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Solvent-free protocol for the green synthesis of benzamide analogs of dibenzoazepine

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ABSTRACT

Dibenzoazepine represents an important class of heterocycles, exhibiting potent antidepressant and anticonvulsant activities. Beside, various modifications on this nucleus, amide analogs at *N*-5 position showed potent antidepressant activities. A previously reported method for the synthesis of benzamide analogs of dibenzoazepine use hazardous and toxic solvents. Herein, we report a new, efficient and solvent-free green method for the synthesis of dibenzoazepine benzamides (6-21).

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1. Introduction

Dibenzoazepine (**1**) (Figure 1) represents an important class of nitrogen containing benzo fused heterocycles that are particularly known for antidepressant and anticonvulsant therapies [1-3]. Carbamazpeine (**2**) (Figure 1), commonly marketed under the trade name of Tegretol®, is urea analog of compound **1** and used for the treatment of neuropathic pain, seizures, and trigeminal neuralgia [4,5]. Modification of double bond at C-10, and C-11 position to ketone moiety resulted in oxcarbazepine (**3**) (Figure 1), which is not only effective against epilepsy, but also used for the treatment of Parkinson's disease, and AIDS-related CNS disorders [6]. In addition, a number of other biological activities were also reported in the literature for dibenzazepine analogs, including antileishmanial, antioxidant, anti-inflammatory, antihistaminic, antiallergic, fungicidal, cardioselective anti-muscarinic, and anti-tumor activities, as well as acts as NMDA channel blockers, dopamine agonists, topoisomerase, and dihydrofolate reductase inhibitors [7-13].

Various modifications have been done on dibenzoazepine nucleus, but urea formation at *N*-5 of compound **1** showed promising CNS-related activities, such as for major marketed drugs **2** and **3** [4-6]. Moreover, in 2009 Balaure *et al.* documented heterocyclic analogs of dibenzoazepine urea **4**-**5** (Figure 1), which were found to be potent psycologically active compounds [14].

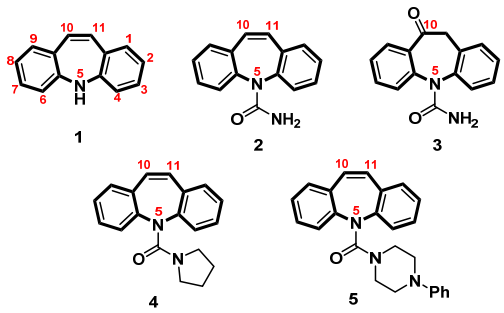

Figure 1. Dibenzoazepine **1** and its biologically potent analogs **2**-**5**.

Previously Martinez group reported a library of benzamide analogs of dibenzazepine [15], which were found to exhibit antidepressant as well as tranquilizer activity.

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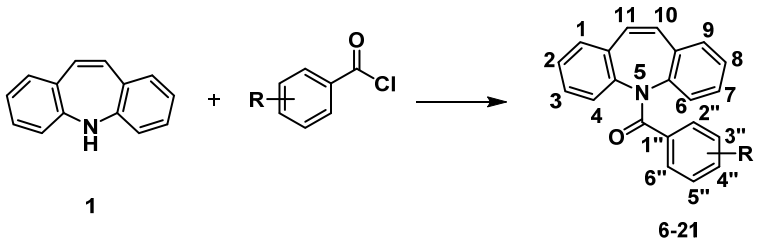

1 6-21

Martinez *et al.* Method [15] : NaH, C_6H_6, reflux, 4.25 h, 34-39%
Our Method : NEt_3, 120 °C, 0.3 h, 40-98%

Compound	R	Compound	R
6	H	14	3″-OMe
7	2″-F	15	4″-OMe
8	4″-F	16	3″-NO_2
9	2″-Cl	17	4″-NO_2
10	4″-Cl	18	2″,6″-di-F
11	2″-Br	19	3″-NO_2-4″-Cl
12	4″-Br	20	3″-NO_2-4″-Me
13	4″-Me	21	3″,4″,5″-tri-OMe

Scheme 1

These compounds were synthesized by sodium hydride catalyzed amidation of compound **1** with different substituted benzoyl chlorides using benzene as a solvent (Scheme 1). Disadvantages, such as low yields and tedious chemical synthesis, decrease utility of this method.

Most of organic reactions are carried out in solutions using toxic, flammable, and hazardous solvents. Solvent-free protocol is considered as one of the eco-friendly alternates to replace hazardous solvents. This method prompted us to explore new green methodology for the synthesis of previously reported antiepileptic dibenzoazepine benzamides under solvent-free conditions.

2. Experimental

2.1. Instrumentation

Dibenzoazepine and all other starting materials were purchased from Sigma-Aldrich, and used without purification. The progress of reactions was monitored by using silica gel pre-coated aluminum TLC plates (Kieselgel 60, 254, E. Merck, Germany). The chromatograms were visualized under ultraviolet light (254 nm) and vanillin dips. The silica gel 60, E. Merck was used for column chromatography. ^{1}H NMR spectra were obtained on Bruker 500 and 600 MHz spectrometers. EI-MS was obtained on JEOL MS Route 600 H spectrometer. HR-EIMS was recorded on Thermo Finnigan MAT 95XP instrument.

2.2. Synthesis

2.2.1. Diisopropylethyl amine (DIPEA) catalyzed amide synthesis of (5′H-dibenzo[b,f]azepin-5′-yl)(4″-nitrophenyl) methanone (17)

To a solution of dibenzoazepine (1.0 mmol) in tetrahydro furan (THF), *p*-nitrobenzoyl chloride (1.4 mmol) was added followed by slow addition of DIPEA (1.4 mmol) at 0 °C. After that, the reaction mixture was refluxed for 4 h, diluted with distilled water and extracted with ethyl acetate (2×20 mL). The combined organic layers were dried over $MgSO_4$ (anhydrous), filtered, concentrated, and purified by column chromatography (10-20% ethyl acetate in hexanes as an eluent) to afford compound **17** in 80% yield (Table 1).

2.2.2. Triethylamine (NEt_3) catalyzed amide synthesis of (5′H-dibenzo[b,f]azepin-5′-yl)(4″-nitrophenyl)methanone (17)

To a solution of dibenzoazepine (1.0 mmol) in dichloro methane (DCM), *p*-nitrobenzoyl chloride (3.4 mmol) was added. At 0 °C, NEt_3 (1.2 mmol) was added dropwise, and the reaction mixture was allowed to stir for 1.8 h at room temperature. Upon completion, the reaction mixture was diluted with distilled water, and extracted with ethyl acetate (2×20 mL). The combined organic layers were dried (anhydrous $MgSO_4$), filtered, and evaporated to dryness. The crude mixture was purified by silica gel column chromatography using 10-20% ethyl acetate in hexanes to get pure benzamide **17** in 93% yield (Table 1).

2.2.3. Sodium bicarbonate ($NaHCO_3$) catalyzed solvent-free synthesis of (5′H-dibenzo[b,f]azepin-5′-yl)(4″-nitrophenyl) methanone (17)

Round bottomed flask was charged with dibenzoazepine (1.0 mmol) and $NaHCO_3$ (2.0 mmol), followed by the addition of *p*-nitrobenzoyl chloride (1.5 mmol) at 0 °C. The reaction mixture was then heated at 140 °C for 30 min. After completion of reaction, it is cooled to room temperature, diluted with distilled water, and extracted with ethyl acetate (2×20 mL). The combined organic layers were dried over $MgSO_4$ (anhydrous), filtered, concentrated, and purified by column chromatography (10-20% ethyl acetate in hexanes as an eluent) to obtain compound **17** in 60% yield (Table 1).

2.2.4. NEt_3 catalyzed solvent-free synthesis of dibenzoazepine benzamides (6-21)

To a suspension of dibenzoazepine (1 mmol) in NEt_3 (1.5 mmol), substituted benzoyl chloride (1.5 mmol) was added at 0 °C, and heated neat at 120 °C for 20 min. Upon complete consumption of starting material, the reaction mixture was cooled to room temperature, diluted with distilled water, and extracted with ethyl acetate (2×20 mL). The organic layers were then washed with saturated solution of $NaHCO_3$. The combined organic layers were dried (anhydrous $MgSO_4$), filtered, and evaporated to dryness. The crude mixture was purified by silica gel column chromatography using 10-20% ethyl acetate in hexanes to afford dibenzoazepine benzamides in 40-98% yields (Scheme 1).

Table 1. Optimization of (5'*H*-dibenzo[b,f]azepin-5'-yl)(4"-nitrophenyl)methanone (**17**).

Entry	Base	Equivalence of 1: benzoyl chloride: base	Solvent	Temp (°C)	Time (h)	Yield (%)
1	DIPEA	1:1.4:1.4	THF	50	4.0	80
2	NEt_3	1:3.4:1.2	DCM	25	1.8	93
3	$NaHCO_3$	1:1.5:2	-	140	0.5	60
4	NEt_3	1:1:1.5	-	25	24.0	Traces
5	NEt_3	1:1:1.5	-	50	24.0	54
6	NEt_3	1:1:1.5	-	100	2.0	76
7	NEt_3	1:1:1.5	-	120	0.3	82
8	**NEt_3**	**1:1.5:1.5**	**-**	**120**	**0.3**	**98**

(5'H-Dibenzo[b, f]azepin-5'-yl)(phenyl)methanone (**6**): Color: Off white. Yield: 90%. FT-IR (KBr, ν, cm^{-1}): 3024, 1657 (C=O) (amide), 1562 (C=C), 1491, 1445 (C=C), 1344 (C-N). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.70-7.30 (m, 8H, H-1′, H-2′, H-3′, H-4′, H-6′, H-7′, H-8′, H-9′), 7.25 (app t, 1H, $J_{4'',(3'',5'')}$ = 7.5 Hz, H-4″), 7.20-7.18 (m, 4H, H-3″, H-5″, H-10′, H-11′), 7.14 (d, 2H, $J_{2'',3''/6'',5''}$ = 8.5 Hz, H-2″, H-6″). MS (EI, *m/z* (%)): 297 (M^+, 46). HRMS (EI, *m/z*) calcd. for $C_{21}H_{15}ON$, 297.1154; found 297.1159.

(5'H-Dibenzo[b, f]azepin-5'-yl)(2"-fluorophenyl)methanone (**7**): Color: Light yellow. Yield: 90%. FT-IR (KBr, ν, cm^{-1}): 2926, 2856, 1666 (C=O) (amide), 1616 (C=C), 1491 (C=C), 1352 (C-N). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.62 (d, 1H, $J_{4',3'}$ = 8.0 Hz, H-4′), 7.55-7.52 (m, 2H, H-1′, H-9′), 7.59-7.45 (t, 1H, $J_{3',(2',4')}$ = 7.5 Hz, H-3′), 7.38 (d, 1H, $J_{6',7'}$ = 7.0 Hz, H-6′), 7.28-7.23 (m, 2H, H-4″, H-6″), 7.20-7.01 (m, 7H, H-3″, H-5″, H-2′, H-7′, H-8′, H-10', H-11′). MS (EI, *m/z* (%)): 315 (M^+, 27). HRMS (EI, *m/z*) calcd. for $C_{21}H_{14}FON$, 315.1059; found 315.1061.

(5'H-Dibenzo[b, f]azepin-5'-yl)(4"-fluorophenyl)methanone (**8**): Color: White. Yield: 71%. FT-IR (KBr, ν, cm^{-1}): 3063, 1657 (C=O) (amide), 1601 (C=C), 1497 (C=C), 1342 (C-N), 1229. ^1H NMR (600 MHz, DMSO-d_6, δ, ppm): 7.48-7.17 (m, 12H, H-2″, H-6″, H-1′, H-2′, H-3′, H-4′, H-6′, H-7′, H-8′, H-9′, H-10′, H-11′), 7.04 (t, 2H, $J_{3'',(2'',F)/5'',(6'',F)}$ = 8.8 Hz, H-3″, H-5″). MS (EI, *m/z* (%)): 315 (M^+, 99). HRMS (EI, *m/z*) calcd. for $C_{21}H_{14}FON$, 315.1059; found 315.1056.

(2"-Chlorophenyl)(5'H-dibenzo[b, f]azepin-5'-yl)methanone (**9**): Color: Off white. Yield: 81%. FT-IR (KBr, ν, cm^{-1}):3022, 1659 (C=O) (amide), 1595 (C=C), 1489 (C=C), 1344 (C-N). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.59-7.54 (m, 3H, H-4′, H-3″, H-4″), 7.43 (t, 1H, $J_{5'',(4'',6'')}$ = 8.0 Hz, H-5″), 7.38-7.31 (m, 3H, H-1′, H-9′, H-6″), 7.36-7.09 (m, 7H, H-2′, H-3′, H-6′, H-7′, H-8′, H-10′, H-11′). MS (EI, *m/z* (%)): 331 (M^+, 42). HRMS (EI, *m/z*) calcd. for $C_{21}H_{14}ClON$, 331.0764; found 331.0773.

(4"-Chlorophenyl)(5'H-dibenzo[b, f]azepin-5'-yl)methanone (**10**): Color: Off white. Yield: 73%. FT-IR (KBr, ν, cm^{-1}):3434, 1670 (C=O) (amide), 1624 (C=C), 1466 (C=C), 1354 (C-N). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.70-7.30 (m, 8H, H-1′, H-2′, H-3′, H-4′, H-6′, H-7′, H-8′, H-9′), 7.29 (d, 2H, $J_{2'',3''/6'',5''}$ = 8.5 Hz, H-2″, H-6″), 7.17 (s, 2H, H-10′, H-11′), 7.15 (d, 2H, $J_{3'',2''/5'',6''}$ = 8.5 Hz, H-3″, H-5″). MS (EI, *m/z* (%)): 331 (M^+, 22). HRMS (EI, *m/z*) calcd. for $C_{21}H_{14}ClON$, 331.0764; found 331.0772.

(2"-Bromophenyl)(5'H-dibenzo[b, f]azepin-5'-yl)methanone (**11**): Color: Brown. Yield: 72%. FT-IR (KBr, ν, cm^{-1}): 3059, 3022, 1657 (C=O) (amide), 1591 (C=C), 1489 (C=C), 1344 (C-N). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.57-7.43 (m, 6H, H-1′, H-4′, H-9′, H-4″, H-5″, H-6″), 7.39 (d, 1H, $J_{3'',2''}$ = 6.5 Hz, H-3″), 7.29 (d, 1H, $J_{6',5'}$ = 7.5 Hz, H-6′), 7.20-7.10 (m, 6H, H-2′, H-3′, H-7′, H-8′, H-10′, H-11′). MS (EI, *m/z* (%)): 377 (M^++2, 41), 375 (M^+, 41). HRMS (EI, *m/z*) calcd. for $C_{21}H_{14}BrON$, 375.0259; found 375.0267.

(4"-Bromophenyl)(5'H-dibenzo[b, f]azepin-5'-yl)methanone (**12**): Color: Light yellow. Yield: 80%. FT-IR (KBr, ν, cm^{-1}): 3059, 3020, 1659 (C=O) (amide), 1591 (C=C), 1489 (C=C), 1344 (C-N). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.77-7.17 (m, 12H, H-1′, H-2′, H-3′, H-4′, H-6′, H-7′, H-8′, H-9′, H-10′, H-11′, H-2″, H-6″), 7.08 (d, 2H, $J_{3'',2''/5'',6''}$ = 8.0 Hz, H-3″, H-5″). MS (EI, *m/z* (%)): 377 (M^++2, 53), 375 (M^+, 56). HRMS (EI, *m/z*) calcd. for $C_{21}H_{14}BrON$, 375.0259; found 375.0263.

(5'H-Dibenzo[b, f]azepin-5'-yl)(p-tolyl)methanone (**13**): Color: White. Yield: 78%. FT-IR (KBr, ν, cm^{-1}): 1657 (C=O) (amide), 1611 (C=C), 1491 (C=C), 1340 (C-N). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.46-7.20 (m, 8H, H-1′, H-2′, H-3′, H-4′, H-6′, H-7′, H-8′, H-9′), 7.17 (s, 2H, H-10′, H-11′), 7.03 (d, 2H, $J_{3'',2''/5'',6''}$ = 8.1 Hz, H-3″, H-5″), 6.99 (d, 2H, $J_{2'',3''/6'',5''}$ = 8.0 Hz, H-2″, H-6″), 2.19 (s, 3H, CH_3). MS (EI, *m/z* (%)): 311 (M^+, 40). HRMS (EI, *m/z*) calcd. for $C_{22}H_{17}ON$, 311.1310; found 311.1320.

(5'H-Dibenzo[b, f]azepin-5'-yl)(3"-methoxyphenyl)methanone (**14**): Color: White. Yield: 82%. FT-IR (KBr, ν, cm^{-1}): 1655 (C=O) (amide), 1578 (C=C), 1491 (C=C), 1340 (C-N), 1254 (C-O). ^1H NMR (600 MHz, DMSO-d_6, δ, ppm): 7.70-7.20 (m, 8H, H-1′, H-2′, H-3′, H-4′, H-6′, H-7′, H-8′, H-9′), 7.18 (s, 2H, H-10′, H-11′), 7.10 (t, 1H, $J_{5'',(4'',6'')}$ = 7.9 Hz, H-5″), 6.80 (dd, 1H, $J_{4'',3''}$ = 8.3 Hz, $J_{4'',5''}$ = 2.5 Hz, H-4″), 6.72 (d, 1H, $J_{4'',3''}$ = 7.7 Hz, H-6″), 6.67 (s, 1H, H-2″), 3.60 (s, 3H, OCH_3). MS (EI, *m/z* (%)): 327 (M^+, 52). HRMS (EI, *m/z*) calcd. for $C_{22}H_{17}O_2N$, 327.1259; found 327.1257.

(5'H-Dibenzo[b, f]azepin-5'-yl)(4"-methoxyphenyl)methanone (**15**): Color: White. Yield: 79%. FT-IR (KBr, ν, cm^{-1}): 1651 (C=O) (amide), 1605 (C=C), 1499 (C=C), 1339 (C-N), 1252 (C-O). ^1H NMR (600 MHz, DMSO-d_6, δ, ppm): 7.48-7.20 (m, 8H, H-1′, H-2′, H-3′, H-4′, H-6′, H-7′, H-8′, H-9′), 7.17 (s, 2H, H-10′, H-11′), 7.09 (d, 2H, $J_{3'',2''/5'',6''}$ = 8.7 Hz, H-3″, H-5″), 6.73 (d, 2H, $J_{2'',3''/6'',5''}$ = 8.7 Hz, H-2″, H-6″), 3.68 (s, 3H, OCH_3). MS (EI, *m/z* (%)): 327 (M^+, 25). HRMS (EI, *m/z*) calcd. for $C_{22}H_{17}O_2N$, 327.1259; found 327.1255.

(5'H-Dibenzo[b, f]azepin-5'-yl)(3"-nitrophenyl)methanone (**16**): Color: White. Yield: 80%. FT-IR (KBr, ν, cm^{-1}): 1663 (C=O) (amide), 1601 (C=C), 1522 (N-O) (nitro), 1491 (C=C), 1342 (C-N). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 8.13-8.11 (m, 1H, H-4′), 8.01 (s, 1H, H-2″), 7.78-7.10 (m, 12H, H-1′, H-2′, H-3′, H-6′, H-7′, H-8′, H-9′, H-10′, H-11′, H-4″, H-5″, H-6″). MS (EI, *m/z* (%)): 342 (M^+, 95). HRMS (EI, *m/z*) calcd. for $C_{21}H_{14}O_3N_2$, 342.1004; found 342.1000.

(5'H-Dibenzo[b, f]azepin-5'-yl)(4"-nitrophenyl)methanone (**17**): Color: Yellow. Yield: 98%. FT-IR (KBr, ν, cm^{-1}): 1661 (C=O) (amide), 1601 (C=C), 1520 (N-O) (nitro), 1491 (C=C), 1340 (C-N). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 8.08 (d, 2H, $J_{3'',2''/5'',6''}$ = 8.7 Hz, H-3″, H-5″), 7.71 (d, 1H, $J_{4',5'}$ = 8.0 Hz, H-4′), 7.55 (d, 2H, $J_{1',2'/9',8'}$ = 5.0 Hz, H-1′, H-9′), 7.42 (m, 4H, H-3′, H-7′, H-2″, H-6″), 7.67 (m, 5H, H-2′, H-6′, H-8′, H-10′, H-11′). MS (EI, *m/z* (%)): 342 (M^+, 42). HRMS (EI, *m/z*) calcd. for $C_{21}H_{14}O_3N_2$, 342.1004; found 342.1001.

(5'H-Dibenzo[b, f]azepin-5'-yl)(2",6"-difluorophenyl)methanone (**18**): Color: White. Yield: 96%. FT-IR (KBr, ν, cm^{-1}): 3024, 2878, 1672 (C=O) (amide), 1624 (C=C), 1593, 1491 (C=C), 1466, 1356 (C-N). ^1H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.57-7.52 (m, 3H, H-1′, H-4′, H-9′), 7.44 (td, 1H, $J_{3',(2',4')}$ = 9.0 Hz, $J_{3',1'}$ = 2.0 Hz, H-3′), 7.42 (d, 1H, $J_{7',6'}$ = 8.0 Hz, H-7′), 7.37-7.31 (m, 1H, H-6″), 7.26-7.21 (m, 3H, H-2′, H-10′, H-11′), 7.15-7.06 (m, 3H, H-6′, H-3″, H-5″), 6.83 (t, 1H, $J_{8',(7',9')}$ = 8.5 Hz, H-8′). MS (EI, *m/z* (%)): 333 (M^+, 24). HRMS (EI, *m/z*) calcd. for $C_{21}H_{13}F_2ON$, 333.0965; found 333.0978.

(4"-Chloro-3"-nitrophenyl)(5'H-dibenzo[b, f]azepin-5'-yl) methanone (**19**): Color: Off white. Yield: 91%. FT-IR (KBr, ν, cm^{-1}): 3026, 2928, 2856, 1662 (C=O) (amide), 1603 (C=C), 1535 (N-O) (nitro), 1491 (C=C), 1348 (C-N).

Table 2. Synthesis of benzamide analogs of dibenzoazepine (**6**-**21**).

Entry	Compound	R	Yield (%)	Entry	Compound	R	Yield (%)
1	6	H	90	9	14	3″-OMe	82
2	7	2″-F	72	10	15	4″-OMe	79
3	8	4″-F	71	11	16	3″-NO_2	80
4	9	2″-Cl	81	12	17	4″-NO_2	98
5	10	4″-Cl	73	13	18	2″,6″-di-F	96
6	11	2″-Br	72	14	19	3″-NO_2-4″-Cl	91
7	12	4″-Br	80	15	20	3″-NO_2-4″-Me	75
8	13	4″-Me	78	16	21	3″,4″,5″-tri-OMe	40

^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.89 (d, 1H, $J_{2'',6''}$ = 1.5 Hz, H-2″), 7.69 (d, 1H, $J_{4',5'}$ = 9.0 Hz, H-4′), 7.64 (d, 1H, $J_{6'',5''}$ = 1.5 Hz, H-6″), 7.78-7.39 (m, 4H, H-1′, H-3′, H-7′, H-9′), 7.33-7.29 (m, 3H, H-2′, H-8′, H-5″), 7.25-7.12 (m, 3H, H-6′, H-10′, H-11′). MS (EI, *m/z* (%)): 376 (M^+, 10). HRMS (EI, *m/z*) calcd. for $C_{21}H_{13}ClO_3N_2$, 376.0615; found 376.0624.

5′H-Dibenzo[b, f]azepin-5′-yl)(4″-methyl-3″-nitrophenyl)methanone (**20**): Color: White. Yield: 75%. FT-IR (KBr, ν, cm^{-1}): 1657 (C=O) (amide), 1622 (C=C), 1528 (N-O) (nitro), 1493 (C=C), 1344 (C-N). ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.78 (s, 1H, H-2″), 7.68-7.20 (m, 12H, H-1′, H-2′, H-3′, H-4′, H-6′, H-7′, H-8′, H-9′, H-10′, H-11′, H-5″, H-6″), 2.42 (s, 3H, CH_3). MS (EI, *m/z* (%)): 356 (M^+, 38). HRMS (EI, *m/z*) calcd. for $C_{22}H_{16}O_3N_2$, 356.1161; found 356.1146.

(5′H-Dibenzo[b, f]azepin-5′-yl)(3″,4″,5″-trimethoxyphenyl)methanone (**21**): Color: Light yellow. Yield: 40%. FT-IR (KBr, ν, cm^{-1}): 2926, 2855, 1657 (C=O) (amide), 1580 (C=C), 1458 (C=C), 1348 (C-N), 1238 (C-O), 1126 (C-O). ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 7.50-7.33 (m, 8H, H-1′, H-2′, H-3′, H-4′, H-6′, H-7′, H-8′, H-9′), 7.21 (s, 2H, H-2″, H-6″), 6.42 (s, 2H, H-10′, H-11′), 3.57 (s, 6H, 2×OCH_3), 3.56 (s, 3H, OCH_3). MS (EI, *m/z* (%)): 387 (M^+, 60). HRMS (EI, *m/z*) calcd. for $C_{24}H_{21}O_4N$, 387.1471; found 387.1456.

3. Results and discussion

Dibenzoazepine amides (**6**-**21**) were synthesized in single step from benzoylation of dibenzoazepine, as shown in Scheme 1. Previously dibenzoazepine amides (**6**-**21**) were prepared by Martinez *et al.* [15] using sodium hydride as a base and carcinogenic benzene as a solvent. Hazardous conditions used in this method drew our attention to explore other eco-friendly reaction conditions.

At first, optimization of the reaction was done using *p*-nitrobenzoyl chloride with different combination of solvents and bases (Table 1). Results revealed that refluxing DIPEA as a base in THF for 4 h gave benzamide **17** in 80% yield. However, switching DIPEA to NEt_3 in DCM increased yield up to 93%. Although excellent yield was obtained, this method required excess benzoyl chloride for the complete consumption of starting material and used hazardous DCM as the solvent. Therefore, in order to switch our finding into "green process" we explored different solvent-free conditions for the synthesis of compound **17**. $NaHCO_3$ and NEt_3 were screened as base for this reaction, and best results were obtained using NEt_3 as a base. To investigate optimum temperature, benzoylation was carried out at 25, 50, 100 and 120 °C. Results revealed that at room temperature there was negligible consumption of starting material; however, increasing temperature up to 50 °C gave appreciable amount of product (54%). The impact of temperature was further studied by raising temperature up to 100 °C and 120 °C. Results showed that at 100 °C, reaction is completed in 2 h and gave 76% yield, while at 120 °C reaction takes only 20 min for completion and gave 82% yield. These results showed that raising temperature not only gave excellent yield, but also reduced reaction time; which suggested that high temperature is important to accelerate benzoylation reaction. Further screening was done to explore optimal equivalence of *p*-nitrobenzoyl chloride. Accordingly, the ideal conditions were achieved by using *p*-nitrobenzoyl chloride up to 1.5 equivalence using NEt_3 as base. As this reaction procedure takes only a couple of minutes for complete consumption of starting material and did not require any hazardous solvent, this protocol is an efficient and environmentally friendly method.

With these optimized conditions, the scope of reaction was investigated by treating compound **1** with different substituted benzoyl chlorides. A variety of benzamide analogs of dibenzoazepine (**6**-**21**) were smoothly prepared in 40-98% yield (Table 2). Dibenzoazepine benzamides (**17**-**19**) with electron withdrawing group give excellent yields. However, compound **21** with three electron donating methoxy groups gave low yield (40%). Comparison between disubstituted compounds **19** and **20** also revealed that replacing the electron withdrawing chloro group with the electron donating methyl group at position-4″ resulted in lowering of yield from 91 to 75%, keeping nitro group fixed at C-3″.

4. Conclusion

In summary, we have developed an efficient and solvent-free green method for the synthesis of previously reported antidepressant benzamide analogs of dibenzoazepine. A library of dibenzazepine benzamides with varying substitutions was prepared. Most yields were excellent with one exception for highly electron rich compound **21**. These methodologies for amidation could be widely applicable.

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