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HIGHLY EFFICIENT SYNTHESIS OF 3,4-DIHYDRO-2(1*H*)-QUINOLINONE DERIVATIVES UNDER MICROWAVE HEATING

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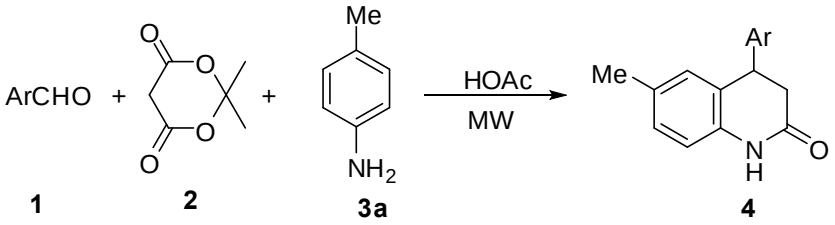
Abstract – A sequential three-component reaction of aromatic aldehydes with aromatic amine, and Meldrum's acid in EtOH under microwave irradiation has been developed. In this one-pot reaction, a series of 3,4-dihydro-2(1*H*)-quinolinone derivatives were synthesized with high chemical yields. The present green synthesis shows several advantages including operational simplicity and fast reaction rate, which makes it a useful and attractive process for library generation for drug discovery.

INTRODUCTION

The benzo-fused lactam skeleton is a significant element in a number of pharmacologically and biologically active compounds. The 3,4-dihydro-2(1*H*)-quinolinone scaffold is one important member of this class, and its derivatives are found in many natural products and drug candidates,[1,2] especially important for the treatment of schizophreni.[3] Because of these biological activities they exhibit, these compounds have distinguished themselves as heterocycles of profound chemical and biological significance. Thus the synthesis of these molecules has attracted considerable attention.[4-7] 3,4-Dihydro-2(1*H*)-quinolinones are classically synthesized via electrophilic aromatic substitution reactions, such as the Friedel-Crafts reaction,[4] Beckmann rearrangement of indanone oxime,[5] and cyclization of nitrenium ion.[6,7] Recently, various catalytic systems for the preparation of 3,4-dihydro-2(1*H*)-quinolinones have been developed.[8] However, these methods also exist some defects, such as requiring a stoichiometric amount of metal catalyst, limited substrate scope, and long reaction time. Therefore, the development of convenient and step-economical approaches to this family of

heterocyclic compounds, producing less waste and by-products, continues to be of considerable interest and important for modern organic and medicinal chemistry, particularly, for drug discovery and development.

Multicomponent reactions (MCRs) are becoming increasingly prevalent due to their improved efficiency, reduced waste, and rapid access of structural diversity.[9] In the past several years, we have been engaging in the development of new multicomponent domino reactions that can provide easy access to new core structures of chemical and pharmaceutical interest.[10] During our study of this topic, herein we report a selective synthesis of 3,4-dihydro-2(1*H*)-quinolinones **4** through microwave-assisted multicomponent reactions of electron-rich aromatic amines in HOAc (Scheme 1). It is an efficient and promising method to construct the 3,4-dihydro-2(1*H*)-quinolinone skeleton.



Scheme 1

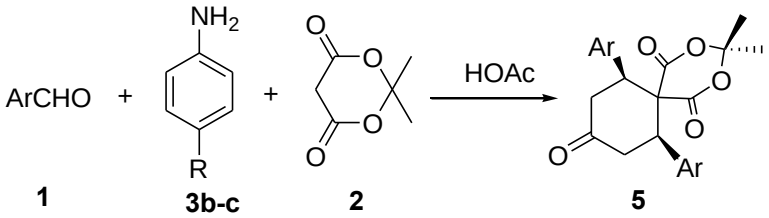
RESULTS AND DISCUSSION

We started this study by subjecting 4-methylbenzaldehyde **1a** and Meldrum's acid **2** to the reactions with *p*-toluidine **3a** under microwave irradiation at 100 °C, using different solvents included ethylene glycol, DMF, EtOH, water, and HOAc as reaction media. Among them, HOAc was proven to be the best solvent (Table 1, entry 5). Subsequently, the reaction was performed in HOAc and repeated many times at different temperatures in a sealed vessel under microwave irradiation for 15 min. The yield of product **4a** was increased from 63% to 87% as the temperature varied from 80 to 100 °C. Further increase of reaction temperature failed to improve the yield of product **4a** (Table 1, entry 7).

Table 1. Solvent optimization for the synthesis of **4d** under MW

Entry	Solvent	T / °C	Time / min	Yield (%)
1	ethylene glycol	100	20	60
2	DMF	100	20	35
3	EtOH	100	18	71
4	water	100	20	trace
5	HOAc	100	15	87
6	HOAc	80	15	63
7	HOAc	120	15	85

With this result in hand, we next examined the substrate scope of this reaction. Under the optimized reaction conditions [HOAc, 100 ^{o}C], a variety of structurally diverse aromatic aldehydes were employed to yield a series of new 3,4-dihydro-2(1*H*)-quinolinones with concomitant formations of three new σ-bonds. As shown in Table 2, a series of aromatic aldehydes, either bearing electron-withdrawing groups or electron-donating groups, was treated with starting materials **2** and **3a** to give the corresponding products **4** in good to excellent chemical yields (83-92%) under the same reaction condition. The results showed that the electronic nature of the substituents **1** on phenyl ring has no significant effect on outcomes of this reaction. Interestingly, when aromatic amines with electron-donating groups employed in this system were replaced by their electron-withdrawing counterparts (such as 4-chlorobenzenamine **3b**, and 4-bromobenzenamine **3c**), the reaction occurred to another direction to form multi-functionalized symmetrical spiro[5.5]undecanes **5** that belong to another family of important scaffolds for organic synthesis and drug design in pharmaceutical sciences such as peptides, peptidomimetics, and proteins.[11] Thus, it is clear that the divergent pathways were controlled by the electronic effects of various groups on arylamine ring. The electron-rich aryl-amines resulted in the 3,4-dihydro-2(1*H*)-quinolinones, whereas electron-withdrawing counterparts were as a catalyst for the synthesis of the spiro[5.5]undecanes. Next, four examples of spiro[5.5]undecanes **5** were synthesized in 70-76% yields using the feed ratio of **1**-**2**-**3b** in 1:1:0.6 (Table 2, Scheme 2).



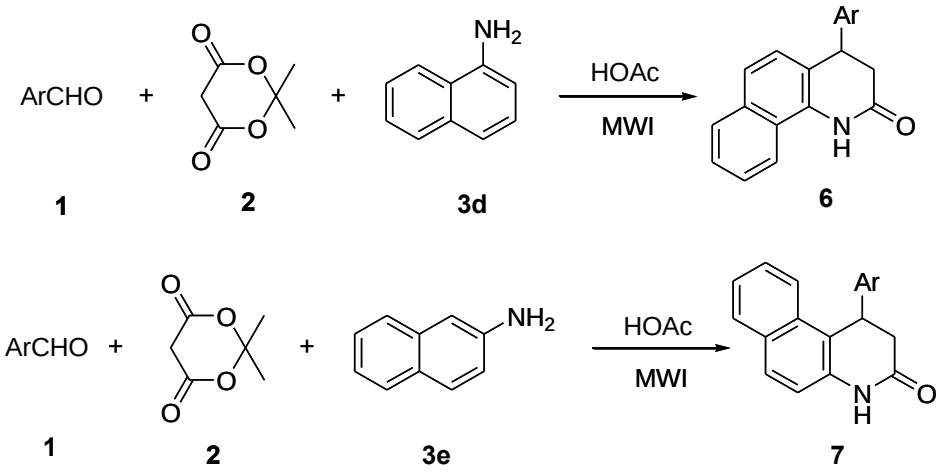
Scheme 2

Table 2. The synthesis of 3,4-dihydro-2(1*H*)-quinolinone **4** and spiro[5.5]undecanes **5**

Entry	**4 or 5**	Ar	Time / min	Yield (%)
1	**4a**	4-MeC_6H_4 (**1a**)	15	87
2	**4b**	4-ClC_6H_4 (**1b**)	12	90
3	**4c**	4-BrC_6H_4 (**1c**)	12	92
4	**4d**	3,4-$Cl_2C_6H_3$ (**1d**)	10	88
5	**4e**	2-ClC_6H_4 (**1e**)	16	83
6	**4f**	2,4-$Cl_2C_6H_3$ (**1f**)	15	85
7	**5a**	4-MeOC_6H_4 (**1g**)	18	70[a]
8	**5b**	4-BrC_6H_4 (**1c**)	16	76[a]
9	**5c**	3,4-$Cl_2C_6H_3$ (**1d**)	15	75[a]
10	**5d**	C_6H_5 (**1h**)	20	71[a]

[a] yield was based on the two equivalent of aldehydes

To further expand the scope of amine substrates, different aldehydes and Meldrum's acid **2** as model substrates and examined various aryl-amines including naphthalen-1-amine **3d**, and naphthalen-2-amine **3e**. In all these cases, the reactions proceeded smoothly to give a set of corresponding benzo[h]quinolinone, benzo[f]quinolinone in good to excellent yields (Scheme 3 and Table 3). The results exhibit the scope and generality of the multicomponent reaction with respect to a range of amine and aldehyde substrates. Indeed, the protocol provides a straightforward pathway to construct highly substituted fused quinolinones, which are generally prepared through conventional heating.[12]



Scheme 3

Table 3. The synthesis of 3,4-dihydro-2(1*H*)-quinolinone derivatives **6** and **7**

Entry	**6** or **7**	Ar	Time / min	Yield (%)
1	**6a**	4-ClC_6H_4	10	89
2	**6b**	4-BrC_6H_4	12	87
3	**6c**	4-MeC_6H_4	16	84
4	**6d**	4-$MeOC_6H_4$	18	81
5	**6e**	3,4-$Cl_2C_6H_3$	16	83
6	**6f**	2-ClC_6H_4	18	80
7	**6g**	2-thiophenyl	16	79
8	**7a**	4-BrC_6H_4	12	88
9	**7b**	4-MeC_6H_4	14	82

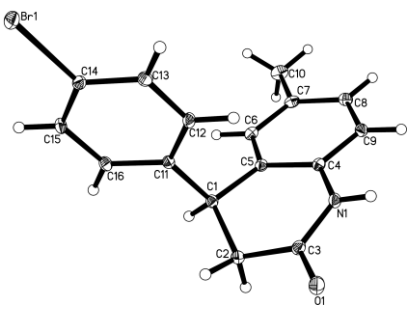


Figure 1. ORTEP diagram of **4c**[13]

In some cases, the complexity of the products resulting from this multicomponent reaction illustrates the remarkable chemoselectivity of the sequence starting from very simple and easily accessible substrates. The structural elucidation and attribution of relative stereochemistry were unequivocally determined by NMR analysis and X-ray diffraction of single crystals that were obtained by slow evaporation of the solvent, as in the case of products **4c, 5d** and **6g** (Figures 1, 2 and 3). Only microwave irradiation can make the present multi-component domino reaction to occur rapidly and efficiently, while normal heating diminished both yield and speed.

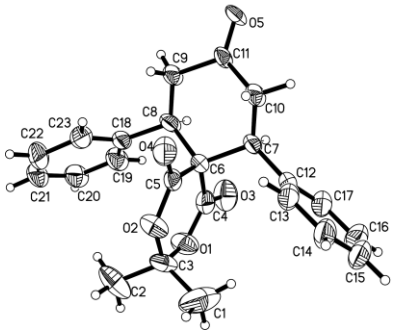


Figure 2. ORTEP diagram of **5d**[14]

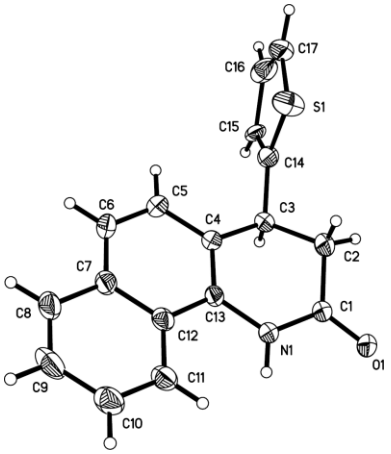
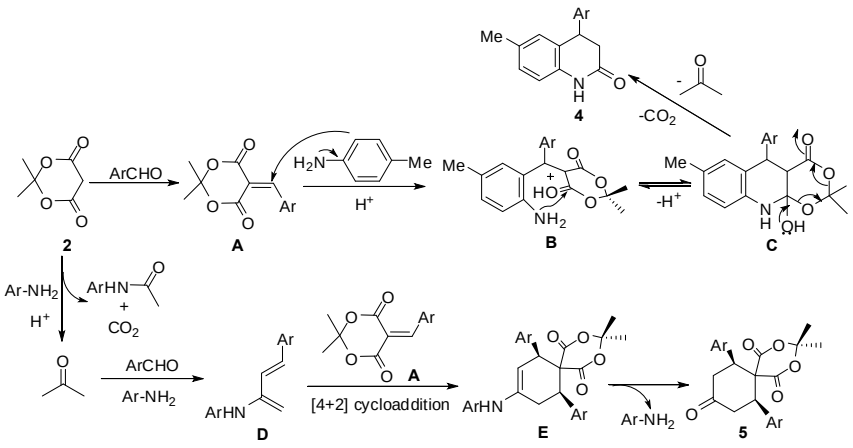


Figure 3. ORTEP diagram of **6g**[15]

A plausible reaction mechanism is proposed in Scheme 4. The initial step involves the Knoevenagel reaction of Meldrum's acid (**2**) with an aldehyde (**1**) to form an intermediate **A**. Due to the stronger nucleophilicity of *β*-position on the electron-rich aryl-amine ring,[16] the Michael addition between intermediate **A** and the aryl-amines **3a** occurs, providing the unstable intermediate **B**. The intermediate **B** undergoes intramolecular cyclization to give the 3,4-dihydro-2(1*H*)-quinolinones **4**. Instead of Michael addition, the electron-deficient aromatic amines prefer to react with Meldrum's acid to release acetone. Subsequently, the arylidene-Meldrum's acid **B** undergoes a Diels–Alder reaction with the soft nucleophilic Barbas dienamine (2-amine-1,3-butadiene)[17] **D**, generated in situ from acetone with an

aldehyde and amine, to produce products **5.** As anticipated, the Diels–Alder reaction follows the *endo* rule, providing the product with the two aromatic rings arranged on the same side, as confirmed by X-ray structural analysis (Figure 2). This hypothesis is supported by the mechanistic investigation of proline-catalyzed spirotriones' formation through the reaction of aldehyde and Meldrum's acid with enones reported by Barbas III group.[18]



Scheme 4

In conclusion, we have developed an efficient synthetic method for the construction of 3,4-dihydro-2(1*H*)-quinolinones under microwave heating without any catalyst. The reactions showed broad substrates of using readily available and inexpensive starting materials of various aromatic aldehydes, Meldrum's acid and aromatic amine including naphthylamine. A reasonable mechanism has been proposed to explain the resulting stereochemistry of spiro[5.5]undecanes products. In addition, this synthesis also shows several attractive characteristics such as simple conditions, short reaction periods, easy work-up, straight forwardness of the procedure and reduced waste production for the lack of any requirement for catalysts.

EXPERIMENTAL

Microwave irradiation was carried out with Initiator from Biotage Company, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shift (δ) given in ppm relative to TMS as internal standard. HRMS (ESI) was determined by using microTOF-QII HRMS/MS instrument (BRUKER). X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer

Synthesis of 4, 6 and 7 under Microwave Irradiation

In a 10 mL reaction vial, aromatic aldehydes (**1**, 1.0 mmol), Meldrum's acid (**2**, 1.0 mmol), aromatic

amines (**3**, 1.0 mmol), and HOAc (1.5 mL) were mixed and then capped. The automatic mode stirring helped the mixing and uniform heating of the reactants. The mixture was heated by microwave irradiation at 100 ^{o}C for a given time. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and filtered to give the crude products, which were further purified by recrystallization from 80% EtOH.

Synthesis of 5 under Microwave Irradiation

In a 10 mL reaction vial, aromatic aldehydes (**1**, 2.0 mmol), Meldrum's acid (**2**, 2.0 mmol), aromatic amines (**3**, 1.2 mmol), and HOAc (1.5 mL) were mixed and then capped. The automatic mode stirring helped the mixing and uniform heating of the reactants. The mixture was heated by microwave irradiation at 100 ^{o}C for a given time. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and filtered to give the crude products, which were further purified by recrystallization from 70% EtOH.

6-Methyl-4-(4-methylphenyl)-3,4-dihydroquinolin-2(1*H*)-one (4a)

White solid, mp 190.8-191.6 ^{o}C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.12 (s, 1H, NH), 7.12 (d, 2H, J=8.0 Hz, ArH), 7.05 (d, 2H, J=8.4 Hz, ArH), 6.98 (dd, 1H, J_1=8.0 Hz, J_2=1.2 Hz, ArH), 6.82 (d, 1H, J=8.0 Hz, ArH), 6.74 (s, 1H, ArH), 4.21 (t, 1H, J=6.4 Hz, CH), 2.77 (dd, 1H, J_1=16.0 Hz, J_2=6.4 Hz, CH_2), 2.66 (dd, 1H, J_1=15.8 Hz, J_2=6.6 Hz, CH_2), 2.27 (s, 3H, CH_3), 2.16 (s, 3H, CH_3);

IR (KBr, ν, cm^{-1}): 3197, 3054, 2921, 1676, 1615, 1503, 1379, 1252, 818.

HRMS (ESI): m/z calcd for $C_{17}H_{17}NNaO$ [M+Na^{+}], 274.1206; found: 274.1218.

6-Methyl-4-(4-chlorophenyl)-3,4-dihydroquinolin-2(1*H*)-one (4b)

White solid, mp 224.0-225.5 ^{o}C;

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.13 (s, 1H, NH), 7.38 (d, 2H, J=8.4 Hz, ArH), 7.18 (d, 2H, J=8.4 Hz, ArH), 7.01 (d, 1H, J=7.2 Hz, ArH), 6.84 (d, 1H, J=8.0 Hz, ArH), 6.77 (s, 1H, ArH), 4.29 (t, 1H, J=6.0 Hz, CH), 2.78 (dd, 1H, J_1=16.0 Hz, J_2=6.4 Hz, CH_2), 2.69 (dd, 1H, J_1=15.8 Hz, J_2=6.4 Hz, CH_2), 2.17 (s, 3H, CH_3);

IR (KBr, ν, cm^{-1}): 3188, 3057, 1659, 1610, 1508, 1386, 1247, 1092, 1013, 840, 765, 608.

HRMS (ESI): m/z calcd for $C_{16}H_{14}ClNNaO$ [M+Na^{+}], 294.0656; found: 294.0671.

6-Methyl-4-(4-bromophenyl)-3,4-dihydroquinolin-2(1*H*)-one (4c)

White solid, mp 239.0-241.0 ^{o}C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.14 (s, 1H, NH), 7.52 (d, 2H, J=8.4 Hz, ArH), 7.13 (d, 2H, J=8.0 Hz, ArH), 7.01 (d, 1H, J=7.6 Hz, ArH), 6.83 (d, 1H, J=8.0 Hz, ArH), 6.77 (s, 1H, ArH), 4.28 (t, 1H,

J=6.4 Hz, CH), 2.80 (dd, 1H, J_1=16.0 Hz, J_2=6.4 Hz, CH_2), 2.67 (dd, 1H, J_1=16.0 Hz, J_2=6.4 Hz, CH_2), 2.17 (s, 3H, CH_3);

IR (KBr, ν, cm^{-1}): 3187, 3053, 2907, 1660, 1617, 1508, 1488, 1388, 1248, 1010, 828, 604.

HRMS (ESI): m/z calcd for $C_{16}H_{14}BrNNaO$ [M+Na^+], 338.0150; found: 338.0168.

6-Methyl-4-(3,4-dichlorophenyl)-3,4-dihydroquinolin-2(1*H*)-one (4d)

White solid, mp 285.9-286.3 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.30 (s, 1H, NH), 7.71 (d, 2H, *J*=8.4 Hz, ArH), 7.63 (d, 1H, *J*=8.4 Hz, ArH), 7.57 (d, 1H, *J*=8.4 Hz, ArH), 7.50 (d, 1H, *J*=8.0 Hz, ArH), 7.41 (s, 1H, ArH), 7.00 (s, 1H, ArH), 4.02 (t, 1H, *J*=6.0 Hz, CH), 2.85 (dd, 1H, J_1=16.0 Hz, J_2=6.0 Hz, CH_2), 2.73 (dd, 1H, J_1=13.2 Hz, J_2=6.4 Hz, CH_2), 2.31 (s, 3H, CH_3);

IR (KBr, ν, cm^{-1}): 3190, 3030, 2901, 1683, 1606, 1512, 1470, 1361, 1134, 1033, 816, 715.

HRMS (ESI): m/z calcd for $C_{16}H_{13}Cl_2NNaO$ [M+Na^+], 328.0266; found: 328.0277.

6-Methyl-4-(2-chlorophenyl)-3,4-dihydroquinolin-2(1*H*)-one (4e)

White solid, mp 285.1-285.6 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.22 (s, 1H, NH), 7.52 (dd, 1H, J_1=7.6 Hz, J_2=1.6 Hz, ArH), 7.30-7.26 (m, 2H, ArH), 7.04 (d, 1H, *J*=7.6 Hz, ArH), 6.91-6.88 (m, 2H, ArH), 6.70 (s, 1H, ArH), 4.64 (t, 1H, *J*=6.0 Hz, CH), 2.84 (dd, 1H, J_1=16.0 Hz, J_2=6.8 Hz, CH_2), 2.69 (dd, 1H, J_1=15.8 Hz, J_2=6.4 Hz, CH_2), 2.16 (s, 3H, CH_3);

IR (KBr, ν, cm^{-1}): 3201, 3051, 2960, 1662, 1620, 1507, 1444, 1387, 1252, 1032, 817, 684.

HRMS (ESI): m/z calcd for $C_{16}H_{14}ClNNaO$ [M+Na^+], 294.0656; found: 294.0664.

6-Methyl-4-(2,4-dichlorophenyl)-3,4-dihydroquinolin-2(1*H*)-one (4f)

White solid, mp 246.6-247.6 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.29 (s, 1H, NH), 7.59 (d, 1H, *J*=8.8 Hz, ArH), 7.40 (dd, 1H, J_1=8.8 Hz, J_2=2.4 Hz, ArH), 7.08 (d, 1H, *J*=8.4 Hz, ArH), 6.91-6.89 (m, 2H, ArH), 6.72 (s, 1H, ArH), 4.63 (t, 1H, *J*=6.4 Hz, CH), 2.85 (dd, 1H, J_1=16.0 Hz, J_2=6.4 Hz, CH_2), 2.73 (dd, 1H, J_1=15.8 Hz, J_2=6.4 Hz, CH_2), 2.18 (s, 3H, CH_3);

IR (KBr, ν, cm^{-1}): 3196, 3058, 2964, 1675, 1608, 1505, 1461, 1382, 1250, 1098, 815.

HRMS (ESI): m/z calcd for $C_{16}H_{13}Cl_2NNaO$ [M+Na^+], 328.0266; found: 328.0279.

3,3-Dimethyl-7,11-di(4-methoxyphenyl)-2,4-dioxaspiro[5,5]undecane-1,5,9-trione (5a)

White solid, mp 234.4-235.0 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 7.10 (d, 2H, *J*=8.4 Hz, ArH), 7.06 (d, 2H, *J*=8.0 Hz, ArH), 6.95 (d, 2H, *J*=8.8 Hz, ArH), 6.91 (d, 2H, *J*=8.4 Hz, ArH), 3.72 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.62 (dd, 2H, J_1=13.8 Hz, J_2=4.4 Hz, CH), 3.40 (dd, 2H, J_1=14.0 Hz, J_2=4.0 Hz, CH_2), 2.66 (dd, 2H, J_1=13.2 Hz,

J_2=3.6 Hz, CH_2), 3.16 (dd, 1H, J_1=14.0 Hz, J_2=4.0 Hz, CH_2), 2.70 (dd, 1H, J_1=14.4 Hz, J_2=4.0 Hz, CH_2), 0.57 (s, 6H, CH_3);

IR (KBr, ν, cm^{-1}): 2996, 2936, 2837, 1760, 1729, 1636, 1611, 1514, 1393, 1286, 1181, 1033, 833.

HRMS (ESI): m/z calcd for $C_{25}H_{26}NaO_7$ [M+Na^+], 461.1570; found: 461.1589.

3,3-Dimethyl-7,11-di(4-bromophenyl)-2,4-dioxaspiro[5,5]undecane-1,5,9-trione (5b)

White solid, mp 266.1-268.0 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 7.67 (d, 2H, J=8.8 Hz, ArH), 6.97 (d, 4H, J=8.4 Hz, ArH), 6.70 (d, 2H, J=8.4 Hz, ArH), 3.95 (dd, 2H, J_1=11.6 Hz, J_2=5.2 Hz, CH), 3.13 (dd, 2H, J_1=16.0 Hz, J_2=6.8 Hz, CH_2), 2.67 (dd, 2H, J_1=15.8 Hz, J_2=4.8 Hz, CH_2), 0.65 (s, 6H, CH_3);

IR (KBr, ν, cm^{-1}): 2990, 2921, 1761, 1733, 1636, 1541, 1489, 1288, 1075, 859.

HRMS (ESI): m/z calcd for $C_{23}H_{20}Br_2NaO_5$ [M+Na^+], 556.9569; found: 556.9589.

3,3-Dimethyl-7,11-di(3,4-dichlorophenyl)-2,4-dioxaspiro[5,5]undecane-1,5,9-trione (5c)

White solid, mp 246.0-248.5 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 7.72 (t, 2H, J=8.4 Hz, ArH), 7.41 (s, 1H, ArH), 7.36 (s, 1H, ArH), 7.20 (dd, 1H, J_1=8.4 Hz, J_2=2.0 Hz, ArH), 7.16 (dd, 1H, J_1=8.4 Hz, J_2=2.0 Hz, ArH), 3.78 (dd, 2H, J_1=13.6 Hz, J_2=4.0 Hz, CH), 3.41 (dd, 2H, J_1=10.6 Hz, J_2=4.4 Hz, CH_2), 3.03 (d, 1H, J =14.4 Hz, CH_2), 2.60 (d, 1H, J=14.4 Hz, CH_2), 0.71 (s, 3H, CH_3), 0.68 (s, 3H, CH_3);

IR (KBr, ν, cm^{-1}): 2996, 2841, 1764, 1733, 1647, 1559, 1472, 1393, 1296, 1032, 898.

HRMS (ESI): m/z calcd for $C_{23}H_{18}Cl_4NaO_5$ [M+Na^+], 536.9800; found: 536.9821.

3,3-Dimethyl-7,11-diphenyl-2,4-dioxaspiro[5,5]undecane-1,5,9-trione (5d)

White solid, mp 256.7-259.0 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 7.41-7.31 (m, 6H, ArH), 7.20 (d, 2H, J=8.0 Hz, ArH), 7.16 (d, 2H, J=7.6 Hz, ArH), 3.79 (dd, 2H, J_1=13.6 Hz, J_2=5.2 Hz, CH), 3.49 (dd, 2H, J_1=16.0 Hz, J_2=4.4 Hz, CH_2), 3.04 (dd, 2H, J_1=15.0 Hz, J_2=4.0 Hz, CH_2), 0.69 (s, 6H, CH_3);

IR (KBr, ν, cm^{-1}): 1763, 1731, 1645, 1507, 1456, 1393, 1285, 1064, 982, 897, 704.

HRMS (ESI): m/z calcd for C23H22NaO5 [M+Na^+], 401.1359; found: 401.1368.

4-(4-Chlorophenyl)-3,4-dihydrobenzo[h]quinolin-2(1*H*)-one (6a)

White solid, mp 210.2-211.0 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.56 (s, 1H, NH), 8.37 (d, 1H, J=8.0 Hz, ArH), 7.89 (d, 1H, J=7.6 Hz, ArH), 7.58-7.52 (m, 3H, ArH), 7.38 (d, 2H, J=8.4 Hz, ArH), 7.23-7.19 (m, 3H, ArH), 4.52 (t, 1H, J=5.6 Hz, CH), 3.04 (dd, 1H, J_1=16.0 Hz, J_2=6.4 Hz, CH_2), 2.80 (dd, 1H, J_1=15.8 Hz, J_2=5.0 Hz, CH_2);

IR (KBr, ν, cm^{-1}): 3228, 2930, 1669, 1616, 1519, 1490, 1369, 1087, 1014, 807, 749, 672.

HRMS (ESI): m/z calcd for $C_{19}H_{14}ClNNaO$ [M+Na^+], 330.0656; found: 330.0667.

4-(4-Bromophenyl)-3,4-dihydrobenzo[h]quinolin-2(1*H*)-one (6b)

White solid, mp 207.0-208.0 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.55 (s, 1H, NH), 8.37 (d, 1H, *J*=8.8 Hz, ArH), 7.89 (d, 1H, *J*=7.6 Hz, ArH), 7.56 (d, 1H, *J*=8.4 Hz, ArH), 7.54-7.50 (m, 3H, ArH), 7.22 (d, 2H, *J*=8.0 Hz, ArH), 7.14 (d, 2H, *J*=8.0 Hz, ArH), 4.51 (t, 1H, *J*=5.8 Hz, CH), 3.04 (dd, 1H, J_1=15.8 Hz, J_2=6.6 Hz, CH_2), 2.80 (dd, 1H, J_1=15.8 Hz, J_2=5.0 Hz, CH_2);

IR (KBr, ν, cm^{-1}): 3226, 3124, 2931, 1671, 1614, 1519, 1469, 1368, 1166, 1070, 1008, 807, 748, 671.

HRMS (ESI): m/z calcd for $C_{19}H_{14}BrNNaO$ [M+Na^+], 374.0150; found: 374.0114.

4-(4-Methylphenyl)-3,4-dihydrobenzo[h]quinolin-2(1*H*)-one (6c)

White solid, mp 181.3-182.4 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.51 (s, 1H, NH), 8.36 (d, 1H, *J*=8.4 Hz, ArH), 7.88 (d, 1H, *J*=8.0 Hz, ArH), 7.55-7.51 (m, 3H, ArH), 7.20 (d, 2H, *J*=8.4 Hz, ArH), 7.12 (d, 2H, *J*=8.4 Hz, ArH), 7.07 (d, 2H, *J*=8.0 Hz, ArH), 4.44 (t, 1H, *J*=5.8 Hz, CH), 3.00 (dd, 1H, J_1=15.8 Hz, J_2=6.6 Hz, CH_2), 2.79 (dd, 1H, J_1=15.8 Hz, J_2=5.4 Hz, CH_2), 2.26 (s, 3H, CH_3);

IR (KBr, ν, cm^{-1}): 3225, 3119, 2924, 1682, 1620, 1515, 1468, 1369, 1155, 1005, 807, 747, 674.

HRMS (ESI): m/z calcd for $C_{20}H_{17}NNaO$ [M+Na^+], 310.1202; found: 310.1215.

4-(4-Methoxyphenyl)-3,4-dihydrobenzo[h]quinolin-2(1*H*)-one (6d)

White solid, mp 192.0-193.5 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.51 (s, 1H, NH), 8.36 (d, 1H, *J*=8.0 Hz, ArH), 7.88 (d, 1H, *J*=6.4 Hz, ArH), 7.55~7.49 (m, 3H, ArH), 7.20 (d, 1H, *J*=8.4 Hz, ArH), 7.10 (d, 2H, *J*=8.8 Hz, ArH), 6.87 (d, 2H, *J*=8.8 Hz, ArH), 4.43 (t, 1H, *J*=5.6 Hz, CH), 3.72 (s, 3H, OCH_3), 2.98 (dd, 1H, J_1=15.8 Hz, J_2=6.6 Hz, CH_2), 2.79 (dd, 1H, J_1=15.8 Hz, J_2=5.4 Hz, CH_2);

IR (KBr, ν, cm^{-1}): 3228, 3118, 2931, 1684, 1610, 1511, 1368, 1254, 1174, 1033, 816, 750, 673.

HRMS (ESI): m/z calcd for $C_{20}H_{17}NNaO_2$ [M+Na^+], 326.1151; found: 326.1117.

4-(3,4-Dichlorophenyl)-3,4-dihydrobenzo[h]quinolin-2(1*H*)-one (6e)

White solid, mp >300 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.69 (s, 1H, NH), 8.38 (d, 1H, *J*=8.4 Hz, ArH), 7.39 (d, 1H, *J*=8.0 Hz, ArH), 7.64-7.57 (m, 4H, ArH), 7.42 (dd, 1H, J_1=8.6 Hz, J_2=2.6 Hz, ArH), 7.14 (d, 1H, *J*=8.4 Hz, ArH), 6.83 (s, 1H, ArH), 4.84 (t, 1H, *J*=5.8 Hz, CH), 3.04 (dd, 1H, J_1=15.8 Hz, J_2=6.6 Hz, CH_2), 2.66 (dd, 1H, J_1=15.8 Hz, J_2=5.0 Hz, CH_2);

IR (KBr, ν, cm^{-1}): 3249, 3120, 1682, 1578, 1521, 1457, 1383, 1164, 1093, 1049, 813, 749.

HRMS (ESI): m/z calcd for $C_{19}H_{13}Cl_2NNaO$ [M+Na^+], 364.0266; found: 364.0279.

4-(2-Chlorophenyl)-3,4-dihydrobenzo[h]quinolin-2(1*H*)-one (6f)

White solid, mp 254.1-255.1 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.64 (s, 1H, NH), 8.40 (d, 1H, *J*=8.0 Hz, ArH), 7.91 (d, 1H, *J*=8.0 Hz, ArH), 7.59-7.54 (m, 4H, ArH), 7.30 (t, 1H, *J*=7.6 Hz, ArH), 7.22 (t, 1H, *J*=7.6 Hz, ArH), 7.14 (d, 1H, *J*=8.4 Hz, ArH), 6.84 (dd, 1H, J_1=8.0 Hz, J_2=1.6 Hz, ArH), 4.84 (t, 1H, *J*=5.2 Hz, CH), 3.10 (dd, 1H, J_1=15.6 Hz, J_2=6.8 Hz, CH_2), 2.79 (dd, 1H, J_1=15.8 Hz, J_2=5.0 Hz, CH_2);

IR (KBr, ν, cm^{-1}): 3229, 3127, 2895, 1667, 1578, 1522, 1467, 1375, 1164, 1034, 815, 752.

HRMS (ESI): m/z calcd for $C_{19}H_{14}ClNNaO$ [M+Na$^+$], 330.0656; found: 330.0674.

4-(2-Thiophenyl)-3,4-dihydrobenzo[h]quinolin-2(1*H*)-one (6g)

White solid, mp 238.2-238.8 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.52 (s, 1H, NH), 8.35 (d, 1H, *J*=8.0 Hz, ArH), 7.91-7.88 (m, 1H, ArH), 7.59 (d, 1H, *J*=8.4 Hz, ArH), 7.54-7.50 (m, 2H, ArH), 7.40 (d, 1H, *J*=8.4 Hz, ArH), 7.36 (d, 1H, *J*=4.8 Hz, 2-thiophenyl-H), 6.95 (t, 1H, *J*=4.4 Hz, 2-thiophenyl-H), 6.87 (d, 1H, *J*=3.2 Hz, 2-thiophenyl-H), 4.74 (t, 1H, *J*=5.0 Hz, CH), 3.12 (dd, 1H, J_1=16.0 Hz, J_2=6.4 Hz, CH_2), 2.87 (dd, 1H, J_1=12.6 Hz, J_2=9.0 Hz, CH_2);

IR (KBr, ν, cm^{-1}): 3208, 3104, 2935, 1683, 1612, 1519, 1373, 1171, 833.

HRMS (ESI): m/z calcd for C17H13NNaOS [M+Na$^+$], 302.0610; found: 302.0624.

4-(4-Bromophenyl)-3,4-dihydrobenzo[f]quinolin-2(1*H*)-one (7a)

White solid, mp 259.2-261.3 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.45 (s, 1H, NH), 7.87 (t, 2H, *J*=7.6 Hz, ArH), 7.79 (d, 1H, *J*=8.4 Hz, ArH), 7.46-7.42 (m, 2H, ArH), 7.35 (t, 1H, *J*=7.4 Hz, ArH), 7.28 (d, 2H, *J*=8.8 Hz, ArH), 7.05 (d, 2H, *J*=8.4 Hz, ArH), 5.03 (t, 1H, *J*=7.2 Hz, CH), 3.18 (dd, 1H, J_1=16.4 Hz, J_2=7.6 Hz, CH_2), 2.63 (d, 1H, *J*=16.0 Hz, CH_2);

IR (KBr, ν, cm^{-1}): 3199, 3078, 2966, 1679, 1626, 1523, 1487, 1385, 1320, 1244, 1011, 817, 737.

HRMS (ESI): m/z calcd for $C_{19}H_{14}BrNNaO$ [M+Na$^+$], 374.0150; found: 374.0119.

4-(4-Methylphenyl)-3,4-dihydrobenzo[f]quinolin-2(1*H*)-one (7b)

White solid, mp 231.4-232.3 °C

^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 10.38 (s, 1H, NH), 7.86 (d, 2H, *J*=8.8 Hz, ArH), 7.80 (d, 1H, *J*=8.4 Hz, ArH), 7.43 (t, 1H, *J*=7.6 Hz, ArH), 7.34 (t, 1H, *J*=7.4 Hz, ArH), 7.26 (d, 1H, *J*=8.8 Hz, ArH), 7.04 (d, 2H, *J*=8.0 Hz, ArH), 6.97 (d, 2H, *J*=8.0 Hz, ArH), 4.96 (t, 1H, *J*=6.8 Hz, CH), 3.15 (dd, 1H, J_1=16.0 Hz, J_2=7.6 Hz, CH_2), 2.61 (d, 1H, *J*=16.0 Hz, CH_2), 2.20 (s, 3H, CH_3);

IR (KBr, ν, cm^{-1}): 3197, 3065, 2944, 1683, 1626, 1522, 1389, 1320, 1241, 1162, 819, 743.

HRMS (ESI): m/z calcd for $C_{20}H_{17}NNaO$ [M+Na$^+$], 310.1202; found: 310.1218.

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13. Crystal data for **4c**: $C_{16}H_{14}BrNO$, white, Monoclinic, space group P2(1)/n, a = 7.6850(11) Å, b = 8.3004(11) Å, c = 21.301(3) Å, $\alpha = \gamma = 90$ °, $\beta = 95.110(2)$°, V = 1353.4(3) Å^3, Mr = 316.19, Z = 4, Dc = 1.552 Mg/m^3, λ = 0.71073 Å, μ(Mo K$_\alpha$) = 3.028 mm^{-1}, F(000) = 640, R = 0.0345, wR_2 = 0.0768, S = 1.027, largest diff. Peak and hole: 0.318 and -0.501 e/Å^3.
14. Crystal data for **5d**: $C_{46}H_{40}O_{10}$, colorless, Monoclinic, space group P2(1)/n, a = 12.226(4) Å, b = 13.067(4) Å, c = 13.203(4) Å, $\alpha = \gamma = 90$°, $\beta = 108.793(8)$°, V = 1996.7(11) Å^3, Mr = 752.78, Z = 2, Dc = 1.252 Mg/m^3, λ = 0.71073 Å, μ(Mo K$_\alpha$) = 0.088 mm^{-1}, F(000) = 792, R = 0.0888, wR_2 = 0.1926, S = 1.138, largest diff. Peak and hole: 0.196 and -0.132 e/Å^3.
15. Crystal data for **6g**: $C_{17}H_{13}NOS$, white, Monoclinic, space group P2(1)/c, a = 10.275(3) Å, b = 14.494(4) Å, c = 9.829(3) Å, $\alpha = \gamma = 90$°, $\beta = 112.612(4)$°, V = 1351.2(7) Å^3, Mr = 279.34, Z = 4, Dc = 1.373 Mg/m^3, λ = 0.71073 Å, μ(Mo K$_\alpha$) = 0.233 mm^{-1}, F(000) = 584, R = 0.0729, wR_2 = 0.1958, S = 1.001, largest diff. Peak and hole: 0.617 and -0.436 e/Å^3.
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