppm; HRMS (EI): *m*/*z*: calcd for $C_{13}H_{15}NO_2Na$: 240.1000; found: 240.0995 $[M+Na]^+$; LCMS: *m*/*z*: 40.0 $[M+Na]^+$, $t_R = 6.02$ min.

Compound 61: **61a**/**61b** 2:1; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.43$ (d, ^3J(H,H) = 7.5 Hz, 0.33H), 7.34 (d, ^3J(H,H) = 7.5 Hz, 1.33H), 7.17 (d, ^3J(H,H) = 7.5 Hz, 0.33H), 5.26 (s, 1.33H), 5.19 (s, 1.33H), 5.13 (s, 1.33H), 4.75 (d, ^3J(H,H) = 5.1 Hz, 0.33H), 4.68 (d, ^3J(H,H) = 5.1 Hz, 1.67H), 0.37 (s, 3H), 0.29 ppm (s, 6H); LCMS: *m*/*z*: 223.0 $[M+H]^+$, $t_R = 8.37$ min.

Compound 62: **62a**/**62b** 2:1; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.25$ (s, 0.67H), 7.06 (s, 0.33H), 6.99 (s, 0.33H), 5.23 (s, 1.33H), 5.15 (s, 1.33H), 5.09 (s, 1.33H), 4.68 (d, ^3J(H,H) = 4.2 Hz, 1.33H), 4.64 (d, ^3J(H,H) = 4.2 Hz, 0.67H), 3.56 (q, ^3J(H,H) = 6.3 Hz, 2H), 2.76 (t, ^3J(H,H) = 7.5 Hz, 1.33H), 2.67 (t, ^3J(H,H) = 7.5 Hz, 0.67H), 1.90–1.75 ppm (m, 4H); LCMS: *m*/*z*: 241.0 $[M+H]^+$, $t_R = 7.92$ min.

Compound 63: **63a**/**63b** 1:1; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.85$ (s, 0.33H), 8.43 (s, 0.33H), 8.19 (d, ^3J(H,H) = 8.1 Hz 0.67H), 7.78 (d, ^3J(H,H) = 8.1 Hz, 0.67H), 3.97–3.85 ppm (m, 6H); LCMS: *m*/*z*: 209.1 $[M+H]^+$, $t_R = 8.14$ min.

Compound 64: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.04$ (s, 1H), 5.24 (s, 2H), 5.22 (s, 2H), 5.08 (s, 2H), 4.69 (d, ^3J(H,H) = 5.4 Hz, 2H), 2.77 (q, ^3J(H,H) = 7.6 Hz, 2H), 2.69 (q, ^3J(H,H) = 7.6 Hz, 2H), 1.26–1.21 ppm (m, 6H); LCMS: *m*/*z*: 207.0 $[M+H]^+$, $t_R = 8.21$ min.

Compound 65: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.19$ (s, 1H), 5.24 (s, 2H), 5.12 (s, 2H), 4.65 (s, 2H), 4.57 (d, ^3J(H,H) = 6.0 Hz, 2H), 4.53 (s, 2H), 3.47 (s, 3H), 3.40 ppm (s, 3H); LCMS: *m*/*z*: 261.0 $[M+Na]^+$, $t_R =$ 5.50 min.

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