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A Highly Efficient Strategy for One-Pot and Pseudo-Six-Component Synthesis of Hexahydroquinolines

Parvin Mohammadikia, Sorour Ramezanpour,* Pezhman Shiri, Wim Dehaen, and Linde Achten

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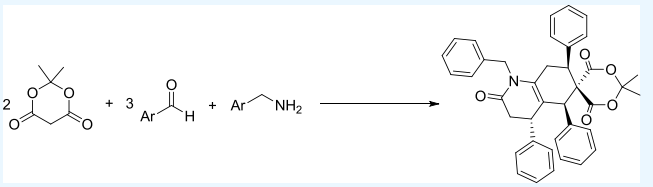
ABSTRACT: In this study, a homogeneous acid-catalyzed reaction of a series of benzaldehydes, benzylamines, and Meldrum's acid was presented, allowing the novel one-pot and multicomponent synthesis of hexahydroquinolines with high stereoselectivity. The current strategy has advantages including high regioselectivity, good efficiency, reasonable diversity, utilization of an inexpensive and safe catalyst, and easy purification of products by simple recrystallization. The current reaction utilizes 2 equiv of Meldrum's acid, 3 equiv of benzaldehyde derivatives, and one equiv of amine derivatives to yield (4′S,5′S,7′S)-1′-benzyl-2,2-dimethyl-4′,5′,7′-triphenyl-3′,4′,7′,8′-tetrahydro-1′*H*-spiro[[1,3]-dioxane-5,6′-quinoline]-2′,4,6(5′*H*)-trione derivatives.



INTRODUCTION

Multicomponent reactions (MCRs) are efficient synthetic strategies that have been utilized in delivering a single product from merging three or more starting materials in a one-pot fashion tandem transformation.[1−3] They are frequently employed as prominent tools to design and discover novel and diverse libraries of biologically important compounds.[4−6] Their popularity in academia and industrial laboratories is based on the simplicity and versatility of experimental approaches.[7,8] The lack of need for the isolation and purification of intermediates saves energy, time, and resources.[9]

Diversity-oriented synthesis (DOS) has been developing as an area of significance in the fields of medicinal and organic chemistry. Multifarious arrays of molecules with biologically active properties are the prominent purpose of DOS. It is noteworthy that DOS is able to provide various heterocyclic scaffolds, themselves of importance as potential new drugs or as analogues of natural products. The emergence of new MCRs has been a great asset for DOS.[10−13]

Heterocycles consist of a cyclic system with one or more (same or different) heteroatoms in their rings.[14−16] Heterocyclic compounds were shown to be a specific category of compounds with natural origin as well as chemical, medicinal, and industrial significance.[17,18] They seem to be significant and useful agents against different types of medical disorders. As previously reported in the literature,[19] approximately 60% of the drugs employed for cancer therapy contain heterocyclic scaffolds. Nowadays, synthetic derivatives of organic products incorporating a heterocyclic ring have attracted scientists' attention due to exhibiting a wide spectrum of significant pharmaceutical activities. Among them, nitrogen-based compounds have been found to be highly effective against fungi, bacteria, and cancer.[20,21] They are also applied in the structure of vitamins and herbicides.[22,23] On the other hand, highly functionalized heterocycles have attracted a great deal of attention in drug discovery and organic chemistry.[24−27] Thus, it has been a high-priority research area for scientists in recent years.

Lately, highly functionalized heterocycle synthesis is one of the most significant research subjects in organic chemistry owing to the ubiquity of these products in molecules of biological priority.[28−31] Significant work has been done by research groups including Guo and co-workers,[32] Lee and co-workers,[33] Doyle and co-workers,[34] and Xu and co-workers[35] who reported their contributions using different catalytic systems. Recent works by Maghsoodlou and co-workers exhibited that phthalic acid was also capable of catalyzing the pseudo-six-component reaction of Meldrum's acid, benzaldehyde derivatives, and aniline derivatives to afford polysubstituted hydroquinoline derivatives under mild reaction conditions (Scheme 1).[36,37] The difference between the current research and the prominent work presented by Maghsoodlou et al. is that the current reaction utilizes 2 equiv of Meldrum's acid, 3 equiv of benzaldehyde derivatives, and 1 equivalent of amine derivatives to yield new structures.

In recent years, our research group has been actively engaged in advancing multicomponent reactions.[38−40] In this context, our current focus is on the development of a one-pot and pseudo-six-component approach for synthesizing hexahy-

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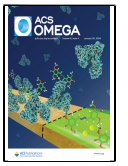
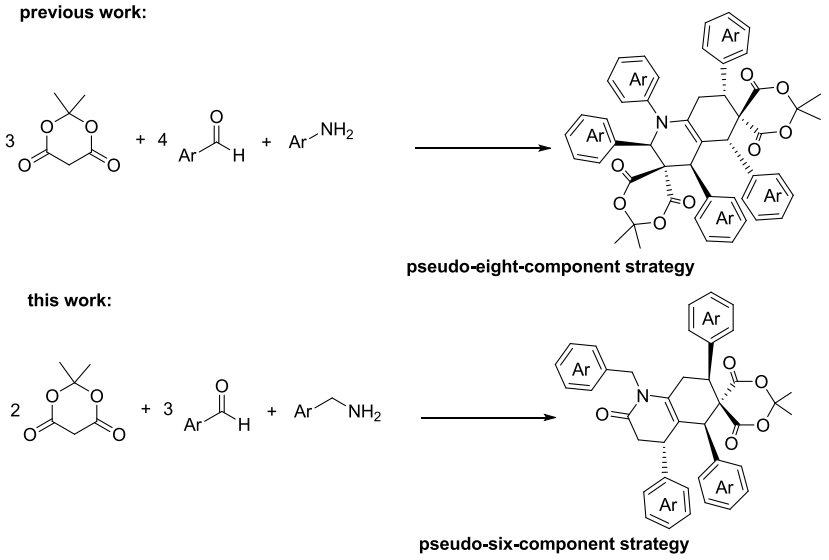


Scheme 1. Comparison between the Current Pseudo-Six-Component Strategy and Previously Reported Pseudo-Eight-Component Strategy

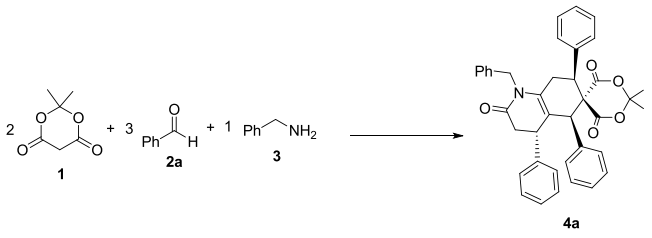


droquinoline derivatives. The benefits of this protocol include using an inexpensive catalyst, mild reaction conditions, high selectivity, and high diversity.

RESULTS AND DISCUSSION

Meldrum's acid (**1**), benzaldehyde (**2a**), and benzylamine (**3**) were selected as model substrates to start our investigations in the presence of TFA or CH_3CO_2H using a variety of solvents at 60 °C. As illustrated in Table 1, entries 4 and 8, no target product **4a** was detected in the presence of TFA or CH_3CO_2H in aqueous media. To achieve the product **4a**, utilization of other solvents such as MeOH, CH_3CN, and EtOH was then explored (Table 1). However, satisfying results were not observed, except for CH_3CN, in which the starting materials were efficiently transferred to the desired product **4a** in the presence of CH_3CO_2H as an inexpensive catalyst (Table 1, entry 6).

Table 1. Optimization of One-Pot and Pseudo-Six-Component Synthesis of Hexahydroquinoline (4a)



entry	catalyst	solvent	isolated yield (%)
1	TFA	MeOH	23
2	TFA	CH_3CN	28
3	TFA	EtOH	25
4	TFA	H_2O	NR
5	CH_3CO_2H	MeOH	30
6	**CH_3CO_2H**	**CH_3CN**	**78**
7	CH_3CO_2H	EtOH	33
8	CH_3CO_2H	H_2O	NR

[a]Reaction conditions: **1** (2.0 mmol), **2a** (3.0 mmol), **3a** (1.0 mmol), catalyst (0.08 mmol), solvent (5 mL), under air.

The scope and limitations of the reaction concerning benzaldehyde derivatives (**2**) and benzylamine derivatives (**3**) were subsequently explored under optimized reaction conditions (Scheme 2). A broad spectrum of aromatic aldehydes (**2**) and benzylamines (**3**) containing electron-poor, electron-rich, and halogen substitutions was tested. All transformations occurred in moderate-to-good yields. When the reaction of benzaldehyde (**2a**) and Meldrum's acid (**1**) with 2-chlorobenzaldehyde (**4b**), 4-bromobenzaldehyde (**4e**), or 3-bromobenzaldehyde (**4f**) was performed, good yields of products were obtained (Scheme 1). It is worth noting that a wide range of substitutions such as NO_2, I, Br, Cl, and F were applied to this approach to give the corresponding products in moderate-to-good yields under optimized reaction conditions. Ortho-substitution at the benzaldehydes does not seem to have a significant effect on the yields (Scheme 2).

Herein, a rational mechanism for the tandem/cyclization preparation of hexahydroquinoline (**4a**) is offered (Scheme 3), which is in analogy to the previously reported articles.[36,41,42] The tandem Knoevenagel and Michael reactions are the key steps of this transformation. Initially, the benzylidene derivative of Meldrum's acid **I** is produced *via* the Knoevenagel transformation, followed by reverting the intermediate **I** to acetone (**III**) and intermediate **II** in an equilibrium reaction. In the next step, acetone is condensed with benzylamine to deliver imine **IV**. This intermediate is tautomerized to enamine **V**. In continuation, Barbas dienamine **VII** (2-amino-1,3-butadiene) is formed *via* the condensation of benzaldehyde with enamine **V**. The resulting intermediate **VII** is transformed to enamine **VIII** by reacting with the Knoevenagel product **I**. The intermediate **VIII** is then added to Knoevenagel product **I** to give intermediate **IX**. In the last step, intermediate **IX** cyclized to afford intermediate **X** and acetone (**III**), followed by the release of a carbon dioxide molecule to arrive at the final product **4a**. In this reaction, acetone (**III**) could be formed directly from Meldrum's acid and in the reaction from **IX**. Indeed, acetone could be present in a small amount via hydrolysis of Meldrum's acid or any of the condensation

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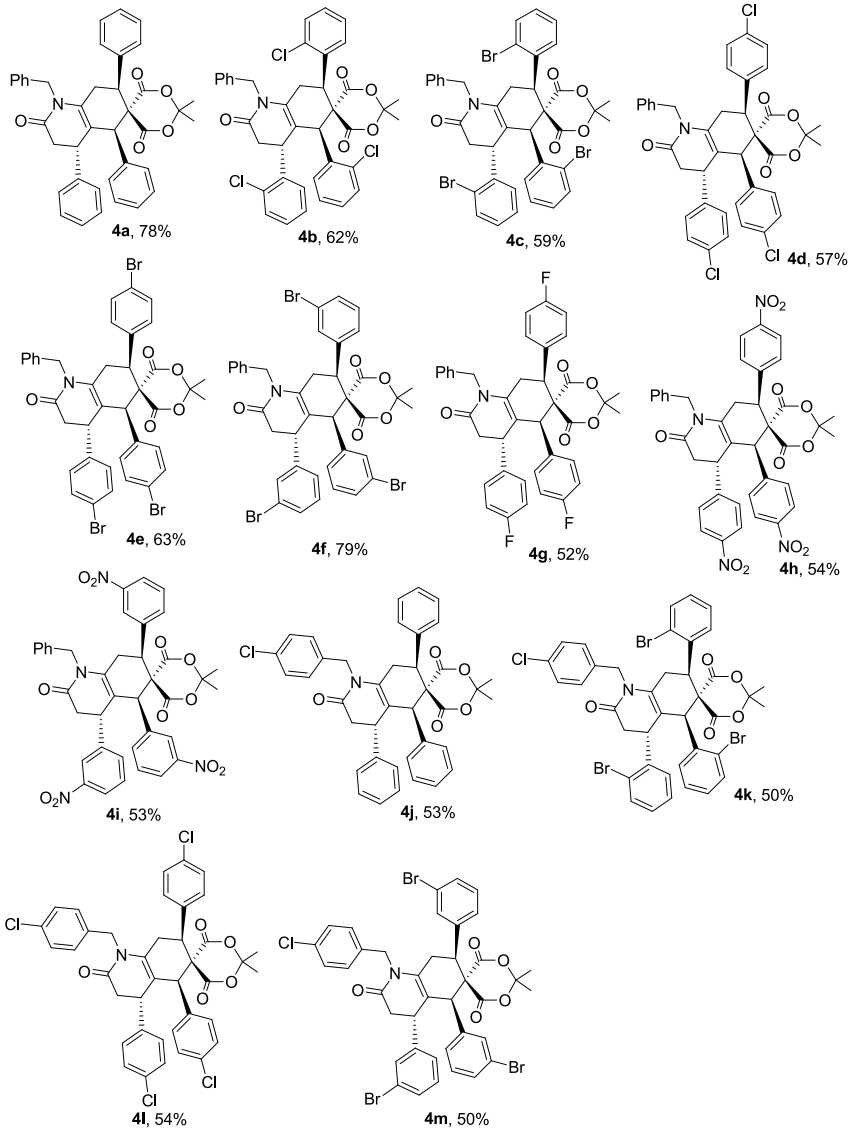
Scheme 2. Substrate Scope of One-Pot and Pseudo-Six-Component Synthesis of Hexahydroquinoline Derivatives (4)



products. It can be regenerated in the step before the last step, as well.

We also propose an alternative mechanism possible not involving the Barbas dienamine for intermediate **VIII**. In the presence of a base (amine) and excess benzaldehyde **2a**, bis benzalacetone **XI** could be formed, and this has been approved to form a spiro compound **XII** with Meldrum's acid in high yield [42]. It can be surmised that intermediate **VIII** (Scheme 4) is formed from spirocyclohexanone **XII** and benzylamine **3**.

The data collected from nuclear magnetic resonance (NMR), infrared (IR) spectroscopy, and X-ray crystallographic analysis were interpreted to confirm the structure of the product **4**. The IR spectrum of **4a** displayed two absorption bands at 1678 and 1730 cm^{-1} which belong to the carbonyl groups of Meldrum's acid and benzylamine ring. The structure was also confirmed by NMR and 2D NMR. The ^{1}H NMR signals at 0.43 and 0.51 ppm integrate for three hydrogens and do not show coupling to other hydrogens. These signals, therefore, belong either to the three hydrogens on carbon 22 or 23. The ^{1}H NMR signals at 4.96 and 5.05 ppm belong to the hydrogens on carbon 33. According to the HSQC and COSY analyses, these hydrogens are geminal and only couple to each other. This can only be in accordance with the proposed assignment. The ^{1}H NMR signals at 6.72, 7.05, 7.15, 7.27, and 7.44 ppm all belong to aromatic hydrogens. This assignment is in accordance with the observed integration values and is supported by the HSQC analysis. The ^{1}H NMR signals at 2.72 and 3.06 ppm were assigned to the hydrogens on carbon 9. According to HSQC, these signals belong to geminal hydrogens. The ^{1}H NMR signals at 2.79 and 3.22 ppm also belong to geminal hydrogens. However, the 2.79 and 3.22 ppm signals do not show any coupling to carbonyl carbons in the HMBC spectrum, whereas the 2.72 and 3.06 ppm signals do. This is in line with the proposed assignment. The ^{13}C NMR signals at 163.0, 168.2, and 168.5 ppm were assigned to carbonyl carbons based on their chemical shift and the observation in the HSQC spectrum that these are quaternary carbons. Subsequently, the ^{1}H NMR signals at 2.79 and 3.22 ppm can be assigned to the hydrogens on carbon 3. At first, only two ^{1}H NMR signals were found by HSQC analysis that could accord to the hydrogens of a nonaromatic CH (3.80 and 4.49 ppm). However, three signals were expected. Upon close inspection of the HSQC spectrum, it became clear that one CH signal was hidden underneath the water peak, as a positive

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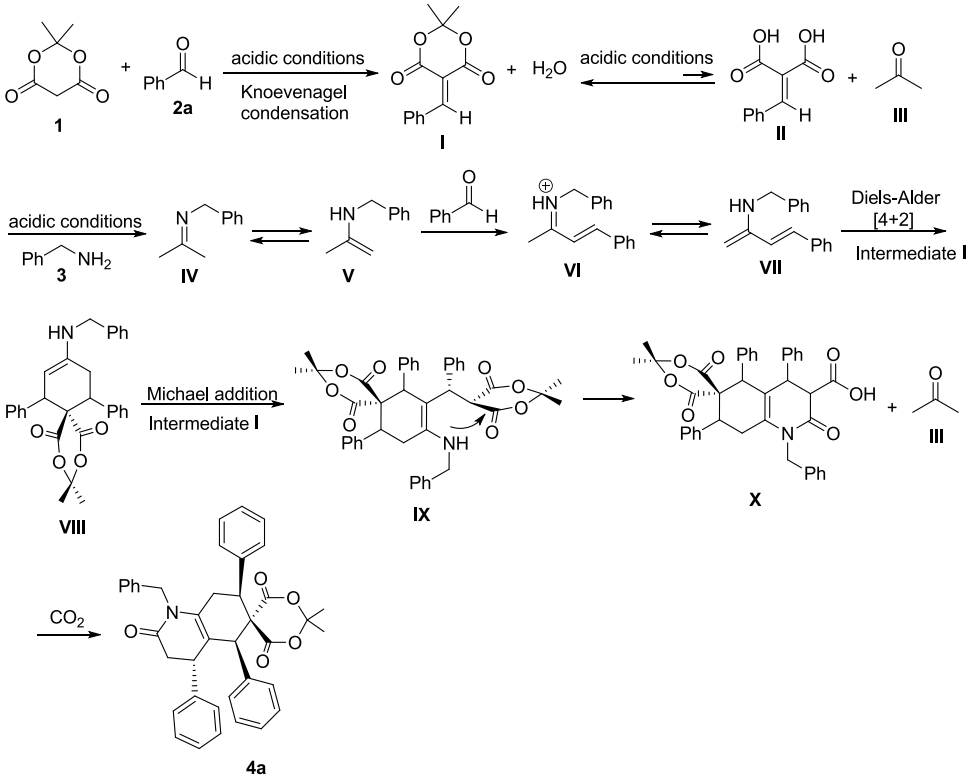
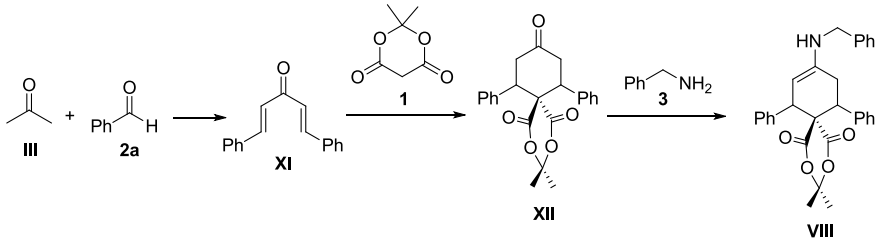
Scheme 3. Proposed Reaction Mechanism for One-Pot and Pseudo-Six-Component Synthesis of Hexahydroquinoline (4a)



Scheme 4. Alternative Mechanism, Not Involving the Barbas Dienamine, for the Formation of Intermediate VIII



peak showed coupling to the 38.1 ppm of ^{13}C NMR signal. The ^{1}H NMR signal at 3.32 ppm (underneath the water peak) was assigned to the hydrogen on carbon 10. Both the other CH signals (3.80 and 4.49 ppm) show coupling to the same carbonyl carbon (163.0 ppm) in the HMBC spectrum. This is only possible if these signals belong to the hydrogens on carbons 2 and 6. The ^{1}H NMR signal at 3.80 ppm was assigned to the hydrogen on carbon 2. In the HSQC spectrum, it was seen that the ^{13}C NMR signal of carbon that directly bonded to this hydrogen appeared at 46.6 ppm. This ^{13}C NMR signal showed coupling to the hydrogens on carbon 3 in the HMBC spectrum. On the other hand, the ^{13}C NMR signal belonging to the carbon that directly bonded to the hydrogen of signal 4.49 ppm was found to be 52.7 ppm by HSQC. This ^{13}C NMR signal did not show coupling to the hydrogens of carbon 3 in the HMBC spectrum and only showed coupling to the 3.80 ppm signal. The assignment of hydrogen on carbon 2 and on carbon 6 could thus be made. The ^{1}H NMR signal at 4.49 ppm was assigned to the hydrogen on carbon 6. Having assigned all aliphatic ^{1}H NMR signals, a NOESY analysis made it clear that the stereochemistry of the phenyl rings connected to positions 2 and 6 is cis, as proposed at the beginning of this section. It could be seen that the hydrogens of carbon 2 and carbon 6 couple in the NOESY spectrum. These hydrogens are, therefore, within 5 Å of each other. This does not correspond with the alternating stereochemistry of the phenyl rings. Yet, it is in accordance with the proposed stereochemistry. Hydrogens 6 and 10, as expected, do not give coupling in NOESY as expected from the X-ray analysis, confirming trans-stereochemistry of the connected phenyl groups (all NMR and 2D NMR data are available in the Supporting Information). Finally, the structure of compound **4a** was further confirmed by X-ray crystallographic analysis (Figure 1).

An efficient and ecofriendly strategy has been presented for the pseudo-six-component diastereoselective synthesis of hexahydroquinoline under homogeneous acidic conditions. This catalytic system starts from commercially available starting materials and involves a highly innovative pseudo-six-component reaction, conducted under mild reaction conditions and allowing for the simple purification of products. It is particularly noteworthy that four stereocenters and ten new bonds were constructed with excellent diastereoselectivity within this transformation. Additional research is currently underway in our laboratory to expand the scope of this reaction and study the reaction mechanism.

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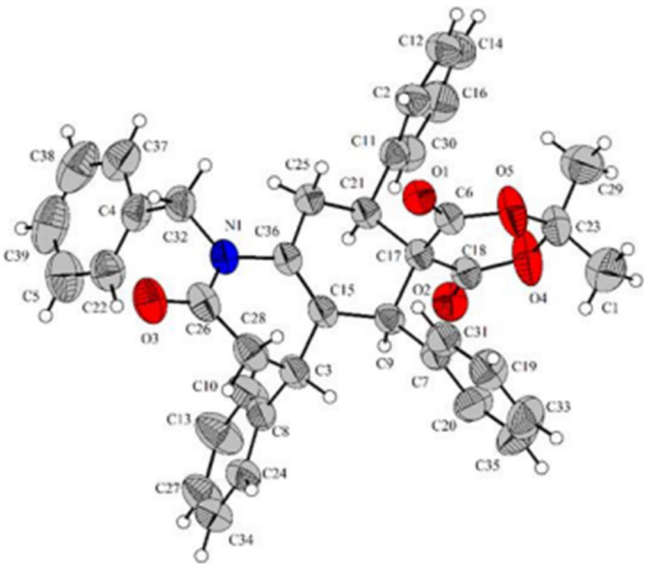

Figure 1. ORTEP diagram of **4a**.

EXPERIMENTAL SECTION

General Information. All reagents and substrates were commercial and used without further purification unless otherwise indicated. All reactions were monitored by TLC, which was performed on precoated aluminum sheets of silica gel 60 (F254) and visualized by exposure to UV light (254 nm). Melting points were measured by using a melting point instrument and were uncorrected.

^{1}H NMR spectra were recorded on a Bruker spectrometer (at 500 MHz) and reported relative to tetramethylsilane as the internal standard. Data for ^{1}H NMR spectra were reported as follows: chemical shift (d/ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J/Hz), and integration. ^{13}C NMR spectra were recorded on a Bruker spectrometer (126 MHz).

Benzaldehyde derivative (3.0 mmol, **2**) was added to a solution of Meldrum's acid (2.0 mmol, **1**) and benzylamine derivative (1.0 mmol, **3**) in acetonitrile (5 mL), followed by the addition of acetic acid (0.08 mmol). Further, the mixture was stirred at 60 °C for 24 h. The reaction progress was monitored by TLC. After completing the reaction, water as an antisolvent was added to the mixture to obtain the desired precipitate. The resulting precipitate was filtered and dried to produce the final powder.

*(4′S,5′S,7′S)-1′-Benzyl-2,2-dimethyl-4′,5′,7′-triphenyl-3′,4′,7′,8′-tetrahydro-1′H-spiro[[1,3]dioxane-5,6′-quinoline]-2′,4,6(5′H)-trione (**4a**).* Powder white. mp: 210 °C; IR (KBr, cm^{-1}): ν 3467, 3014, 2922, 1767, 1730, 1678, 1573. ^{1}H NMR (500 MHz, DMSO) δ 7.43 (td, J = 7.6, 1.5 Hz, 1H, H−Ar), 7.37−7.17 (m, 13H, H−Ar), 7.17−7.10 (m, 2H, H−Ar), 7.09−6.99 (m, 4H, H−Ar), 6.79−6.65 (m, 1H, CH), 5.10−4.91 (m, 2H, CH_2), 4.46 (d, J = 3.0 Hz, 1H, CH), 3.77 (dd, J = 11.8, 5.1 Hz, 1H, CH), 3.26−2.99 (m, 2H, CH_2), 2.81−2.62 (m, 2H, CH_2), 0.50 (s, 3H, CH_3), 0.42 (s, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 168.51, 168.15, 162.97, 140.63, 138.37, 137.47, 137.24, 134.88, 130.54, 129.21, 128.83, 128.56, 128.41, 128.09, 126.94, 126.72, 126.69, 126.16, 111.57, 105.39, 60.11, 52.70, 46.63, 43.72, 38.09, 29.31, 27.84, 27.47. Anal. Calcd for $C_{39}H_{35}NO_5$ (597.70): C, 78.37; H, 5.90; N, 2.34. Found: C, 78.41; H, 6.01; N, 2.39

*Benzyl-4,5,7-Tris(2-chlorophenyl)-2′,2′-dimethyl-1,3,4,5,7,8-hexahydro-2H-spiro[quinoline-6,5′-[1,3]-dioxane]-2,4′,6′-trione (**4b**).* White powder (yield 62%, mp: 224 °C), IR (KBr, cm^{-1}): 3421, 3063, 3002, 2922, 1739,1674, 1567. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 7.50 (dd, J = 7.9, 1.5 Hz, 1H, H−Ar), 7.47−7.40 (m, 1H, HAr),7.40−7.25 (m, 13H, H−Ar), 7.25−7.15 (m, 2H, CH_2), 5.10−4.96 (m, 2H, CH_2), 4.95−4.89 (m,1H, CH), 4.48 (dd, J = 12.0, 5.1 Hz, 1H, CH), 3.69−3.60 (m, 1H, CH), 3.19−3.10 (m, 1H, CH), 2.91 (ddd, J = 17.0, 6.9, 3.8 Hz, 2H, CH_2), 2.63 (dd, J = 16.1, 6.2 Hz, 1H, CH), 0.99 (s, 3H, Me), 0.62 (s, 3H, Me).^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 167.77, 166.86, 164.46, 138.66, 137.35, 137.24, 136.16, 135.40, 134.33, 133.44, 130.99, 130.59, 130.39, 129.43, 128.97, 128.54, 128.36, 128.25, 127.50, 126.95, 111.87, 106.34, 56.50, 48.37, 40.06, 39.90, 28.95, 28.10. Anal. Calcd for $C_{39}H_{32}Cl_3NO_5$ (701.03): C, 66.82; H, 4.60; N, 2.00. Found: C, 66.87; H, 4.63; N, 2.09.

*1-Benzyl-4,5,7-tris(2-bromophenyl)-2′,2′-dimethyl-1,3,4,5,7,8-hexahydro-2H-spiro[quinoline-6,5′-[1,3]-dioxane]-2,4′,6′-trione (**4c**).* White powder (yield 59%, mp: 235 °C), IR (KBr, cm^{-1}): 3430, 3063, 2992, 2925,1751, 1690, 1585. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 7.67 (dd, J = 8.1, 1.3 Hz, 1H, H−Ar), 7.58−7.50 (m, 2H, HAr), 7.45−7.27 (m, 7H, H−Ar), 7.27−7.17 (m, 7H, H−Ar), 5.16 (d, J = 16.3 Hz, 1H, CH), 4.95−4.82 (m, 2H, CH_2), 4.43 (dd, J = 12.0, 5.0 Hz, 1H, CH), 3.58−3.51 (m, 1H, CH), 3.25−3.10 (m, 1H, CH), 3.01 (d, J = 8.1 Hz, 1H, CH), 2.99−2.91 (m, 2H, CH_2), 1.10 (s, 3H, Me), 0.61 (s, 3H, Me). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 167.60, 166.62, 164.67, 138.58, 137.88, 137.11, 136.41, 134.37, 134.12, 133.91, 132.18, 130.94, 130.63, 129.86, 129.27, 128.98, 128.85, 128.79, 128.20, 127.56, 127.13, 126.59, 125.66, 124.52, 111.77, 106.52, 56.25, 51.21, 46.5344.48, 39.10, 37.62, 31.48, 29.10, 28.01. Anal. Calcd for $C_{39}H_{32}Br_3NO_5$ (834.39): C, 56.14; H, 3.87; N, 1.68. Found: C, 56.16; H, 3.82; N, 1.62.

*1-Benzyl-4,5,7-tris(4-chlorophenyl)-2′,2′-dimethyl-1,3,4,5,7,8-hexahydro-2H-spiro[quinolone-6,5′-[1,3]-dioxane]-2,4′,6′-trione (**4d**).* White powder (yield 57%, mp: 242 °C), IR (KBr, cm^{-1}): 3442, 3069, 2992, 2934, 1893, 1724, 1678, 1585. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 7.50 (dd, J = 8.4, 2.4 Hz, 1H, H−Ar), 7.46−7.40 (m, 2H, H−Ar), 7.34−7.21 (m, 8H, H−Ar), 7.21−7.10 (m, 3H, H−Ar), 7.06 (p, J = 2.5 Hz, 3H, H−Ar), 6.67 (dd, J = 8.3, 2.4 Hz, 1H, CH), 4.99 (d, J = 4.6 Hz, 2H, CH_2), 4.43 (d, J = 3.3 Hz, 1H, CH), 3.88 (dd, J = 11.8, 5.2 Hz, 1H, CH), 3.19−3.06 (m, 1H, CH), 2.99 (dd, J = 16.0, 6.7 Hz, 1H, CH), 2.84−2.63 (m, 2H, CH_2), 0.63 (s, 3H, Me), 0.55 (s, 3H, Me). ^{13}C NMR (126 MHz, DMSO-d6) δ (ppm) 28.11,28.58, 29.80, 38.32, 39.34, 39.55,39.75, 39.96, 40.17, 40.38, 40.59, 44.29, 46.48, 52.30, 60.42, 106.13, 111.41, 126.72, 127.32, 128.95, 129.25, 129.44, 129.60, 129.88, 130.82, 131.32, 131.86, 132.71, 133.43, 133.68, 136.03, 136.42, 138.80, 140.13, 163.39, 168.49, 168.42. Anal. Calcd for $C_{39}H_{32}Cl_3NO_5$ (701.03): C, 66.82; H, 4.60; N, 2.00. Found: C, 66.77; H, 4.67; N, 1.96.

*1-Benzyl-4,5,7-tris(4-bromophenyl)-2′,2′-dimethyl-1,3,4,5,7,8-hexahydro-2H-spiro[quinolone-6,5′-[1,3]-dioxane]-2,4′,6′-trione (**4e**).* White powder (yield 63%, mp: 257 °C), IR (KBr, cm^{-1}): 3439, 2989, 2931, 1902, 1727, 1674, 1573. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 7.63 (dd, J = 8.4, 2.3 Hz, 1H, H−Ar), 7.59−7.55 (m, 2H, H−Ar), 7.44−7.40 (m, 3H, H−Ar), 7.32−7.29 (m, 2H, H−Ar), 7.27−7.22 (m, 1H, H−Ar), 7.19−7.13 (m, 3H, H−Ar), 7.01 (ddd, J = 8.6, 5.0, 2.4 Hz, 5H, H−Ar), 6.63 (dd, J = 8.3, 2.4 Hz, 1H,

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CH), 4.98 (d, J = 3.2 Hz, 2H, CH_2), 4.41 (d, J = 3.1 Hz, 1H, CH), 3.85 (dd, J = 11.8, 5.2 Hz, 1H, CH), 3.12 (t, J = 14.5 Hz, 1H, CH), 3.00 (dd, J = 16.1, 6.8 Hz, 1H, CH), 2.81−2.65 (m, 2H, CH_2), 0.63 (s, 3H, Me), 0.55 (s, 3H, Me). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 168.80, 168.49, 163.38, 140.56, 138.80, 137.23, 136.83, 136.05, 133.03, 132.81, 132.38, 132.23, 131.90, 131.65, 131.13, 129.97, 128.90, 127.33, 126.73, 122.21, 121.97, 120.37, 111.28, 106.15, 60.30, 52.42, 46.58, 44.32, 38.35, 29.76, 28.57, 28.11. Anal. Calcd for $C_{39}H_{32}Br_3NO_5$ (834.39): C, 56.14; H, 3.87; N, 1.68. Found: C, 56.11; H, 3.90; N, 1.64.

(5S,7R)-1-Benzyl-4,5,7-tris(3-bromophenyl)-2′,2′-dimethyl-1,3,4,5,7,8-hexahydro-2H-spiro [quinoline-6,5′-[1,3]-dioxane]-2,4′,6′-trione (**4f**). White powder (yield 79%, mp: 205 °C), IR (KBr, cm^{-1}): 3417, 3057, 2992, 2940, 1773, 1739, 1668. 1576, ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 7.55 (d, J = 8.5 Hz, 1H, H−Ar), 7.51−7.47 (m, 1H, H−Ar), 7.34 (td, J = 15.2, 8.0 Hz, 5H, H−Ar), 7.28−7.20 (m, 5H, H−Ar), 7.18 (t, J = 9.7 Hz, 1H, H−Ar), 7.14−7.08 (m, 3H, H−Ar), 7.01 (d, J = 2.2 Hz, 1H, H−Ar), 6.53 (d, J = 6.2 Hz, 1H, CH), 5.11−4.93 (m, 2H, CH_2), 4.47−4.35 (m, 1H, CH), 3.89 (ddd, J = 11.9, 5.1, 2.7 Hz, 1H, CH), 3.52 (t, J = 7.5 Hz, 1H, CH), 3.28−3.14 (m, 1H, CH), 2.84 (d, J = 7.3 Hz, 1H, CH), 2.72 (dt, J = 17.2, 5.9 Hz, 1H, CH), 0.67 (s, 3H, Me), 0.54 (d, J = 5.2 Hz, 3H, Me). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 168.81, 168.66, 168.55, 163.24, 144.06, 140.54, 139.71, 138.85, 136.19, 133.18, 131.63, 131.21, 130.90, 129.96, 128.95, 128.18, 127.26, 126.76, 126.72, 123.00, 122.56, 122.34, 122.17, 111.49, 106.23, 106.18, 60.44, 52.44, 52.38, 46.61, 40.50, 39.10, 28.54, 28.37, 27.98, 27.89. Anal. Calcd for $C_{39}H_{32}Br_3NO_5$ (834.39): C, 56.14; H, 3.87; N, 1.68. Found: C, 56.17; H, 3.91; N, 1.63.

1-Benzyl-4,5,7-tris(4-fluorophenyl)-2′,2′-dimethyl-1,3,4,5,7,8-hexahydro-2H-spiro[quinoline-6,5′-[1,3]-dioxane]-2,4′,6′-trione (**4g**). White powder (yield 52%, mp: 200 °C), IR (KBr, cm^{-1}): 3461, 3103, 3073, 2999, 2934, 1733, 1665, ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 7.46−7.29 (m, 2H, H−Ar), 7.29−7.14 (m, 7H, H−Ar), 7.14−7.01 (m, 8H, H−Ar), 6.65 (ddd, J = 8.2, 5.5, 2.3 Hz, 1H, CH), 5.08−4.96 (m, 2H, CH_2), 4.45 (d, J = 2.0 Hz, 1H, CH), 3.87 (dd, J = 11.8, 5.2 Hz, 1H, CH), 3.23−3.10 (m, 1H, CH), 2.96 (dd, J = 16.0, 6.6 Hz, 1H, CH), 2.83−2.68 (m, 2H, CH_2), 0.62 (s, 3H, Me), 0.53 (s, 3H, Me). ^{13}C NMR (126 MHz, DMSO-d6) δ (ppm): 28.10, 28.57, 39.34, 39.55, 39.75, 39.96, 40.17, 40.38, 40.59, 60.76, 106.02, 115.62, 115.82, 116.18, 126.70, 127.30, 128.90, 129.51, 129.59, 138.84, 163.51, 168.57, 169.01. Anal. Calcd for $C_{39}H_{32}F_3NO_5$ (651.67): C, 71.88; H, 4.95; N, 2.15. Found: C, 71.90; H, 4.99; N, 2.18.

(5S,7R)-1-Benzyl-2′,2′-dimethyl-4,5,7-tris(4-nitrophenyl)-1,3,4,5,7,8-hexahydro-2H-spiro[quinoline-6,5′-[1,3]-dioxane]-2,4′,6′-trione (**4h**). White powder (yield 54%, mp: 243 °C), IR (KBr, cm^{-1}): 3424, 2992, 1779, 1742, 1671, 1567. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.28 (dd, J = 8.5, 4.8 Hz, 3H, H−Ar), 8.06 (d, J = 8.3 Hz, 2H, H−Ar), 8.01 (dd, J = 8.5, 2.6 Hz, 1H, H−Ar), 7.53 (dd, J = 8.7, 2.1 Hz, 1H, H−Ar), 7.45−7.30 (m, 7H, H−Ar), 7.25 (dd, J = 14.3, 7.4 Hz, 3H, H−Ar), 6.81 (dd, J = 8.5, 2.1 Hz, 1H, CH), 5.13−4.94 (m, 2H, CH_2), 4.64 (s, 1H, CH), 4.24−4.19 (m, 1H, CH), 3.64−3.51 (m, 2H, CH_2), 3.00 (dd, J = 16.0, 6.4 Hz, 1H, CH), 2.85 (d, J = 7.1 Hz, 1H, CH), 0.61 (s, 3H, Me), 0.49 (s, 3H, Me). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 168.37, 168.26, 163.14, 149.19, 148.00, 147.66, 146.81, 144.56, 138.66, 136.96, 130.60, 129.42, 128.96, 126.78, 124.58, 124.02, 110.47, 106.45, 59.95, 28.85, 28.17. Anal. Calcd for $C_{39}H_{32}N_4O_{11}$ (732.69): C, 63.93; H, 4.40; N, 7.65. Found: C, 63.98; H, 4.47; N, 7.66.

1-Benzyl-2′,2′-dimethyl-4,5,7-tris(3-nitrophenyl)-1,3,4,5,7,8-hexahydro-2H-spiro[quinoline-6,5′-[1,3]-dioxane]-2,4′,6′-trione (**4i**). White powder (yield 53%, mp: 193 °C), IR (KBr, cm^{-1}): 3445, 3069, 2992, 2925, 2777, 1736, 1674, 1573. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.24−7.95 (m, 5H, H−Ar), 7.73−7.54 (m, 6H, H−Ar), 7.38−7.27 (m, 6H, H−Ar), 5.20−4.90 (m, 2H, CH_2), 4.61 (t, J = 2.0 Hz, 1H, CH), 4.36 (t, J = 5.1 Hz, 1H, CH), 4.24 (ddd, J = 11.8, 5.0, 2.3 Hz, 1H, CH), 3.45 (qd, J = 7.0, 5.1 Hz, 1H, CH), 2.94 (td, J = 15.7, 10.1 Hz, 1H, CH), 2.88−2.73 (m, 2H, CH_2), 0.59 (d, J = 1.8 Hz, 3H, Me), 0.47−0.42 (m, 3H, Me). Anal. Calcd for $C_{39}H_{32}N_4O_{11}$ (732.69): C, 63.93; H, 4.40; N, 7.65. Found: C, 63.90; H, 4.45; N, 7.62.

1-(4-Chlorobenzyl)-2′,2′-dimethyl-4,5,7-triphenyl-1,3,4,5,7,8-hexahydro-2H-spiro[quinoline-6,5′-[1,3]-dioxane]-2,4′,6′-trione (**4j**). White powder (yield 53%, mp: 253 °C), IR (KBr, cm^{-1}): 3445, 3045, 2934, 2879, 1958, 1890, 1730, 1656, 1585. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 7.45 (td, J = 7.6, 1.5 Hz, 1H, H−Ar), 7.39−7.16 (m, 15H, H−Ar), 7.09−7.02 (m, 3H, H−Ar), 6.70 (d, J = 7.6 Hz, 1H, CH), 5.00 (d, J = 3.8 Hz, 1H, CH), 4.48 (s, 1H, CH), 3.84 (dd, J = 11.8, 5.2 Hz, 1H, CH), 3.30−3.00 (m, 2H, CH_2), 2.88−2.58 (m, 2H, CH_2), 2.10 (s, 1H, CH), 0.53 (s, 3H, Me), 0.44 (s, 3H, Me).^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 28.00, 28.37, 29.85, 38.64, 39.33, 39.75, 39.96, 40.17, 40.37, 40.58, 43.65, 47.07, 53.20, 60.63, 105.95, 112.43, 127.24, 127.49, 128.62, 128.72, 128.83, 128.87, 128.99, 129.11, 129.39, 129.75, 131.06, 131.80, 135.27, 137.71, 137.97, 138.00, 141.10, 163.54, 168.79, 169.03. Anal. Calcd for $C_{39}H_{34}ClNO_5$ (632.14): C, 74.10; H, 5.42; N, 2.22. Found: C, 63.90; H, 4.45; N, 2.27.

4,5,7-Tris(2-bromophenyl)-1-(4-chlorobenzyl)-2′,2′-dimethyl-1,3,4,5,7,8-hexahydro-2H-spiro[quinoline-6,5′-[1,3]-dioxane]-2,4′,6′-trione (**4k**). White powder (yield 50%, mp: 215 °C), IR (KBr, cm^{-1}): 3461, 3060, 2999, 2931, 2728, 2641, 1770, 1742, 1681, 1576. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (s, 1H, H−Ar), 7.68−7.66 (m, 1H, H−Ar), 7.60 (dd, J = 8.0, 1.2 Hz, 1H, H−Ar), 7.56−7.50 (m, 3H, H−Ar), 7.48−7.44 (m, 3H, H−Ar), 7.43−7.34 (m, 2H, H−Ar), 7.31−7.25 (m, 3H, H−Ar), 7.23−7.20 (m, 1H, H−Ar), 7.16 (td, J = 5.1, 2.5 Hz, 1H, H−Ar), 5.08 (d, J = 16.6 Hz, 1H, CH), 4.93−4.84 (m, 2H, CH_2), 4.43 (dd, J = 12.0, 5.0 Hz, 1H, CH), 4.04 (s, 1H, CH), 3.53 (d, J = 6.4 Hz, 1H, CH), 3.12 (t, J = 14.8 Hz, 1H, CH), 2.99−2.87 (m, 2H, CH_2), 1.09 (s, 3H, Me), 0.60 (s, 3H, Me). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 167.69, 166.60, 164.65, 137.86, 137.69, 136.95, 133.52, 131.33, 130.64, 129.88, 129.11, 129.02, 128.98, 127.06, 125.69, 124.48, 112.03, 106.54, 56.22, 46.49, 42.08, 29.11, 28.00. Anal. Calcd for $C_{39}H_{31}Br_3NO_5$ (868.83): C, 53.91; H, 3.60; N, 1.61. Found: C, 53.98; H, 3.57; N, 1.67.

1-(4-Chlorobenzyl)-4,5,7-tris(4-chlorophenyl)-2′,2′-dimethyl-1,3,4,5,7,8-hexahydro-2H-spiro[quinoline-6,5′-[1,3]-dioxane]-2,4′,6′-trione (**4l**). White powder (yield 54%, mp: 248 °C), IR (KBr, cm^{-1}): 3451, 3057, 2999, 2925, 1899, 1724, 1674, 1576, ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 7.51−7.42 (m, 3H, H−Ar), 7.38 (d, J = 8.1 Hz, 2H, H−Ar), 7.27 (dd, J = 7.9, 4.3 Hz, 3H, H−Ar), 7.20 (d, J = 7.8 Hz, 3H, H−Ar), 7.10−7.03 (m, 5H, H−Ar), 6.63 (dd, J = 8.4, 2.4 Hz, 1H, CH), 5.08−4.77 (m, 2H, CH_2), 4.42 (s, 1H, CH), 3.91 (dd, J = 11.8, 5.2 Hz, 1H, CH), 3.10 (t, J = 14.6 Hz, 1H, CH), 2.96 (dd, J = 16.1, 6.6 Hz, 1H, CH), 2.83−2.64 (m, 2H, CH_2), 0.63 (s, 3H, Me), 0.54 (s, 3H, Me). ^{13}C NMR (126 MHz, DMSO-

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d_6) δ (ppm) 28.10,28.58, 29.80, 38.38, 39.33, 39.54, 39.75, 39.96, 40.17, 40.38, 40.59, 43.68, 46.41, 52.26, 60.41, 106.14, 111.74, 128.74, 128.95, 129.22, 129.45, 129.60, 130.85, 131.32, 131.85, 132.68, 133.40, 135.86, 136.33, 136.83, 137.87, 140.12, 163.40, 168.57, 168.81. Anal. Calcd for $C_{39}H_{31}Cl_4NO_5$ (735.48): C, 63.69; H, 4.25; N, 1.90. Found: C, 63.72; H, 4.23; N, 1.88.

*4,5,7-Tris(3-bromophenyl)-1-(4-chlorobenzyl)-2′,2′-dimethyl-1,3,4,5,7,8-hexahydro-2H-spiro[quinoline-6,5′-[1,3]dioxane]-2,4′,6′-trione (**4m**).* White powder (yield 50%, mp: 233 °C), IR (KBr, cm^{-1}): 3439, 3060, 3005, 2925,1881, 1764, 1733, 1668, 1576. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 7.55−7.45 (m, 2H, H−Ar), 7.42−7.30 (m, 5H, H−Ar), 7.30−7.23 (m, 4H, H -Ar), 7.20 (tdd, J = 7.2, 5.5, 2.8 Hz, 1H, H−Ar), 7.16−7.04 (m, 4H, H−Ar), 5.05−4.90 (m, 2H, CH_2), 4.36 (s, 1H, CH), 3.91 (dd, J = 11.8, 5.1 Hz, 1H,CH), 3.53−3.43 (m, 1H, CH), 3.15 (t, J = 13.7 Hz, 1H, CH), 2.82 (h, J = 9.5 Hz, 2H, CH_2), 2.69 (dd, J = 17.2, 5.8 Hz, 1H, CH), 0.66 (s, 3H, Me), 0.52 (d, J = 7.9 Hz, 3H, Me). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 168.79, 168.63, 163.26, 144.00, 143.95, 140.53, 139.61, 137.88, 136.00, 133.16, 131.87, 131.70, 131.27, 130.88, 129.94, 128.88, 128.81, 128.78, 128.56, 128.19, 126.76, 122.55, 122.32, 122.13, 106.25, 106.19, 60.43, 52.41, 46.56, 39.33, 28.53, 28.37, 27.97, 27.89. Anal. Calcd for $C_{39}H_{31}Br_3ClNO_5$ (868.83): C, 53.91; H, 3.60; N, 1.61. Found: C, 53.87; H, 3.56; N, 1.57.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c06264.

Crystallographic data for 4a (CIF)

Experimental details, copies of ^{1}H and ^{13}C NMR spectra of products, and 2D NMR data for **4a** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Sorour Ramezanpour − *Department of Chemistry, K. N. Toosi University of Technology, Tehran 19697, Iran;* orcid.org/0000-0002-3901-0391; Email: ramezanpour@kntu.ac.ir

Authors

Parvin Mohammadikia − *Department of Chemistry, K. N. Toosi University of Technology, Tehran 19697, Iran*

Pezhman Shiri − *Department of Chemistry, K. N. Toosi University of Technology, Tehran 19697, Iran*

Wim Dehaen − *Molecular Design and Synthesis, Department of Chemistry, KU Leuven, Leuven 3000, Belgium;* orcid.org/0000-0002-9597-0629

Linde Achten − *Molecular Design and Synthesis, Department of Chemistry, KU Leuven, Leuven 3000, Belgium*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c06264

Notes

The authors declare no competing financial interest.

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