PEG-Polymer-Supported Liquid-Phase Combinatorial Synthesis of Structurally Diverse 2,3-Dihydro-4-pyridones

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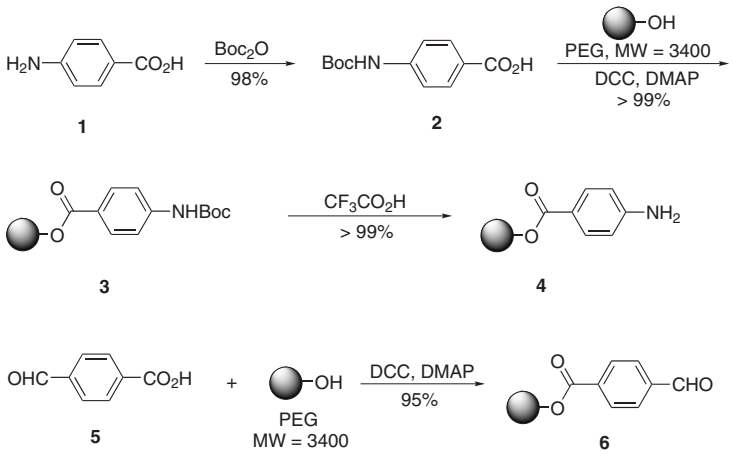
Abstract: A convenient liquid-phase synthetic protocol for the construction of structurally diverse 2,3-dihydro-4-pyridones on soluble polymer support by the aza Diels–Alder reaction has been developed, which utilized a one-pot three-component reaction of either PEG-supported amine, aromatic aldehydes and the Danishefsky's diene, or PEG-supported aldehyde, aromatic amines and Danishefsky's diene.

Key words: PEG, liquid-phase synthesis, combinatorial, aza Diels–Alder reactions, 2,3-dihydro-4-pyridones

Although solid-phase synthetic technique has been successfully applied as a powerful tool throughout the field of combinatorial chemistry, it suffers from some inherent disadvantages owing to the heterogeneous reaction conditions, such as high demands on the compatibility of the individual components, relatively low reactivity and selectivity, harsh reaction conditions, as well as the difficulty for characterization of the insoluble polymer-supported compounds.[1] This led to the development of various approaches for construction of combinatorial libraries in solution, among which liquid-phase synthesis using soluble polymers provides an attractive strategy by incorporating the positive aspects of both classical solution and solid-phase chemistry.[2] With homogeneous reaction conditions and simple sample handling and product isolation protocols, this strategy has recently gained much attention as an effective way for the construction of combinatorial libraries of small organic molecules, especially heterocyclic compounds, of which many are important structural motifs of pharmaceuticals or biologically active compounds. A variety of heterocyclic structures, including benzimidazoles, benzoxazoles and benzothiazoles,[3] benzodiazepine-2,5-diones,[4] 1,2,4-oxadiazolines,[5] quinoxalinones,[6] dihydropyrimidinones,[7] [1,4]oxazepin-7-ones,[8] and several other compound classes,[9] have been successfully generated by applying liquid-phase strategy.

2,3-Dihydro-4-pyridones, with important synthetic applications in natural or unnatural products, can be prepared by employing aza Diels–Alder reaction of Danishefsky's diene with imines as a convenient protocol.[10,11] Wilson reported a solid-phase synthesis of 2,3-dihydro-4-pyridones by the reaction of Danishefsky's diene with the Wang resin-supported imines.[12] In a previous communication, we reported a liquid-phase synthesis of 2,3-dihydro-4-pyridones via an aza Diels–Alder reaction, using a one-pot three-component reaction of PEG-supported amine, aromatic aldehydes and the Danishefsky's diene.[13] Herein, we described in detail the practical liquid-phase synthesis of structurally diverse 2,3-dihydro-4-pyridones using



Scheme 1 Synthesis of PEG-supported amine and aldehyde

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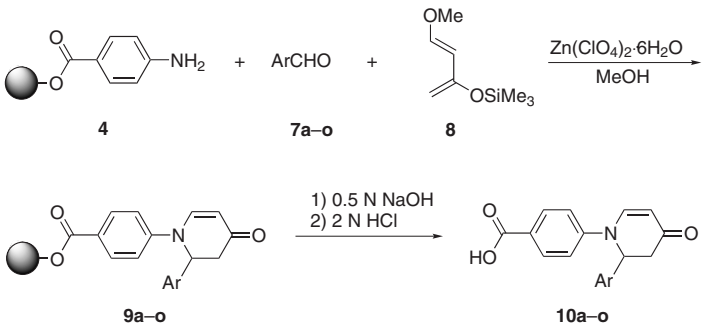
PEG-supported amine or aldehyde through the one-pot three-component aza Diels–Alder reactions.

As shown in Scheme 1, 4-aminobenzoic acid (**1**) was first protected with $(Boc)_2O$ following the literature procedure.[14] Then the Boc-protected aminobenzoic acid **2** was attached onto the soluble support by condensation with PEG (MW = 3400) in the presence of DCC (1,3-dicyclohexylcarbodiimide) and DMAP (4-dimethylaminopyridine). The reaction process was monitored by ^1H NMR analysis using $CDCl_3$ as the solvent. It was found that the condensation reaction completed after stirring for 24 hours at room temperature. The PEG-supported Boc-protected amine **3** was obtained by precipitation in Et_2O in >99% yield. The separated solids were re-dissolved in CH_2Cl_2–CF_3COOH (2:1) mixed solvents and the solution was stirred at room temperature for 24 hours to cleave the Boc group from **3**. The PEG supported amine **4** was easily isolated quantitatively by re-precipitation with Et_2O and simple filtration of the resulting mixtures. The preparation of **4** could be carried on a 0.1-mole scale without decrease of efficiency. Therefore, this procedure provided a practical synthesis of the PEG-supported aromatic amine. In parallel with the synthesis of **4**, the PEG-supported aromatic aldehyde **6** was also easily synthesized in 95% yield from 4-formylbenzoic acid (**5**) via a similar procedure (Scheme 1).

The PEG-supported amine **4** was subsequently used in the liquid-phase parallel (combinatorial) synthesis of *N*-(4-carboxyphenyl)-2-aryl substituted 2,3-dihydro-4-pyridone (**10**) library, as exemplified in Scheme 2. The PEG-bound amine **4** reacted with 10 equivalents of aromatic aldehyde **7** and 12 equivalents of Danishefsky's diene **8** in the presence of 0.1 equivalent of $Zn(ClO_4)_2{\cdot}6H_2O$ in MeOH at room temperature for 12 hours. The PEG-bound cycloadduct **9** was obtained by precipitation with Et_2O and simple filtration of the reaction mixture. To cleave the product from the PEG support, **9** was dissolved in an aqueous 0.5 N NaOH solution and stirred at room temperature for 12 hours. The resulting solution was acidified with 2 N HCl solution after hydrolysis, and the hardly soluble **10** was precipitated out, collected by filtration and the structure was confirmed by NMR and MS spectra. In some cases, a trace amount of the PEG residue might contaminate the final products **10**. This problem could be easily solved by passing the crude product through a pad of silica gel using acetone–MeOH (1:1) as the eluent. A variety of aromatic aldehydes were shown to be amenable to this synthetic protocol, and in most cases the target compounds **10** could be obtained in satisfactory yields and purities (Table 1). It can be seen that electron-donating group on the aromatic aldehydes exhibited a favorable substituent effect, affording the corresponding products in higher yields and purities than their electron-withdrawing group counterparts. Particularly, in the case of 4-Cl-, 3-Br-, or 3,5-dichlorobenzaldehyde (entries 7, 10, and 13, respectively), the corresponding products can be obtained in relatively high yields or purities in only 30 minutes for the cycloaddition step. In addition, the reaction of 4-cyanobenzaldehyde under same experimental conditions gave the corresponding PEG-bound product **9k** in >90% conversion, but the purity of final product **10k** after hydrolysis was only ca. 50%. NMR, HPLC and HRMS analyses showed the presence of amido derivative of **10k**, presumably caused by the partial hydrolysis of the cyano groups in **9k** during its alkaline cleavage from **PEG**. The cycloaddition reactions of olefinic and aliphatic aldehydes (such as *trans*-cinnamaldehyde and 3-phenylpropionaldehyde) were also examined under various experimental conditions, but the conversion from PEG-bound amine **7** to the corresponding PEG-bound products **9** was only modest (<50%). In a previous work, we found the aza Diels–Alder reaction could be accomplished without acidic (Lewis or Brønsted) catalyst by using MeOH as reaction solvent.[15] Therefore ,the one-pot reactions of PEG-supported amine, aromatic aldehydes and the Danishefsky's diene were also examined in the absence of $Zn(ClO_4)_2{\cdot}6H_2O$, but the conversion of PEG-bound amine to the cycloaddition product was always very poor.

On the other hand, the liquid phase combinatorial synthesis of another type of pyridones, *N*-aryl substituted 2-(4-carboxyphenyl)-2,3-dihydro-4-pyridones **13**, was also accomplished by a three-component aza Diels–Alder reaction using the PEG-supported aldehyde **6** instead of amine **4** as the polymeric substrate, in combination with an aromatic amine and the Danishefsky's diene **8** (Scheme 3). For these reactions, the reagent addition sequence was somewhat different from that described above for synthe-



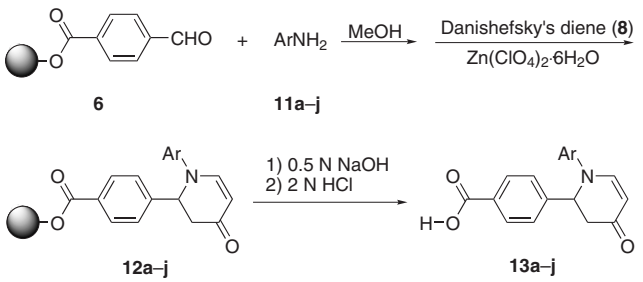
Scheme 2 Synthesis of *N*-(4-carboxyphenyl) substituted 2-aryl-2,3-dihydro-4-pyridones using soluble polymer-supported amine **4** through aza Diels–Alder reaction

Table 1 Liquid-Phase Synthesis of *N*-(4-Carboxyphenyl)-2-aryl-substituted 2,3-Dihydro-4-pyridones by One-Pot Aza Diels–Alder Reaction of PEG-Supported Amine **4** with Aromatic Aldehydes and Danishefsky's Diene

Entry	ArCHO (**7**)	Pyridones (**10**)	Yield (%)[a]	Purity (%)[b]
1	PhCHO (**a**)	**10a**	83	89
2	4-MeC_6H_4CHO (**b**)	**10b**	99	71
3	3-MeC_6H_4CHO (**c**)	**10c**	87	98
4	4-MeOC_6H_4CHO (**d**)	**10d**	96	79
5	3-MeOC_6H_4CHO (**e**)	**10e**	89	96
6	3-FC_6H_4CHO (**f**)	**10f**	92	70
7[c]	4-ClC_6H_4CHO (**g**)	**10g**	90	66
8	3-ClC_6H_4CHO (**h**)	**10h**	99	77
9	4-BrC_6H_4CHO (**i**)	**10i**	95	82
10[c]	3-BrC_6H_4CHO (**j**)	**10j**	83	79
11	4-NCC_6H_4CHO (**k**)	**10k**	80	48
12	3,5-$F_2C_6H_3$CHO (**l**)	**10l**	84	60
13[c]	3,5-$Cl_2C_6H_3$CHO (**m**)	**10m**	78	82
14	2-Naphthaldehyde (**n**)	**10n**	84	82
15	Furfural (**o**)	**10o**	99	81

[a] Isolated yield based on loading of original HO-PEG-OH.
[b] Purity determined by HPLC analysis of the crude products.
[c] The reaction time for cycloaddition step was 0.5 h.

sis of **10**. In a preliminary screening of the reaction conditions, simultaneous addition of PEG-supported aldehyde **6**, aniline (**11a**), and Danishefsky's diene **8** in one pot followed by hydrolytic treatment of the reaction product gave the corresponding product **13a** in 50% yield and 63% purity. Interestingly, when the same reaction was performed in a stepwise manner, i.e., **6** was first reacted with 1.1 equivalents of amine **11a** in MeOH at room temperature for 24 hours, followed by the addition of 10 equivalents of the Danishefsky's diene **8** and 0.1 equivalent of $Zn(ClO_4)_2{\cdot}6H_2O$, **13a** could be obtained in significantly higher yield (86%) and better purity (88%). Therefore, the stepwise protocol was adopted for all the aromatic amines in Scheme 3, and the same workup procedure as before was used to afford the target products **13**. The results were summarized in Table 2, and the structures of all products were confirmed by NMR and MS spectra.



Scheme 3 Synthesis of *N*-aryl-2-(4-carboxyphenyl)-substituted 2,3-dihydro-4-pyridones using soluble polymer-supported aldehyde **6** through aza Diels–Alder reaction

Table 2 Liquid-Phase Synthesis of *N*-Aryl-substituted 2-(4-Carboxyphenyl)-2,3-dihydro-4-pyridones by Stepwise Aza Diels–Alder Reaction of PEG-supported Aldehyde **6** with Aromatic Amines and Danishefsky's Diene

Entry	$ArNH_2$ (**11**)	Pyridones (**13**)	Yield (%)[a]	Purity (%)[b]
1	$PhNH_2$ (**a**)	**13a**	86	88
2	4-Me$C_6H_4NH_2$ (**b**)	**13b**	68	96
3	4-MeO$C_6H_4NH_2$ (**c**)	**13c**	71	94
4	4-F$C_6H_4NH_2$ (**d**)	**13d**	77	86
5	4-Cl$C_6H_4NH_2$ (**e**)	**13e**	70	78
6	3-Cl$C_6H_4NH_2$ (**f**)	**13f**	82	67
7	4-Br$C_6H_4NH_2$ (**g**)	**13g**	69	88
8	4-I$C_6H_4NH_2$ (**h**)	**13h**	61	93
9	3,5-$Cl_2C_6H_3NH_2$ (**i**)	**13i**	79	80
10	2-Naphthalenamine (**j**)	**13j**	95	90

[a] Isolated yield based on loading of original HO-PEG-OH.
[b] Purity determined by HPLC analysis of the crude products.

As shown in Table 2, the liquid-phase combinatorial strategy was also well applicable to the library synthesis of **13**, affording in most cases the desired products in moderate to good yields and purities. A variety of aromatic amines were shown to be suitable amino substrates for this synthetic strategy. The substituent effect was not so remarkable as before, with the different aromatic amines giving the corresponding products in nearly same yields and purities. A notable exception is 2-naphthalenamine (entry 10), which afforded the target compound **13j** in excellent yield and purity. The same aza Diels–Alder reaction protocol was also employed for PEG-bound aliphatic amines (such as butylamine, cyclohexylamine or benzylamine) under various experimental conditions, but the conversion to the corresponding PEG-bound products **12** was always unsatisfactory (< 50%).

In conclusion, we have developed a convenient liquid-phase synthetic procedure for 2,3-dihydro-4-pyridones by a one-pot three-component reaction of the soluble polymer (PEG) supported amine, aromatic aldehydes and Danishefsky's diene, or in another way, by a mixed-component reaction of PEG supported aldehyde, aromatic amines and Danishefsky's diene. Moreover, the polymer-bound 2,3-dihydro-4-pyridone may be employed as a useful scaffold for other synthetic transformations.[16]

All anhydrous reactions were conducted under Ar unless otherwise stated. Air and moisture sensitive liquid reagents were added via a dry syringe or oven-dried cannula. Most chemicals were purchased from Acros or Aldrich. The solvents used in the reactions were freshly distilled from drying agent under Ar (THF, Et_2O and toluene were distilled from sodium–benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2). Flash chromatography was performed using silica gel (200–300 Mesh). HPLC analyses were carried out on a Perkin Elmer liquid chromatography with a UV-Vis detector operated at 254 nm. Melting points are uncorrected. IR spectra were recorded on a BIO-RAD FTS-185 Fourier transform spectrometer in KBr pellelts. ^{1}H NMR spectra were measured on a Varian spectrometer (300 MHz) with $CDCl_3$, MeOH-d_4 or DMSO-d_6 as solvent and recorded in ppm. Coupling constants, *J*, are listed in Hz. Mass spectra (ESI) were taken on a HP5989A spectrometer. HRMS data were determined on an IonSpec 4.7 Tesla FTMS operated under the MALDI (Matrix-Assisted Laser Desorption Ionization) mode using DHB (2,5-dihydroxybenzoic acid) as the matrix.

4-*tert*-Butoxycarbonylaminobenzoic Acid (2)

To a mixture of *p*-aminobenzoic acid (**1**) (1.00 g, 7.3 mmol) in dioxane (25 mL) and water (12.5 mL) were added Et_3N (2.04 mL, 14.60 mmol) and *tert*-butyl carbonic anhydride [$(Boc)_2O$] (3.18 g, 14.60 mmol). The reaction mixture was stirred at r.t. for 24 h. Solvent was removed under reduced pressure, and aq HCl acid (3 N, 15 mL) was added dropwise to the residue. The resultant precipitate was filtered, washed with water, dried, and recrystallized from MeOH; yield: 1.7 g (98%); colorless plate crystals; mp 190–192 °C (Lit.[14] 191–192 °C).

IR (KBr): 3370, 2983, 2670, 2546, 1708, 1681, 1610, 1507, 1423, 1411, 1390, 1370, 1312, 1234, 1160, 774, 760, 644 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.59 (s, 1 H), 9.71 (s, 1 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.55 (d, *J* = 8.1 Hz, 1 H), 1.46 (s, 9 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.0, 152.5, 143.7, 130.3, 123.9, 117.2, 79.6, 28.0.

PEG-Supported 4-*tert*-Butoxycarbonylaminobenzoate (3)

To a solution of polyethylene glycol (PEG 3400, 1.7 g, 0.5 mmol) in CH_2Cl_2 (10 mL) were added 4-*tert*-butoxycarbonylaminobenzoic acid (**2**; 0.948 g, 4 mmol), 1,3-dicyclohexylcarbodiimide (DCC, 0.824 g, 4 mmol), and 4-dimethylaminopyridine (DMAP, 0.061 g, 0.5 mmol). The reaction mixture was stirred for 48 h, filtered through a thin pad of Celite to give a clear filtrate. Et_2O was added to the filtrate with vigorous stirring at 0 °C. The resultant precipitate was filtered, washed with Et_2O (3 ×), and dried under vacuum; yield: 1.87 g (97%), white solid.

IR (KBr): 2887, 1720, 1610, 1595, 1537, 1468, 1412, 1361, 1344, 1280, 1242, 1149, 1114, 1060, 964, 842, 771 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.7 Hz, 4 H), 7.49 (d, *J* = 9.0 Hz, 4 H), 4.44–4.48 (m, 4 H), 3.39–3.91 [m, poly(ethylene glycol) peaks], 1.54 (s, 18 H).

PEG-Supported 4-Aminobenzoate (4)

To a solution of PEG-supported 4-*tert*-butoxycarbonyl-aminobenzoate (**3**; 0.3838 g, 0.1 mmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (TFA) (0.5 mL). The reaction mixture was stirred at r.t. for 24 h. The solvent and TFA were removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (1 mL). To the solution was added Et_2O under vigorous stirring at 0 °C, and the resultant precipitate was filtered and washed with Et_2O (3 ×); yield: 0.36 g (>99%); white solid.

IR (KBr): 2887, 1702, 1605, 1520, 1467, 1360, 1344, 1280, 1243, 1149, 1114, 1061, 964, 842, 772 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.7 Hz, 4 H), 6.64 (d, *J* = 9.0 Hz, 4 H), 4.40–4.44 (m, 4 H), 3.40–3.90 [m, poly(ethylene glycol) peaks].

PEG-Supported 4-Formylbenzoate (6)

To a solution of PEG 3400 (10.6 g, 3.1 mmol) in CH_2Cl_2 (60 mL) were added 4-formylbenzoic acid (**5**, 4.7 g, 31.3 mmol), 1,3-dicyclohexylcarbodiimide (DCC, 6.5 g, 31.6 mmol), and 4-dimethylaminopyridine (DMAP, 0.25 g, 2.0 mmol). The reaction mixture was stirred for 48 h. The resultant precipitates were removed by filtration through a thin pad of Celite. Et_2O was added to the filtrate with vigorous stirring at 0 °C. The resultant precipitate was filtered, washed with Et_2O (3 ×), and dried; yield: 11.3 g (>99%); white solid.

IR (KBr): 2887, 1720, 1467, 1361, 1344, 1280, 1243, 1149, 1114, 1061, 964, 842, 761, 734 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.12 (s, 2 H), 8.23 (d, *J* = 8.4 Hz, 4 H), 7.96–7.99 (m, 4 H), 4.51–4.54 (m, 4 H), 3.40–3.91[m, poly(ethylene glycol) peaks].

1-Methoxy-3-trimethylsilyloxybuta-1,3-diene (Danishefsky's diene, 8)

Under Ar, to a flame-dried three-necked flask (1000 mL) containing freshly distilled anhyd Et_3N (151 mL, 1.08 mol) was added $SOCl_2$-treated anhyd $ZnCl_2$ (2.0 g, 14.67 mmol). The resulting mixture was stirred at r.t. for 1 h, and a white slurry formed, to which was successively added a solution of 4-methoxybut-3-en-2-one (53.4 g, 0.532 mmol) in anhyd toluene (80 mL) and freshly distilled trimethylchlorosilane (134 mL, 1.04 mmol). The color of the reaction mixture immediately turned into violet, and the heat released from the exothermic reaction raised the temperature to ca 60 °C. The mixture was cooled to 40 °C and stirred at this temperature overnight before it was cooled to r.t. and extracted with anhyd Et_2O (5 × 200 mL). The combined Et_2O extracts were evaporated, and the residue was fraction-distilled with a Vigreux column under reduced pressure; yield: 59.02g (65%); 94% purity (the major impurity was 4-methoxybut-3-en-2-one); colorless liquid; bp 74–76 °C/20 Torr.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.82 (d, *J* = 12.3 Hz, 1 H), 5.34 (d, *J* = 12.3 Hz, 1 H), 4.08 (d, *J* = 12.6 Hz, 2 H), 3.58 (s, 3 H), 0.24 (s, 9 H).

Synthesis of 1-(4-Carboxyphenyl)-2-aryl-2,3-dihydro-4-pyridone 10 (Table 1); General Procedure

The PEG supported amine **4** [0.23 g, 6.25×10^{-2} mmol, containing NH_2 (0.125 mmol)], aromatic aldehyde **7** (1.25 mmol), $Zn(ClO_4)_2 \cdot 6H_2O$ (4.65 mg, 1.25×10^{-2} mmol) and the Danishefsky's diene **8** (0.40 mL, 94% purity, 1.50 mmol) were added to MeOH (0.5 mL) and the reaction mixture was stirred at r.t. for 12 h. After completion of the reaction, Et_2O (40 mL) was added to allow the precipitation of the PEG-bound product **9**, which was collected by filtration and washed with Et_2O (3 ×). The obtained product **9** was dissolved in aq 0.5 N NaOH solution (2 mL) and stirred at r.t. overnight. The resultant solution was acidified to pH 2–3 using 2 N HCl and the final product **10** was precipitated. After filtration, the collected solids were re-dissolved in small amount of MeOH–acetone (1:1) mixed solvent and the solution was allowed to pass through a short column of silica gel using MeOH–acetone (1:1) as the eluent. The combined filtrate was evaporated under reduced pressure to give the product **10** as a pale yellow solid.

1-(4-Carboxyphenyl)-2-phenyl-2,3-dihydro-4-pyridone (10a)

IR (KBr): 3406, 2930, 1702, 1638, 1610, 1567, 1494, 1411, 1277, 1182, 1108, 1018, 861, 759, 697 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.7 Hz, 2 H), 7.79 (d, *J* = 7.5 Hz, 1 H), 7.25–7.37 (m, 5 H), 7.08 (d, *J* = 8.4 Hz, 2 H), 5.38–5.44 (m, 2 H), 3.33–3.41 (m, 1 H), 2.88 (d, *J* = 16.5 Hz, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.2, 152.3, 145.7, 132.3, 131.3, 130.7, 130.1, 127.6, 126.1, 120.3, 102.4, 62.4, 43.8.

HRMS (MALDI–DHB): *m/z* calcd for $C_{18}H_{16}NO_3$ [M + H$^+$]: 294.1125; found: 294.1127.

1-(4-Carboxyphenyl)-2-(4-methylphenyl)-2,3-dihydro-4-pyridone (10b)

IR (KBr): 3851, 2923, 1710, 1650, 1585, 1568, 1513, 1454, 1409, 1367, 1321, 1280, 1184, 1101, 924, 852, 815, 774, 730, 699 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.05 (d, *J* = 7.5 Hz, 1 H), 7.92 (d, *J* = 9.0 Hz, 2 H), 7.10–7.17 (m, 6 H), 5.47 (d, *J* = 5.4 Hz, 1 H), 5.26 (d, *J* = 7.8 Hz, 1 H), 3.33–3.40 (m, 1 H), 2.67–2.73 (m, 1 H), 2.27 (s, 3 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.9, 170.0, 150.6, 148.9, 138.9, 135.8, 132.3, 130.7, 128.6, 127.2, 118.7, 103.9, 62.0, 44.2, 21.1.

HRMS (MALDI–DHB): *m/z* calcd for $C_{19}H_{18}NO_3$ [M + H$^+$]: 308.1281; found: 308.1285.

1-(4-Carboxyphenyl)-2-(3-methylphenyl)-2,3-dihydro-4-pyridone (10c)

IR (KBr): 2925, 1710, 1650, 1567, 1513, 1411, 1366, 1321, 1220, 1184, 1102, 850, 773, 699 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.13 (d, *J* = 7.8 Hz, 1 H), 7.96 (d, *J* = 9.0 Hz, 2 H), 7.19–7.25 (m, 3 H), 7.07–7.12 (m, 3 H), 5.54 (d, *J* = 5.7 Hz, 1 H), 5.30 (d, *J* = 7.8 Hz, 1 H), 3.34–3.42 (m, 1 H), 2.71–2.77 (m, 1 H), 2.31 (s, 3 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.8, 169.5, 150.5, 149.1, 140.1, 138.9, 132.4, 130.4, 130.0, 129.7, 127.8, 124.3, 118.7, 104.1, 62.1, 44.2, 21.6.

HRMS (MALDI–DHB): *m/z* calcd for $C_{19}H_{18}NO_3$ [M + H$^+$]: 308.1281; found: 308.1277.

1-(4-Carboxyphenyl)-2-(4-methoxyphenyl)-2,3-dihydro-4-pyridone (10d)

IR (KBr): 2927, 2618, 2257, 1701, 1655, 1586, 1569, 1512, 1459, 1411, 1370, 1284, 1253, 1222, 1182, 1100, 1027, 996, 827, 773, 708, 654 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.06 (d, *J* = 7.5 Hz, 1 H), 7.93 (d, *J* = 8.7 Hz, 2 H), 7.18 (m, 4 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 5.48 (d, *J* = 5.1 Hz, 1 H), 5.27 (d, *J* = 7.8 Hz, 1 H), 3.74 (s, 3 H), 3.32 (m, 1 H), 2.67–2.73 (m, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 190.0, 167.2, 158.5, 147.1, 146.8, 130.7, 129.4, 127.3, 116.6, 114.2, 103.3, 69.8, 59.0, 55.0, 43.3.

HRMS (FT–MS): *m/z* [M$^+$] calcd for $C_{19}H_{18}NO_4$: 323.1152; found: 323.1160.

1-(4-Carboxyphenyl)-2-(3-methoxyphenyl)-2,3-dihydro-4-pyridone (10e)

IR (KBr): 3063, 2935, 2617, 1699, 1634, 1583, 1565, 1514, 1489, 1411, 1368, 1287, 1218, 1191, 1097, 1034, 977, 857, 773, 699 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.12–8.14 (m, 1 H), 7.97 (d, *J* = 9.0 Hz, 2 H), 7.21–7.29 (m, 3 H), 6.84–6.89 (m, 3 H), 5.55 (d, *J* = 5.7 Hz, 1 H), 5.30 (d, *J* = 7.5 Hz, 1 H), 3.75 (s, 3 H), 3.34–3.42 (m, 1 H), 2.72–2.78 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.8, 161.7, 150.6, 149.0, 140.6, 132.3, 131.7, 131.3, 121.0, 119.3, 118.7, 114.1, 113.2, 104.0, 62.1, 55.8, 44.1.

HRMS (MALDI–DHB): *m/z* [M + H$^+$] calcd for $C_{19}H_{18}NO_4$: 324.1230; found: 324.1220.

1-(4-Carboxyphenyl)-2-(3-fluorophenyl)-2,3-dihydro-4-pyridone (10f)

IR (KBr): 3073, 1708, 1585, 1569, 1513, 1489, 1447, 1412, 1365, 1322, 1274, 1220, 1186, 1101, 896, 852, 773, 730, 695 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.09 (d, *J* = 7.5 Hz, 1 H), 7.95 (d, *J* = 9.0 Hz, 2 H), 7.32–7.39 (m, 1 H), 6.98–7.18 (m, 5 H), 5.58 (d, *J* = 5.7 Hz, 1 H), 5.30 (d, *J* = 7.8 Hz, 1 H), 3.33–3.41 (m, 1 H), 2.70–2.76 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.4, 170.0, 150.4, 148.7, 142.0, 132.4, 132.1, 132.0, 118.6, 115.9, 115.6, 114.5, 114.2, 104.2, 61.6, 43.9.

HRMS (MALDI–DHB): *m/z* [M + H$^+$] calcd for $C_{18}H_{15}FNO_3$: 312.1031; found: 312.1046.

1-(4-Carboxyphenyl)-2-(4-chlorophenyl)-2,3-dihydro-4-pyridone (10g)

IR (KBr): 2926, 1705, 1650, 1583, 1568, 1513, 1492, 1406, 1321, 1210, 1093, 1014, 925, 826, 773, 701 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.11–8.14 (m, 1 H), 7.97 (d, *J* = 9.0 Hz, 2 H), 7.29–7.38 (m, 4 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 5.60 (d, *J* = 5.4 Hz, 1 H), 5.29–5.32 (m, 1 H), 3.34–3.46 (m, 1 H), 2.70–2.76 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.5, 150.4, 148.8, 137.8, 134.8, 132.4, 130.5, 130.2, 129.1, 118.7, 104.2, 61.5, 44.0.

HRMS (MALDI–DHB): *m/z* [M + H$^+$] calcd for $C_{18}H_{15}ClNO_3$: 328.0735; found: 328.0735.

1-(4-Carboxyphenyl)-2-(3-chlorophenyl)-2,3-dihydro-4-pyridone (10h)

IR (KBr): 2920, 1709, 1651, 1584, 1568, 1513, 1474, 1412, 1364, 1321, 1283, 1205, 1182, 1101, 997, 851, 791, 772, 697, 616 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.10 (d, *J* = 8.1 Hz, 1 H), 7.91–7.98 (m, 2 H), 7.11–7.35 (m, 6 H), 5.57 (d, *J* = 6.0 Hz, 1 H), 5.30 (d, *J* = 7.8 Hz, 1 H), 3.34–3.41 (m, 1 H), 2.69–2.75 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.3, 170.0, 150.4, 148.6, 141.5, 136.0, 132.4, 131.7, 129.2, 128.6, 127.4, 125.8, 118.6, 104.2, 61.6, 43.9.

HRMS (MALDI–DHB): *m/z* [M + H$^+$] calcd for $C_{18}H_{15}ClNO_3$: 328.0735; found: 328.0737.

1-(4-Carboxyphenyl)-2-(4-bromophenyl)-2,3-dihydro-4-pyridone (10i)

IR (KBr): 3065, 2924, 1652, 1581, 1567, 1511, 1488, 1455, 1401, 1364, 1322, 1283, 1220, 1100, 1074, 1010, 993, 970, 821, 784, 702, 659 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.07–8.10 (m, 1 H), 7.94 (d, *J* = 8.7 Hz, 2 H), 7.47–7.52 (m, 2 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 7.14 (d, *J* = 8.7 Hz, 2 H), 5.55 (d, *J* = 4.5 Hz, 1 H), 5.26–5.29 (m, 1 H), 3.33–3.46 (m, 1 H), 2.68–2.75 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.4, 172.2, 151.0, 147.8, 138.4, 133.1, 132.1, 129.4, 122.7, 118.7, 103.6, 61.7, 43.9.

HRMS (MALDI–DHB): *m/z* [M + H$^+$] calcd for $C_{18}H_{15}BrNO_3$: 372.0230; found: 372.0240.

1-(4-Carboxyphenyl)-2-(3-bromophenyl)-2,3-dihydro-4-pyridone (10j)

IR (KBr): 3050, 2910, 1700, 1652, 1582, 1568, 1513, 1473, 1409, 1363, 1320, 1283, 1219, 1205, 1101, 996, 933, 852, 786, 695 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.11 (d, *J* = 7.8 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 2 H), 7.44–7.49 (m, 2 H), 7.16–7.29 (m, 4 H), 5.59 (d, *J* = 5.7 Hz, 1 H), 5.30 (d, *J* = 8.1 Hz, 1 H), 3.33–3.46 (m, 1 H), 2.32–2.35 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.3, 170.5, 150.5, 148.5, 141.7, 132.4, 132.2, 131.8, 130.4, 126.3, 124.0, 118.6, 104.2, 61.5, 43.9.

HRMS (MALDI–DHB): *m/z* [M + H$^+$] calcd for $C_{18}H_{15}BrNO_3$: 372.0230; found: 372.0242.

1-(4-Carboxyphenyl)-2-(4-cyanophenyl)-2,3-dihydro-4-pyridone (10k)

IR (KBr): 3063, 2925, 2854, 2230, 1706, 1604, 1585, 1570, 1513, 1456, 1410, 1365, 1321, 1262, 1207, 1179, 1102, 1018, 929, 835, 773, 699, 649 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.10 (d, *J* = 7.8 Hz, 1 H), 7.95 (d, *J* = 8.7 Hz, 2 H), 7.69 (d, *J* = 8.7 Hz, 2 H), 7.49 (d, *J* = 8.1 Hz, 2 H), 7.13 (d, *J* = 8.7 Hz, 2 H), 5.66 (d, *J* = 6.0 Hz, 1 H), 5.29 (d, *J* = 7.5 Hz, 1 H), 3.36–3.44 (m, 1 H), 2.71–2.80 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.1, 150.3, 148.8, 144.8, 134.0, 132.5, 128.6, 127.8, 119.4, 118.6, 113.0, 104.6, 61.7, 43.6.

HRMS (MALDI–DHB): *m/z* [M + H$^+$] calcd for $C_{19}H_{15}N_2O_3$: 319.1077; found: 319.1094.

1-(4-Carboxyphenyl)-2-(3,5-difluorophenyl)-2,3-dihydro-4-pyridone (10l)

IR (KBr): 3082, 2928, 1670, 1625, 1600, 1515, 1408, 1364, 1320, 1280, 1216, 1187, 1120, 993, 900, 854, 775, 695 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.09 (d, *J* = 8.1 Hz, 1 H), 7.97 (d, *J* = 8.7 Hz, 2 H), 7.16 (d, *J* = 8.7 Hz, 2 H), 6.91–6.96 (m, 3 H), 5.60 (d, *J* = 6.6 Hz, 1 H), 5.30 (d, *J* = 8.1 Hz, 1 H), 3.33–3.44 (m, 1 H), 2.70–2.76 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.5, 170.0, 150.4, 148.8, 137.8, 134.8, 132.4, 130.5, 130.2, 129.1, 118.7, 104.2, 61.5, 44.0.

HRMS (MALDI–DHB): *m/z* [M + H$^+$] calcd for $C_{18}H_{14}F_2NO_3$: 330.0936; found: 330.0933.

1-(4-Carboxyphenyl)-2-(3,5-dichlorophenyl)-2,3-dihydro-4-pyridone (10m)

IR (KBr): 2923, 1710, 1627, 1584, 1565, 1512, 1416, 1364, 1338, 1321, 1285, 1218, 1204, 1102, 931, 852, 799, 713, 631 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.13 (d, *J* = 7.5 Hz, 1 H), 7.99–8.01 (m, 2 H), 7.38 (d, *J* = 0.90 Hz, 1 H), 7.29 (s, 2 H), 7.19–7.21 (m, 2 H), 5.61 (d, *J* = 6.0 Hz, 1 H), 5.33 (d, *J* = 7.8 Hz, 1 H), 3.31–3.43 (m, 1 H), 2.62–2.75 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.1, 169.5, 150.2, 148.7, 143.3, 136.9, 132.6, 129.2, 126.2, 118.6, 104.6, 61.2, 43.6.

HRMS (MALDI–DHB): *m/z* [M + H$^+$] calcd for $C_{18}H_{14}Cl_2NO_3$: 362.0345; found: 362.0359.

1-(4-Carboxyphenyl)-2-(2-naphthalenyl)-2,3-dihydro-4-pyridone (10n)

IR (KBr): 2930, 1706, 1565, 1511, 1411, 1372, 1332, 1262, 1217, 1184, 1100, 1018, 856, 818, 773, 750, 697 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.20 (d, *J* = 7.8 Hz, 1 H), 7.73–7.96 (m, 6 H), 7.43–7.49(m, 3 H), 7.24 (d, *J* = 9.0 Hz, 2 H), 5.73 (d, *J* = 6.3 Hz, 1 H), 5.34 (d, *J* = 7.8 Hz, 1 H), 3.41–3.49 (m, 1 H), 2.84–2.90 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.8, 150.6, 149.2, 136.0, 134.7, 134.3, 132.4, 130.2, 129.0, 128.7, 127.6, 127.4, 126.2, 125.0, 118.7, 104.2, 62.3, 44.0.

HRMS (MALDI–DHB): *m/z* [M + H$^+$] calcd for $C_{22}H_{18}NO_3$: 344.1281; found: 344.1281.

1-(4-Carboxyphenyl)-2-(2-furanyl)-2,3-dihydro-4-pyridone (10o)

IR (KBr): 3404, 2920, 1702, 1639, 1604, 1567, 1514, 1390, 1220, 1178, 1105, 1017, 854, 775, 700 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.01 (d, *J* = 9.0 Hz, 2 H), 7.81 (d, *J* = 7.8 Hz, 1 H), 7.46 (d, *J* = 0.9 Hz, 1 H), 7.32 (d, *J* = 9.0 Hz, 2 H), 6.34–6.36 (m, 1 H), 6.25–6.26 (m, 1 H), 5.60 (d, *J* = 6.0 Hz, 1 H), 5.23–5.26 (m, 1 H), 3.20–3.28 (m, 1 H), 2.78–2.85 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 194.0, 171.5, 160.9, 151.0, 148.4, 132.1, 131.6, 130.8, 128.6, 118.9, 115.4, 103.4, 61.9, 44.3.

HRMS (MALDI–DHB): *m/z* [M + H$^+$] calcd for $C_{16}H_{14}NO_4$: 294.0917; found: 284.0929.

Synthesis of 1-Aryl-2-(4-carboxyphenyl)-2,3-dihydro-4-pyridone 13 (Table 2); General Procedure

To the solution of PEG supported aldehyde **6** [0.23 g, 6.25×10^{-2} mmol, containing CHO (0.125 mmol)] in MeOH (0.5 mL), was added aromatic amines **11** (0.1375 mmol). The reaction mixture was stirred at r.t. for 24 h before $Zn(ClO_4)_2 \cdot 6H_2O$ (4.65 mg, 1.25×10^{-2} mmol) and the Danishefsky's diene **8** (0.27 mL, 94% purity, 1.25 mmol) were added. The mixture was stirred for additional 2 h. After completion of the reaction, Et_2O (40 mL) was added to allow the precipitation of the PEG-bound product **12**, which was collected by filtration and washed with Et_2O (3 ×). The crude product **12** was dissolved in an aq 0.5 N NaOH solution (2 mL) and stirred at r.t. overnight. Then, the solution was acidified to pH 2–3 using 2 N HCl and the final product **13** was precipitated. After filtration, the collected solids were redissolved in small amount of MeOH–acetone (1:1) mixed solvent and the solution was allowed to pass through a short column of silica gel with MeOH–acetone (1:1–3:1) as the eluent to give the product **13** as a pale yellow solid.

1-Phenyl-2-(4-carboxyphenyl)-2,3-dihydro-4-pyridone (13a)

IR (KBr): 3406, 2926, 1710, 1637, 1566, 1494, 1412, 1363, 1322, 1279, 1222, 1108, 1018, 972, 855, 758, 695 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.96–8.03 (m, 3 H), 7.42 (d, *J* = 8.1 Hz, 2 H), 7.29–7.34 (m, 2 H), 7.10–7.15 (m, 3 H), 5.57 (d, *J* = 4.8 Hz, 1 H), 5.24 (d, *J* = 7.5 Hz, 1 H), 3.33–3.51 (m, 1 H), 2.70–2.76 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.2, 170.0, 152.4, 145.6, 144.6, 132.0, 131.4, 130.7, 127.7, 126.1, 120.3, 102.4, 62.4, 43.8.

HRMS (MALDI–DHB): *m/z* [M + H$^+$] calcd for $C_{18}H_{16}NO_3$: 294.1125; found: 294.1103.

1-(4-Methylphenyl)-2-(4-carboxyphenyl)-2,3-dihydro-4-pyridone (13b)

IR (KBr): 3398, 2924, 2619, 1714, 1636, 1612, 1565, 1511, 1411, 1328, 1276, 1208, 1180, 1108, 1018, 972, 813, 735, 657 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.96–7.99 (m, 3 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 7.04 (d, *J* = 8.7 Hz, 2 H), 5.52–5.55 (m, 1 H), 5.21 (d, *J* = 7.8 Hz, 1 H), 3.31–3.39 (m, 1 H), 2.69–2.75 (m, 1 H), 2.27 (s, 3 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.0, 170.0, 152.7, 144.7, 143.3, 136.3, 132.1, 131.3, 131.1, 127.7, 120.6, 101.8, 62.5, 43.7, 20.7.

HRMS (MALDI–DHB): *m/z* [M + H$^+$] calcd for $C_{19}H_{18}NO_3$: 308.1281; found: 308.1285.

1-(4-Methoxyphenyl)-2-(4-carboxyphenyl)-2,3-dihydro-4-pyridone (13c)

IR (KBr): 2927, 1712, 1612, 1561, 1510, 1412, 1328, 1285, 1250, 1222, 1180, 1109, 1031, 971, 829, 772, 654 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.97 (d, *J* = 8.4 Hz, 2 H), 7.87 (d, *J* = 6.9 Hz, 1 H), 7.43 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 9.0 Hz, 2 H), 5.47–5.50 (m, 1 H), 5.18 (d, *J* = 7.8 Hz, 1 H), 3.73 (s, 3 H), 3.31–3.37 (m, 1 H), 2.68–2.75 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 192.9, 170.0, 159.0, 153.6, 144.8, 139.1, 131.3, 127.8, 122.9, 115.8, 101.0, 63.1, 56.0, 43.7.

HRMS (MALDI–DHB): *m*/*z* [M + H$^+$] calcd for $C_{19}H_{18}NO_4$: 324.1230; found: 324.1241.

1-(4-Fluorophenyl)-2-(4-carboxyphenyl)-2,3-dihydro-4-pyridone (13d)

IR (KBr): 3396, 2922, 1713, 1644, 1611, 1567, 1508, 1412, 1322, 1276, 1218, 1158, 1108, 1017, 972, 834, 771, 628 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.92–8.00 (m, 3 H), 7.44 (d, *J* = 8.1 Hz, 2 H), 7.16–7.20 (m, 2 H), 7.03–7.09 (m, 2 H), 5.52–5.56 (m, 1 H), 5.23 (d, *J* = 7.8 Hz, 1 H), 3.31–3.39 (m, 1 H), 2.70–2.77 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.1, 170.5, 163.1, 152.9, 144.3, 142.2, 131.4, 127.7, 122.9, 122.8, 117.3, 117.0, 102.2, 62.9, 43.9.

HRMS (MALDI–DHB): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{15}FNO_3$: 312.1030; found: 312.1036.

1-(4-Chlorophenyl)-2-(4-carboxyphenyl)-2,3-dihydro-4-pyridone (13e)

IR (KBr): 2927, 1714, 1636, 1567, 1494, 1409, 1322, 1222, 1181, 1097, 1012, 971, 823, 754, 703 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.97–8.00 (m, 3 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.29–7.33 (m, 2 H), 7.12 (d, *J* = 9.3 Hz, 2 H), 5.54–5.58 (m, 1 H), 5.25 (d, *J* = 7.8 Hz, 1 H), 3.31–3.41 (m, 1 H), 2.71–2.78 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.1, 169.5, 151.7, 144.4, 131.4, 131.2, 130.6, 127.7, 121.7, 103.0, 62.4, 43.8.

HRMS (MALDI–DHB): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{15}ClNO_3$: 328.0735; found: 328.0730.

1-(3-Chlorophenyl)-2-(4-carboxyphenyl)-2,3-dihydro-4-pyridone (13f)

IR (KBr): 3399, 2924, 1714, 1636, 1612, 1581, 1565, 1482, 1413, 1363, 1319, 1220, 1102, 1042, 978, 855, 776, 686 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.99–8.04 (m, 3 H), 7.43 (d, *J* = 8.7 Hz, 2 H), 7.27–7.32 (m, 1 H), 7.14 (t, *J* = 0.9 Hz, 1 H), 7.05–7.12 (m, 2 H), 5.58–5.62 (m, 1 H), 5.27 (d, *J* = 7.8 Hz, 1 H), 3.31–3.42 (m, 1 H), 2.72–2.78 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.3, 169.6, 151.4, 146.8, 144.2, 136.3, 131.9, 131.4, 127.6, 125.7, 120.1, 118.3, 103.5, 62.2, 43.9.

HRMS (MALDI–DHB): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{15}ClNO_3$: 328.0735; found: 328.0734.

1-(4-Bromophenyl)-2-(4-carboxyphenyl)-2,3-dihydro-4-pyridone (13g)

IR (KBr): 3397, 2924, 1714, 1595, 1565, 1491, 1405, 1321, 1220, 1108, 1077, 929, 820, 745, 605 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.94–8.00 (m, 3 H), 7.41–7.47 (m, 4 H), 7.06 (d, *J* = 9.0 Hz, 2 H), 5.55 (d, *J* = 7.5 Hz, 1 H), 5.26 (d, *J* = 7.5 Hz, 1 H), 3.31–3.41 (m, 1 H), 2.71–2.77 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.2, 169.7, 151.6, 144.8, 144.3, 133.6, 132.1, 131.4, 127.6, 121.9, 118.7, 103.1, 62.3, 43.8.

HRMS (MALDI–DHB): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{15}BrNO_3$: 372.0230; found: 372.0224.

1-(4-Iodophenyl)-2-(4-carboxyphenyl)-2,3-dihydro-4-pyridone (13h)

IR (KBr): 3413, 2924, 1710, 1639, 1593, 1562, 1488, 1363, 1322, 1208, 1106, 1005, 928, 814, 700 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.98–8.02 (m, 3 H), 7.64 (d, *J* = 8.7 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 6.94 (d, *J* = 9.0 Hz, 2 H), 5.56–5.57 (m, 1 H), 5.26 (d, *J* = 7.8 Hz, 1 H), 3.31–3.42 (m, 1 H), 2.71–2.77 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.2, 170.0, 151.4, 145.4, 144.1, 139.7, 131.4, 127.6, 122.0, 103.2, 89.0, 62.2, 43.8.

HRMS (MALDI–DHB): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{15}INO_3$: 420.0091; found: 420.0112.

1-(3,5-Dichlorophenyl)-2-(4-carboxyphenyl)-2,3-dihydro-4-pyridone (13i)

IR (KBr): 2924, 2854, 1716, 1630, 1563, 1468, 1392, 1311, 1286, 1208, 1096, 909, 816, 778, 646 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.99 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 7.8 Hz, 1 H), 7.45–7.51 (m, 1 H), 7.34–7.40 (m, 3 H), 7.15–7.18 (m, 1 H), 5.05 (d, *J* = 7.8 Hz, 1 H), 4.73–4.77 (m, 1 H), 2.94–3.02 (m, 1 H), 2.56–2.63 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.8, 155.9, 144.4, 143.7, 134.4, 132.8, 131.2, 130.8, 130.0, 129.7, 128.7, 101.6, 64.3, 44.5.

HRMS (MALDI–DHB): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{14}Cl_2NO_3$: 362.0345; found: 362.0329.

1-(2-Naphthalenyl)-2-(4-carboxyphenyl)-2,3-dihydro-4-pyridone (13j)

IR (KBr): 2924, 1714, 1630, 1583, 1508, 1470, 1411, 1367, 1312, 1282, 1190, 1104, 1018, 980, 852, 733, 674 cm^{-1}.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.15 (d, *J* = 7.5 Hz, 1 H), 7.99 (d, *J* = 8.1 Hz, 2 H), 7.72–7.85 (m, 3 H), 7.34–7.56 (m, 6 H), 5.72 (d, *J* = 4.2 Hz, 1 H), 5.30 (d, *J* = 7.5 Hz, 1 H), 3.39–3.47 (m, 1 H), 2.76–2.82 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 193.1, 169.3, 152.2, 144.6, 143.0, 135.1, 132.2, 131.8, 131.4, 130.8, 128.7, 128.6, 128.2, 127.7, 126.7, 119.7, 117.2, 102.8, 62.4, 43.8.

HRMS (MALDI–DHB): *m*/*z* [M + H$^+$] calcd for $C_{22}H_{18}NO_3$: 344.1281; found: 344.1267.

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