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A Sequential Synthetic Strategy towards Unexplored Dibenzo[*b*,*f*][1,4]thiazepine Carboxamides: Copper Catalysed C-S Cyclisation followed by Ugi type 3CC Cascade

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A two-step diversity oriented synthetic protocol to a novel class of dihydrodibenzo[*b*,*f*][1,4]thiazepine-11-carboxamides has been developed. The first step ensures the synthesis of dibenzothiazepine *via* copper-mediated condition followed by Ugi-Joullié reaction of the resultant cyclic imine in the second.

Introduction

Dibenzothiazepines have been tagged as "Privileged Scaffolds" owing to their remarkable pharmacological properties.[1] These have proven to be the active pharmaceutical ingredients (API) of marketed drugs, such as clotiapine **1,** used as an anti-psychotic drug and quetiapine fumarate **2** to treat CNS disorders.[2] Also Ethyl 4-(11- propyldibenzo[*b*,*f*][1,4]thiazepine-2 carboxamido) piperidine-1-carboxylate **3** is reported as a potential cannabinoid-1 inverse agonist.[3] Amongst more diversified benzothiazepines, *N*-hydroxy-6-(11-oxodibenzo[*b*,*f*][1,4] thiazepin-10(11*H*)-yl)- hexanamide **4** exhibits antitumor activities and 5-[*N*-[2-(3,4-dimethoxypheny)ethyl]-*b*-alanyl]-2,3,4,5-tetrahydro-1,5-benzothiazepine **5** is under phase II clinical trials for antihypertensive, antiarrhythmic activities (Fig 1).[3]

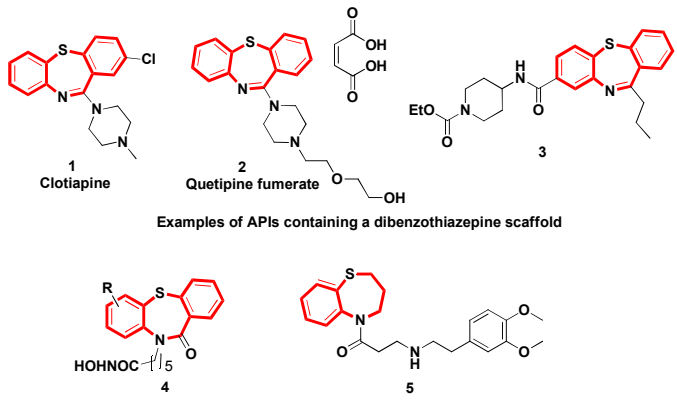


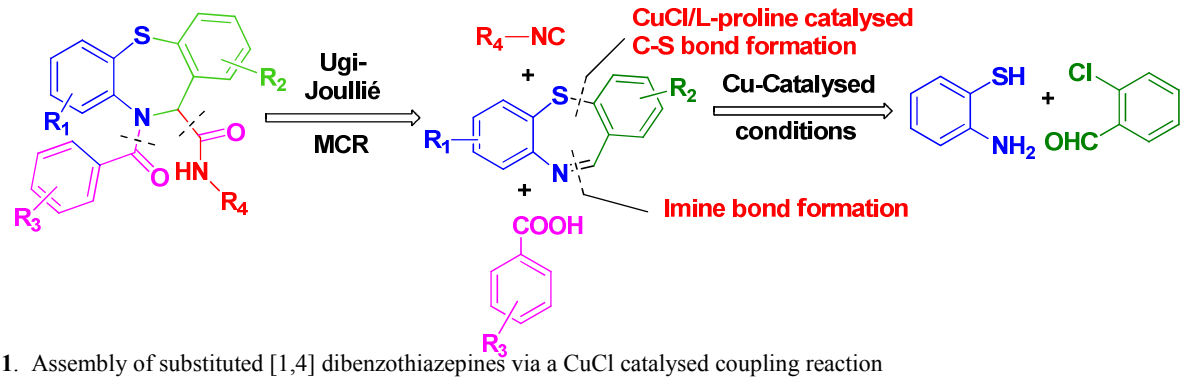
Figure 1. Representative pharmacologically active dibenzothiazepines and carboxamide derivatives.

Since appendages on the seven- membered thiazepine ring are least explored, diversity oriented synthesis of benzothiazepines specifically aimed at the seven membered ring are scanty. A few notable ones include synthesis of seven-membered carboxamides through Ugi/reduction cyclization sequence[4], Ugi/Staudinger/aza-Wittig sequence[5], Ugi reaction of arylglyoxals followed by a Staudinger/ aza-Wittig cyclization[6] and Gewald/Ugi-Deprotection-Cyclization (UDC) strategy.[7] Alternatively, entry of a preformed imine to Ugi three-component (U-3CR) gives an access to such compounds. For instance, a two-step approach *via* Mannich/Staudinger/aza-Wittig cyclization followed by Ugi–Joullie´ sequence afforded more diversified benzazepines.[8]

Based on the above, we decided a novel synthesis of an unprecedented class of dibenzothiazepine carboxamides of general structure **1**. The retrosynthetic strategy depicted in **Scheme 1**, allows introduction of atleast four diversity points including two on the seven membered ring.

We realized that the critical step in our synthetic strategy remains the three component Ugi-Joullié reaction on cyclic imines.[9-11] The inherent potential of this reaction to produce various drug-like heterocycles is widely applied in peptidomimetics, combinatorial and medical chemistry. In this reaction, isocyanide and carboxylic acid components induct two new points of diversity on the existing seven membered ring. Most of the reports on Ugi-Joullié reaction to date involve pyrrolidines or piperidines as cyclic imines.[12,13] Besides, there have been reports on the synthesis of novel morpholin-2-one-3-carboxamides by Ugi-joullié reaction[14] and oxidative Ugi-type reactions of secondary benzylic imines.[15] A classical example of Ugi-Joullié reaction has been demonstrated by synthesis of

substituted benzazepines coupled with organocatalytic and enzymatic procedures.[8]



Scheme 1. Assembly of substituted [1,4] dibenzothiazepines via a CuCl catalysed coupling reaction

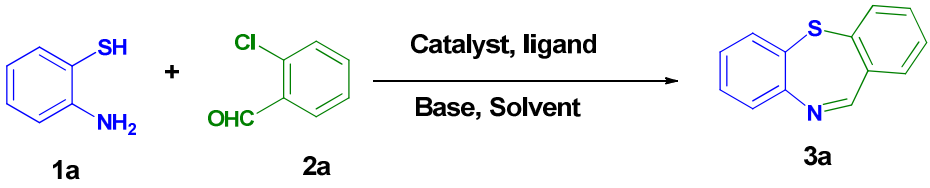
As far the construction of cyclic imine is concerned, several synthetic approaches have been explored till date. In most of the examples the benzothiazepine nucleus has been obtained by Bischler-Napieralski cyclizations,[16] denitrocyclisation reactions,[17] click-cyclisation of sulphonamides,[18] reaction of thiosalicylic acid with 2-chloro-3-nitrobenzene,[19] reaction of 4-chlorobenzenethiol and 3-aminochloropyridine,[20] Ullman coupling of 2-mercaptobenzoic acid with 1-bromo-4-methoxy-2-nitrobenzene.[21] Also condensation of *o*-aminothiophenol with reactive *o*-chlorophenylaldehydes through S_NAr route,[22,23] amidst shortcomings such as limited substrate, harsh reaction conditions, average yields etc. A transition metal assisted C-S bond formation has been reported only once with bromobenzaldehydes[24] and to the best of our knowledge, a similar methodology involving unactivated *o*-chlorobenzaldehydes has not been reported till date.

In this light, we present a successful two step diversity oriented synthesis of a novel class of dihydrodibenzo[*b*,*f*][1,4]thiazepine-11-carboxamides in which dibenzothiazepines are synthesized using *o*-aminothiophenol and *o*-chlorobenzaldehydes through copper-catalysed cyclization in the first step followed by Ugi-Joullié reaction on the resulting cyclic imine to afford title compounds in the second.

Results and Discussion

In our work, we identified copper assisted C-S bond formation[25] as a significant step for the cyclisation of dibenzothiazepines. The synthetic methodology in the first step, utilize a standard base-catalysed condensation of amine with aldehyde resulting in the formation of imine followed by "ligated" Cu catalysed intramolecular S-arylation[26] to afford cyclized dibenzothiazepines.

Table 1. Optimisation of the reaction conditions for the synthesis of **3a**[a]



S No	Catalyst[b]	Ligand	Base	Solvent	Conditions[c]	Yield[d]
1.	---	---	Et_3N	DMF	MW(120°C,15min.)	55%
2.	---	---	Na^+t-BuO^-	DMF	MW(120°C,15 min.)	50%
3	---	---	KOH	DMF	MW(120°C,15 min.)	70%
4.	CuI	L-Proline	Na^+t-BuO^-	Toluene	MW(120°C,15 min.)	32%
5.	CuI	L-Proline	Na^+t-BuO^-	Dioxane	MW(120°C,15 min.)	36%
6.	CuI	L-Proline	Na^+t-BuO^-	IPA	MW(120°C,15 min.)	38%
7.	CuI	L-Proline	Na^+t-BuO^-	DMSO	MW(120°C,15 min.)	20%
8.	CuI	L-Proline	Na^+t-BuO^-	DMF	MW(120°C,15 min.)	68%
9.	CuI	L-Proline	Na^+t-BuO^-	DMF	120°C, 24hrs.	36%
10.	CuI	L-Proline	Na^+t-BuO^-	DMF	MW(120°C,15 min.)	68%
11.	CuI	L-Proline	Cs_2CO_3	DMF	MW(120°C,15 min.)	45%
12.	CuI	L-Proline	K_3PO_4	DMF	MW(120°C,15 min.)	38%
13.	CuI	L-Proline	NaOH	DMF	MW(120°C,15 min.)	67%
14.	CuI	L-Proline	KOH	DMF	MW(120°C,15 min.)	75%
15.	CuI	*N*-methyl glycine	Na^+t-BuO	DMF	MW(120°C,15 min.)	60%
16.	CuI	*N*-methyl glycine	KOH	DMF	MW(120°C,15 min.)	48%
17.	CuI	1,10- phenanthroline	Na^+t-BuO	DMF	MW(120°C,15 min.)	72%
18.	CuI	1,10- phenanthroline	KOH	DMF	MW(120°C,15 min.)	56%
19.	CuI	Ethylene glycol	Na^+t-BuO	DMF	MW(120°C,15 min.)	52%
20.	CuI	*trans*-cyclohexyl 1,2-diamine	Na^+t-BuO	DMF	MW(120°C,15 min.)	61%
21.	CuI	D-Pipecolinic acid	Na^+t-BuO	DMF	MW(120°C,15 min.)	45%
22.	$CuCl_2$	L-Proline	Na^+t-BuO	DMF	MW(120°C,15 min.)	No product
23.	**CuCl**	**L-Proline**	**Na^+t-BuO**	**DMF**	**MW(120°C,15 min.)**	**95%**
24.	CuBr	L-Proline	Na^+t-BuO	DMF	MW(120°C,15 min.)	51%
25.	$Cu(OAc)_2$	L-Proline	Na^+t-BuO	DMF	MW(120°C,15 min.)	No product

[a]General conditions: 2-aminothiophenol (1mmol), 2-chlorobenzaldehyde (1mmol), Base (2 eq.) Solvent (4-5 ml), [b]Catalyst loading: (10 mol%); 20 mol% of ligand was used; [c]Anton Paar Monowave 300 reactor. Irradiation Power: 850 W; Ramp time: 15 min. 120 °C; [d]Isolated yield; [e] Reaction was conducted in a sealed vial for the above mentioned time.

In a modular reaction, 2-aminothiophenol **(1a)** and 2-chlorobenzaldehyde **(2a)** were reacted to afford dibenzo[*b,f*][1,4]thiazepine **(3a)** under different conditions. Initially the synthesis was attempted without any catalyst with different bases and solvents under microwave irradiation amongst which only KOH/DMF proved effective with 70% yield of **3a** (Table 1, Entry 3). It is worth noting that in all these cases, the major product is the Schiff base formed out of the reaction of aniline with aldehyde which could be easily isolated (see supporting information).

Introducing catalytic amounts of copper in the above reaction remained ineffective and produced **3a** in 30%, 22%, 41% and 56% yields employing 10 mol% of CuI, 20 mol% of L-Proline and sodium tert-butoxide at 120°C for 15 min in toluene, dioxane, IPA and DMSO respectively (Table 1, entries 4-7). However, when the solvent was changed to DMF, the yield increased to 68% (Table 1, entry 8) which ascertained DMF as an ideal solvent for this transformation. Changing the reaction temperature or mode of heating did not improve the yield further (Table1, entries 9-10). Later, various combinations of copper catalyst (amongst $CuCl_2$, CuBr, $Cu(OAc)_2$ and CuCl), ligand (amongst L-Proline, *N*-methyl glycine, 1,10-phenanthroline, ethylene glycol, *trans*-cyclohexyl-1,2-diamine, D-pipecolinic acid) and a base (amongst KOH and sodium *tert*-butoxide) were tried (Table 1, entries 11-25) and the results proved CuCl, L-Proline with Na^+t-BuO^- in DMF to be the best combination giving 95% of the desired product (Table 1, entry 23).

Having optimized conditions in hand, we next decided to examine the robustness of our optimized protocol. To this end, assorted starting materials as depicted in **figure 2** were subjected to the optimised conditions to prepare diversely substituted dibenzothiazepines.

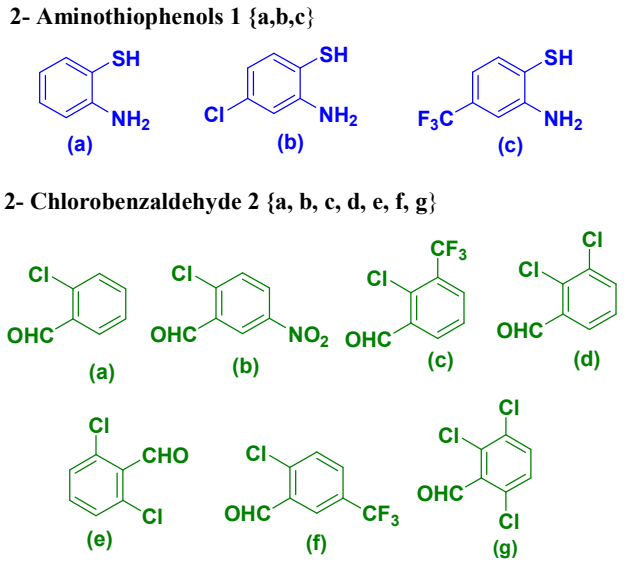
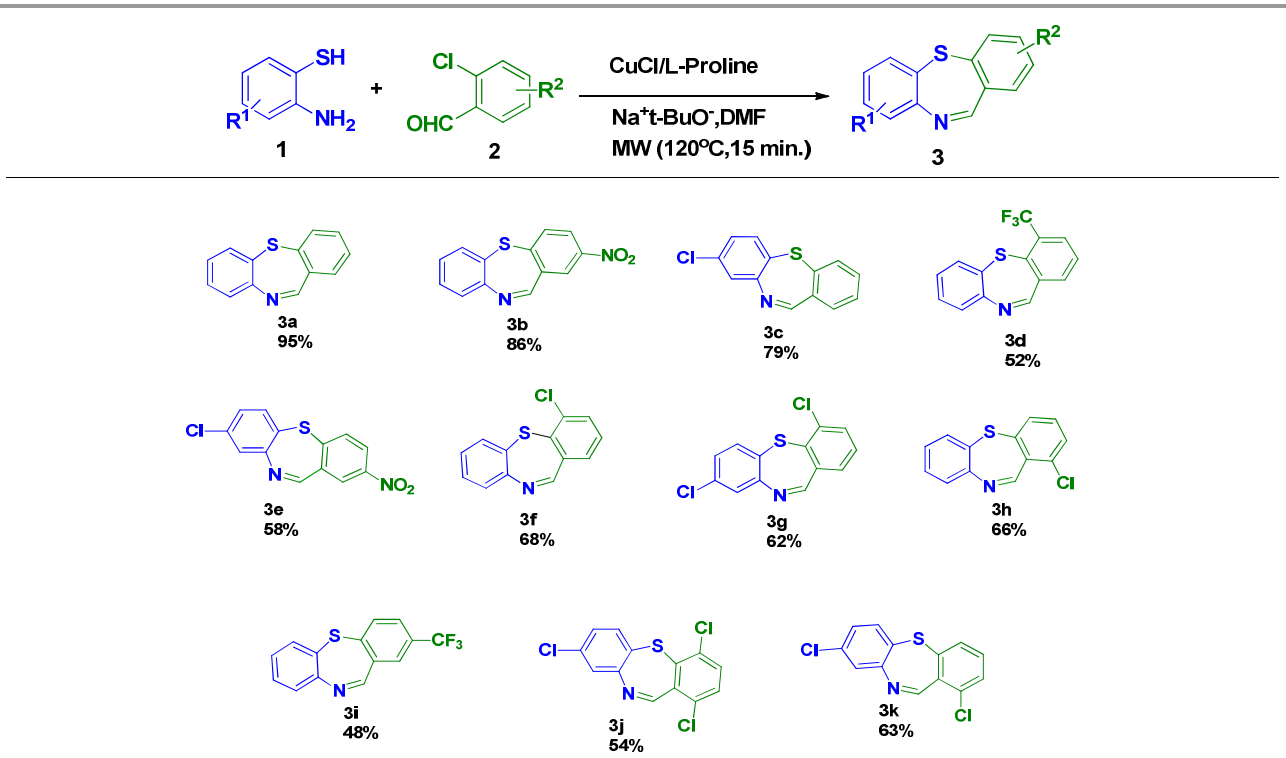


Figure 2. Diversity elements employed for library synthesis: 2- aminothiophenol 1{a,b,c} and 2-chlorobenzaldehyde 2 {a, b, c, d, e, f, g}.



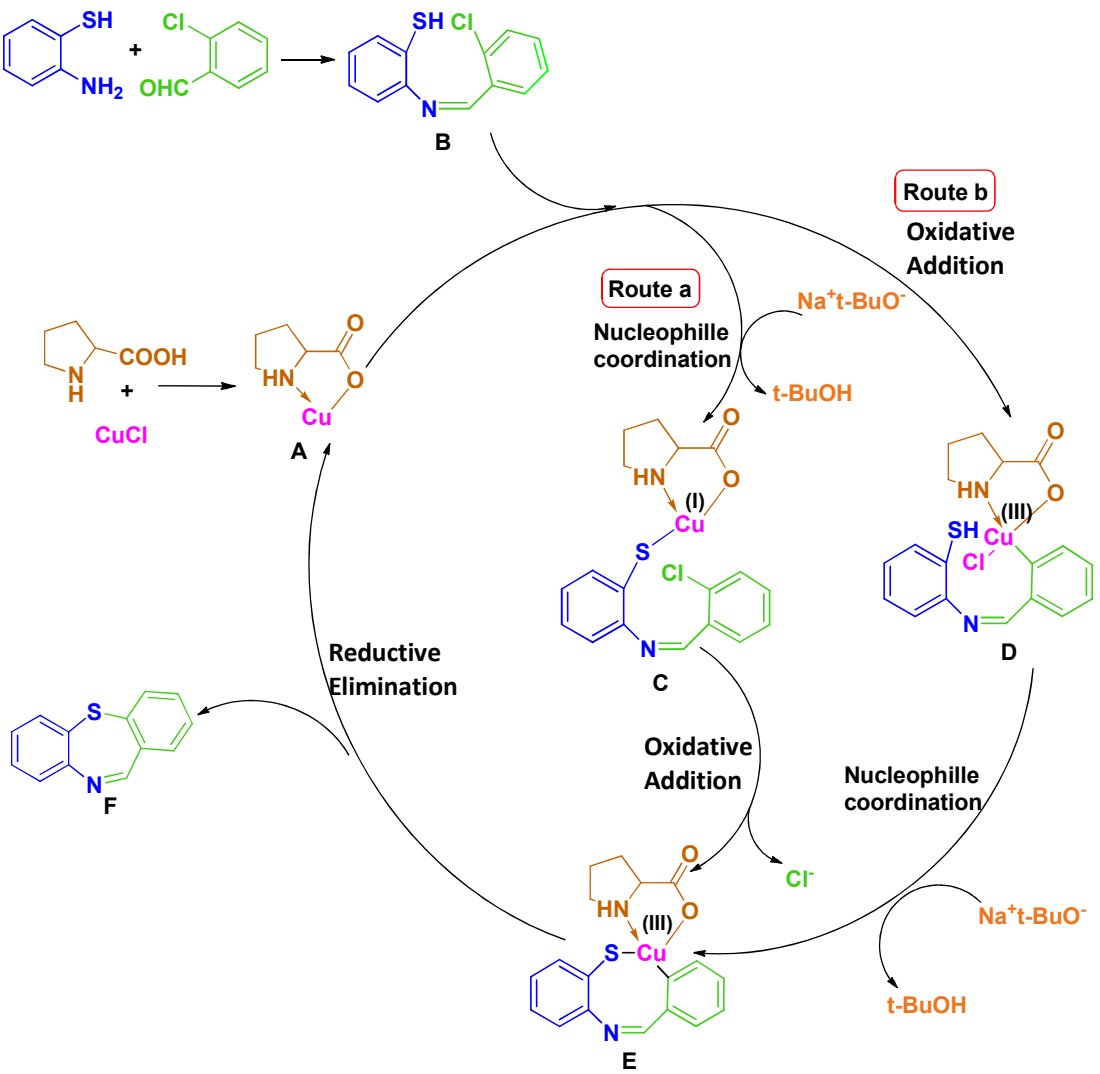
Scheme 3. Synthesis of dibenzo[*b,f*][1,4]thiazepine derivatives

The reaction yields of the analogues were sensitive to substitutions on aminothiol and aldehyde partner. Higher yields were obtained with 5-nitro (**3b**, 86%) followed by 3-chloro (**3f**, 68%) and 6-chloro (**3h**, 66%) substituted aminothiols. Reaction yields comparatively decreased when aminothiol ring was chloro substituted (**3e**, **3g**, **3j**, **3k**) except **3c** which was obtained in 79% yield. The presence of trifluoromethyl group on the aldehydic component (**3d**, 52%; **3i**, 48%) proved detrimental to the yield.

No reaction took place with 2-amino-4-(trifluoromethyl)benzenethiol **1c**. Amongst all, the unsubstituted dibenzo[*b,f*][1,4]thiazepine **3a** remained the highest yielding (95%) thiazepine indicating that steric rather

than electronic effects were important in deciding the course of this reaction.

Based on the previous inquest of Ullman coupling[27] and experimental results, we propose that the reaction would proceed *via* the formation of the Schiff base **B** which was confirmed during optimisation reactions as described before. Here, L-Proline acts as a promoter for the intramolecular S-nucleophilic coupling reaction. Proline ligated Cu(I) complex **A** undergo Cu(I)/Cu(III) catalytic cycle *via* two plausible pathways based on the coordination of nucleophile. In the first case, the coordination of base-deprotonated thiolate ion to Cu(I) complex may occur before oxidative addition resulting in intermediate **C** (route **a**). On the contrary, this coordination may occur after oxidative addition and lead to intermediate **D** (route **b**). Finally in both the cases, reductive elimination and removal of copper catalyst system in **E** may yield the target product **F**.



Scheme 4. Plausible mechanism for the formation of dibenzo[*b*,*f*][1,4]thiazepine.

Apart from the above metal-catalysed reaction mechanism, we also anticipated some undercurrents of S_NAr in the above reaction. In order to understand the mechanism from this perspective, a few control experiments were conducted as shown in **Scheme 5**.

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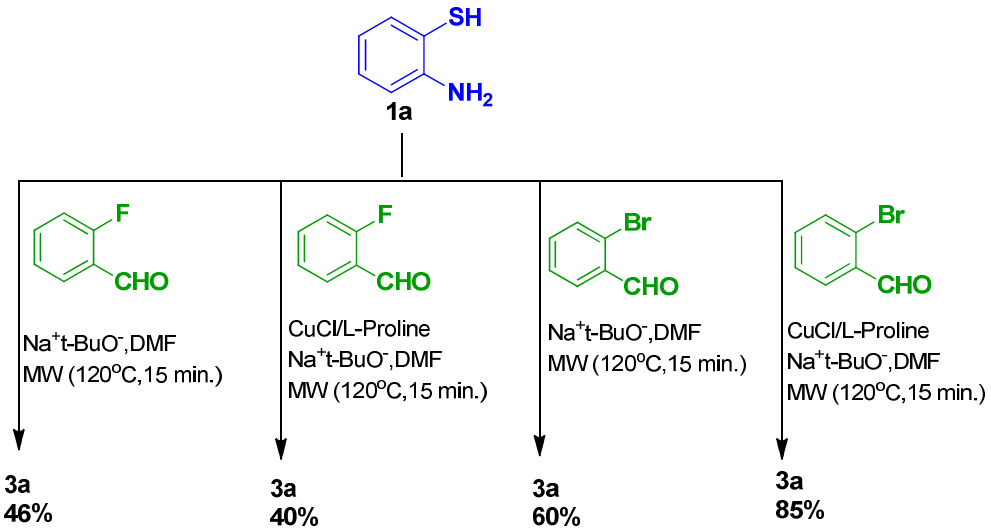
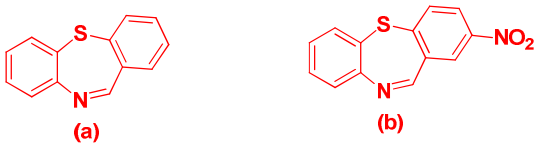


Scheme 5 Control experiments of **1a** with o-fluorobenzaldehyde and o-bromobenzaldehyde.

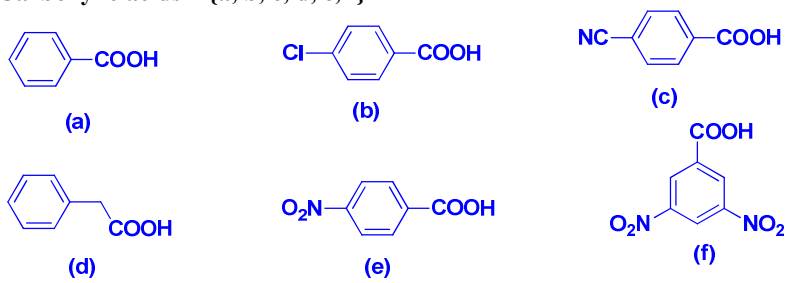
Reaction of **1a** with o-fluorobenzaldehyde under Cu catalyzed conditions provided reduced yields of **3a** (40%) as compared to uncatalysed conditions (46%). Whereas reaction with o-bromobenzaldehyde afforded better yields (85%) under Cu-catalysed conditions over uncatalysed conditions (60%) (**Scheme 5**). These observations indicate that the actual mechanistic pathway strives between a competitive S_NAr and Cu- catalysed transformation to an extent where both complement each other.

Having achieved success with the first step, the product dibenzo[*b*,*f*][1,4]thiazepine was reacted with aryl carboxylic acids and isocyanide via the classical Ugi-Joullié reaction. In a typical reaction, dibenzo[*b*,*f*][1,4]thiazepine **(3a)**, p-chlorobenzoic acid **(4b)** and *t*-butyl isocyanide **(5a)** were stirred in methanol at room temperature for 24hrs to afford *N*-(*tert*-Butyl)-10-(4-chlorobenzoyl)-10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepine-11-carboxamide **(6b)** in good yield (82%). A set of varied precursors, dibenzothiazepines (**3**), carboxylic acids (**4**) and isocyanides (**5**) were then submitted to the classical Ugi-Joullié reaction conditions to obtain the title compounds (Figure 3). As shown in **Scheme 6**, higher yields (**6k**, 90%; **6d**, 85%) were obtained for a combination of unsubstituted dibenzo[*b*,*f*][1,4]thiazepine, electron-withdrawing carboxylic acid and aromatic isocyanide. The presence of nitro group on the thiazepine nucleus provided good yields (**6l**, 78%; **6m**, 80%) whereas moderate yields were obtained for electron-rich carboxylic acids along with aliphatic isocyanides (**6a**,75%;**6c**,82%).

Dibenzothiazepines 3 {a, b}



Carboxylic acids 4 {a, b, c, d, e, f}



Isocyanides 5 {a, b, c, d}

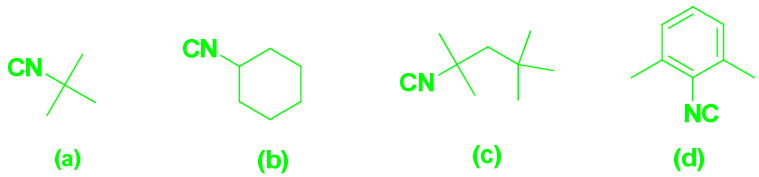
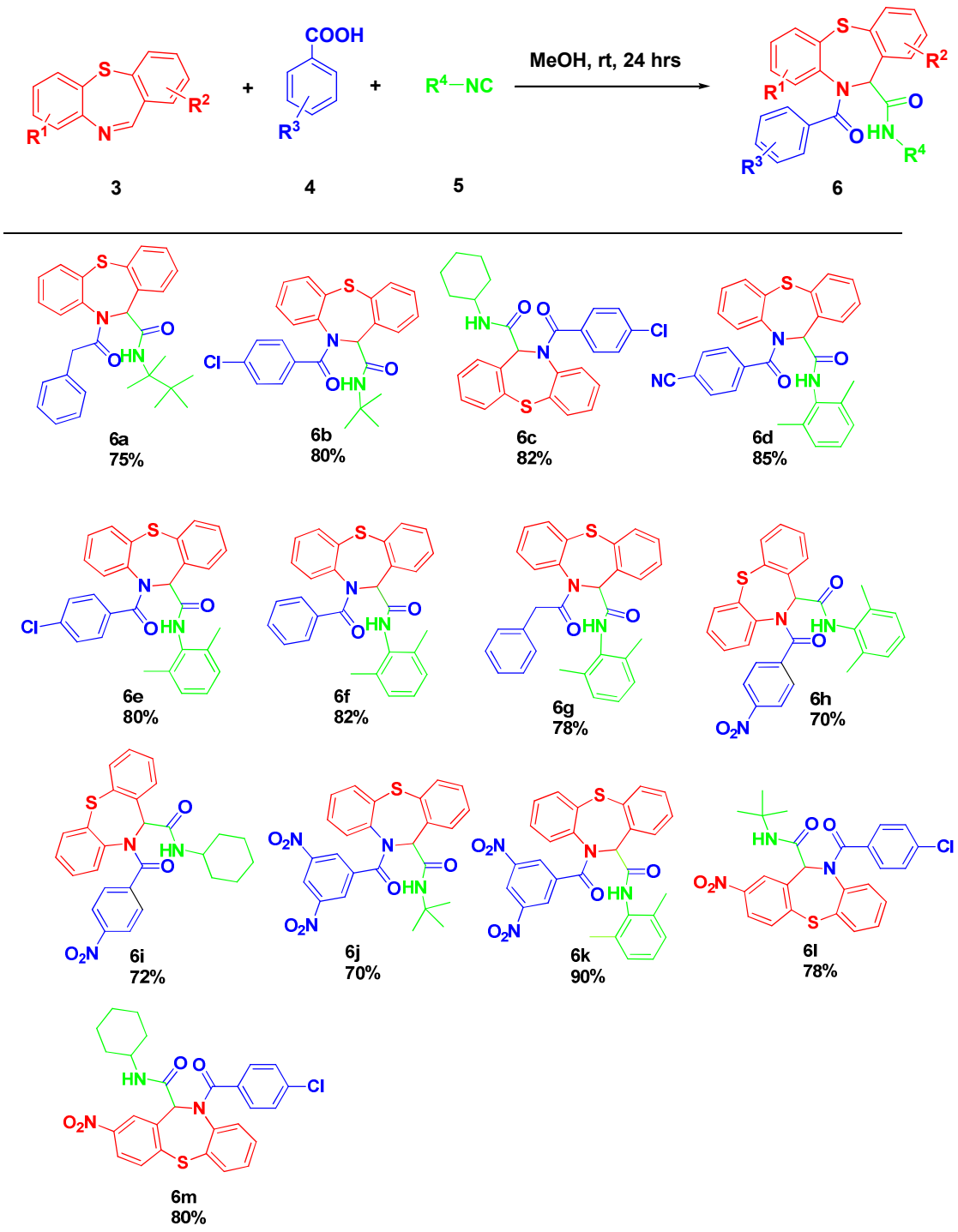


Figure 3. Diversity elements employed for library synthesis: a) Dibenzothiazepines {a,b}; b) Carboxylic acids {a-f}; c) Isocyanides {a-d}.



Scheme 6. Assembly of synthesized substituted 10, 11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamides.

Conclusion

In summary, we have developed an expedient and economical synthetic methodology to assemble novel dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamides in good to excellent yields. The classical Ugi-Joullié protocol gives an easy access to these diverse scaffolds with four points of diversity thereby providing entry to a library of novel benzo-fused analogues of biologically active thiazepines. Assessment of this array of novel thiazepines as therapeutic candidates will be actively pursued in future.

Experimental

Commercially available substituted benzaldehydes, *o*-aminothiophenols and the other chemicals were purchased from Sigma–Aldrich and were of analytical grade. Reactions were performed on Anton Paar Monowave 300 reactor. The reactions were monitored by thin layer chromatography. UV light and iodine vapors were used for the detection of compounds. Organic extracts were dried with anhydrous Na_2SO_4. Purification of isolated products was carried out by column chromatography. Compounds were characterized by spectroscopic and analytical methods.

The chemical structures of the obtained compounds were determined by IR spectroscopy, nuclear magnetic resonance spectroscopy (^{1}H and ^{13}C) and high-resolution mass spectroscopy (HRMS). ^{1}H NMR spectra were recorded on a Bruker Biospin GmbH (500MHz) spectrometer and Jeol JNM-ECX400II spectrometer in $CDCl_3$ and DMSO-d_6. HRMS were recorded on a Bruker micrOTOF-QII and GC-MS were recorded in a Perkin Elmer spectrophotometer. Chemical shifts were given as δ values against tetramethylsilane as internal standard and J values were given in Hz. Melting points (°C) were determined in a OPTIMELT automated melting point system. The IR spectra (in KBr pellets) were recorded on a Thermo scientific Nicolet 67000 FT-IR spectrophotometer.

General procedure for the synthesis of dibenzo[*b,f*][1,4]thiazepine 3

A mixture of 2-aminothiophenols **1a-c** (1 mmol), substituted benzaldehydes (1mmol), **2a-g** sodium *tert*-butoxide (2 mmol), copper (I) chloride (10 mol%), L-proline (20 mol%) and DMF (5 mL) was placed into a 10mL reaction vessel. After the vessel was sealed, the sample was irradiated at 120 °C for 15 minutes (Irradiation Power 850W). After completion, reaction mixture was partitioned between ethyl acetate (100 mL) and water (60 mL). Organic layer was washed with brine (3 x100 mL), dried over sodium sulphate and evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography using hexane ethyl acetate mixtures to afford dibenzo[*b,f*][1,4]thiazepines (**3a-k**)

Dibenzo[*b,f*][1,4]thiazepine 3a. Light yellow crystals (yield 95%); R_f 0.87 (10% EtOAc/PE); mp 123-124 °C; IR (cm^{-1}) 1630, 1583, 1558, 1458, 1430; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.90 (s, 1H), 7.41-7.45 (m, 2H), 7.40 (t, 1H, *J*= 2Hz), 7.37-7.39 (m, 1H), 7.34-7.37 (m, 1H), 7.30-7.33 (m, 2H), 7.15-7.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 162.3, 148.5, 139.3, 137.2, 132.8, 131.6, 131.5, 129.4, 129.3, 128.9, 128.3, 127.2, 127.0; HRMS (ESI^+) m/z calcd. for $C_{13}H_9NS$ $[M+H]^+$ 212.0655, found 212.0689.

2-Nitrodibenzo[*b,f*][1,4]thiazepine 3b. Yellow crystals (yield 86%); R_f 0.86 (10% EtOAc/PE); mp 182.2-183 °C; IR (cm^{-1}) 1518, 1458, 1432, 1342, 1305; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.90 (s, 1H,), 8.24 (s, 1H), 8.22 (dd, 1H, *J* = 10Hz, *J* = 2Hz), 7.61 (d, 1H, *J* = 5Hz), 7.30-7.45 (m, 3H),7.22 (t, 1H, *J* = 10Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 159.8, 148.1, 147.7, 147.6, 137.7, 133.1, 132.6, 130.1, 128.0, 127.2, 127.0, 125.7, 124.2 ppm; HRMS (ESI^+) m/z calcd. for $C_{13}H_8N_2O_2S$ $[M+H]^+$ 257.0379, found 257.0380.

8-Chlorodibenzo[*b,f*][1,4]thiazepine 3c. Yellow solid (yield 79%); R_f 0.84 (10% EtOAc/PE); mp 77.7-78 °C; IR (cm^{-1}) 3347, 1639, 1561, 1441; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.03 (s, 1H), 7.41(dd, 1H, *J* = 7.5Hz, *J* = 1Hz), 7.35 (t, 1H, *J* = 2.5Hz), 7.31-7.34 (m, 3H), 7.29-7.31 (m, 1H), 7.15 (dt, 1H, *J* = 7.5Hz, *J* = 1.5Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 161.1, 149.3, 142. 6, 135.4, 134.9, 133.8, 133.6, 132.2, 130.1, 129.9, 126.9, 126.8, 125.9; HRMS (ESI^+) m/z calculated for $C_{13}H_8ClNS$ $[M+H]^+$ 246.0340, found 246.0322.

4-(trifluoromethyl)dibenzo[*b,f*][1,4]thiazepine 3d. Light yellow solid (yield 52%); R_f 0.75 (10% EtOAc/PE); mp 106 °C; IR (cm^{-1}) 3420, 1641, 1565, 1412; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.98 (s, 1H), 7.78 (d, 1H, *J* = 5Hz), 7.57 (d, 1H, *J* = 10Hz), 7.52 (d, 1H, *J* = 5Hz), 7.45 (t, 1H, *J* = 10Hz), 7.30-7.41 (m, 2H), 7.22 (t, 1H, *J* = 5Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 161.1, 148.7, 139.3, 137.9, 133.4, 132.0, 131.5, 131.4 (q, J_{F-C} = 45Hz), 131.3, 130.0, 128.6 (q, J_{F-C} = 40Hz), 128.0, 127.7, 127.6, 126.4, 124.3, 123.2 (q, J_{F-C} = 545Hz); HRMS (ESI^+) m/z calcd. for $C_{14}H_8F_3NS$ $[M+H]^+$ 280.0402, found 280.0420.

8-Chloro-2-nitrodibenzo[*b,f*][1,4]thiazepine 3e. Orange yellow solid (yield 58%); R_f 0.69 (10% EtOAc/PE); mp 148.7-150 °C; IR (cm^{-1}) 1630, 1598, 1575, 1523, 1455, 1377; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.91 (s, 1H), 8.23-8.27 (m, 2H), 7.60 (d, 1H, *J* = 5Hz), 7.32-7.34 (m, 2H), 7.2 (dd, 1H, *J* = 10Hz, *J* = 5Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 160.9, 150.0, 147.8, 147.2, 137.5, 135.9, 133.9, 132.7, 127.9, 126.9, 126.0, 125.5, 124.2; HRMS (ESI^+) m/z calcd. for $C_{13}H_7ClN_2O_2S$ $[M+H]^+$ 291.0001, found 291.0032.

4-Chlorodibenzo[*b,f*][1,4]thiazepine 3f. Brown crystals (yield 68%); R_f 0.76 (10% EtOAc/PE); mp 92 °C; IR (cm^{-1}) 3053, 2927, 1628 1583, 1553; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.88 (s, 1H), 7.51 (d, 2H, *J* = 5Hz), 7.36 (t, 1H, *J* =10 Hz), 7.31 (d, 1H, *J* = 5Hz), 7.26-7.30 (m, 2H), 7.20 (td, 1H, *J* = 10Hz, *J* = 5Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 161.5, 148.6, 138.7, 137.8, 135.8, 133.7, 131.7, 129.8, 128.9, 127.6, 127.5, 127.4, 126.6; HRMS (ESI^+) m/z calcd. for $C_{13}H_8ClNS$ $[M+H]^+$ 246.0138, found 246.0103.

4,8-Dichlorodibenzo[*b,f*][1,4]thiazepine 3g. Brown crystals (yield 62%); R_f 0.74 (10% EtOAc/PE); mp 153-155 °C; IR (cm^{-1}) 3308, 2927, 2855, 1633, 1575, 1452; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.88 (s, 1H), 7.53 (t, 1H, *J* = 5Hz), 7.43 (d, 1H, *J* = 5Hz), 7.28-7.32 (m, 3H), 7.17 (dd, 1H, *J* = 8.5Hz, *J* = 2Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 162.5, 149.3, 138.6, 137.5, 135.9, 135.5, 134.4, 132.0, 129.1, 127.6, 127.3, 126.3, 126.1; HRMS (ESI^+) m/z calcd. for $C_{13}H_7Cl_2NS$ $[M+Na]^+$ 301.9574, found 301.9510.

1-Chlorodibenzo[*b,f*][1,4]thiazepine 3h. Yellow solid (yield 66%); R_f 0.72 (10% EtOAc/PE); mp 124-126 °C; IR (cm^{-1}) 1620, 1570, 1560, 1460, 1432; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.03 (s, 1H), 7.42 (dd, 1H, *J* = 10Hz, *J* = 1Hz), 7.36 (t, 1H, *J* = 5Hz), 7.31-7.35 (m, 3H), 7.31 (d, 1H, *J* = 1.5Hz), 7.27-7.30 (m, 1H), 7.16 (td, 1H, *J* = 10Hz, *J* = 1.5Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm)

160.1, 148.5, 143.0, 134.8, 133.9, 132.8, 132.0, 130.1, 129.7, 129.6, 128.4, 127.0, 126.2; HRMS (ESI^+) m/z calcd. for $C_{13}H_8ClNS$ $[M+H]^+$ 246.0138, found 246.0147.

2-(Trifluoromethyl)dibenzo[*b,f*][1,4]thiazepine 3i. Orangish Yellow solid (yield 48%); R_f 0.70 (10% EtOAc/PE); mp 88.8 °C; IR (cm^{-1}) 1695, 1620, 1570; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.89 (s, 1H), 7.59-7.64 (m, 2H), 7.55 (d, 1H, *J* = 12Hz), 7.41 (dd, 1H, *J* = 10Hz, *J* = 5Hz), 7.28-7.38 (m, 2H), 7.20 (td, 1H, *J* = 4Hz, *J* = 1.9Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 160.8, 148.3, 143.9, 137.4, 133.0, 132.1, 130.7 (q, J_{F-C} = 66.25 Hz),129.8, 127.8 (q, J_{F-C} = 6.2 Hz), 127.9, 127.7, 127.1, 126.1, 126.1 (q, J_{F-C} = 7.5Hz) 124.6, 123.44 (q, J_{F-C} = 541Hz), 122.4; HRMS (ESI^+) m/z calcd. for $C_{14}H_8F_3NS$ $[M+H]^+$ 280.0436, found 280.0413.

1,4,8-Trichlorodibenzo[*b,f*][1,4]thiazepine 3j. Yellow solid (yield 54%); R_f 0.69 (10% EtOAc/PE); mp 131.4-133.5 °C; IR (cm^{-1}) 1641, 1565, 1412; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.97 (s, 1H), 7.41-7.47 (m, 2H), 7.30 (d, 2H, *J* = 12Hz), 7.15 (dd, 1H, *J* = 8Hz, *J* = 4Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 160.6, 149.4, 140.9, 136.0, 134.9, 134.4, 134.1, 132.8, 132.4, 130.3, 127.1, 125.7, 125.6; HRMS (ESI^+) m/z calcd. for $C_{13}H_6Cl_3NS$ $[M+H]^+$ 313.9356, found 313.9346.

1,8-Dichlorodibenzo[*b,f*][1,4]thiazepine 3k. Yellow solid (yield 63%); R_f 0.65 (10% EtOAc/PE); mp 118-119 °C; IR (cm^{-1}) 1623, 1573, 1455; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.01 (s, 1H), 7.33 (s, 1H), 7.30-7.32 (m, 3H), 7.29 (d, 1H, *J* = 2.4Hz), 7.11(dd, 1H, *J* = 8.4Hz, *J* = 2.4Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 161.1, 149.3, 142.6, 135.4, 134.9, 133.8, 133.6, 132.2, 130.1, 129.9, 126.9, 126.9, 125.9; HRMS (ESI^+) m/z calcd. for $C_{13}H_7Cl_2NS$ $[M+H]^+$ 279.9746, found 279.9743.

General procedure for the synthesis of 10, 11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamides 6.

A mixture of dibenzothiazepines **3a-b** (1.0 mmol), carboxylic acid **4a-f** (1.1 mmol), isocyanide **5a-d** (1.1 mmol) and 5 ml methanol was placed in a 10 ml round bottom flask. This reaction mixture was stirred at room temperature for 24 hrs. The completion of the reaction was monitored by thin layer chromatography. After the completion of the reaction, the reaction mixture was evaporated under vacuum. The residue was diluted with dichloromethane. The organic layer was then washed with saturated sodium bicarbonate (3x60ml) solution. It was further washed with brine solution (3x60ml), dried over anhydrous sodium sulphate and evaporated under reduced pressure. The solid residue obtained was purified by silica gel column chromatography using hexane, ethyl acetate mixtures to afford 10,11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamides **(6a-m)**.

10-(2-Phenylacetyl)-*N*-(2,3,3-trimethylbutan-2-yl)-10,11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamide 6a. White solid **(**yield: 75%); R_f 0.58 (30% EtOAc/PE); mp 102-103 °C; IR (cm^{-1}) 3333, 2957, 1688, 1665, 1644, 1447; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.63 (s, 9H), 0.83 (s, 3H), 1.08 (s, 3H), 3.52 (s, 2H), 5.23 (s, 1H), 6.50 (s, 1H), 7.01-7.07 (m, 2H), 7.13-7.23 (m, 6H), 7.28-7.37 (m, 3H), 7.37-7.41 (m, 1H), 7.48-7.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 170.6, 166.3, 141.2, 134.8, 134.7, 132.9, 132.4, 131.2, 130.4, 129.4, 129.3, 129.1, 128.8, 128.6, 128.3, 126.7, 126.6, 64.2, 55.4, 55.2, 40.7, 31.2, 28.0, 27.4; HRMS (ESI^+) m/z calcd. for $C_{29}H_{32}N_2O_2S$ $[M+H]^+$ 473.2257, found 473.2223.

***N*-(*tert*-Butyl)-10-(4-chlorobenzoyl)-10,11-dihydrodibenzo[*b,f*][1,4]thiazepine-11carboxamide 6b.** Light yellow solid (yield 80%); R_f 0.43 (30% EtOAc/PE); mp 156 °C ; IR (cm^{-1}) 3309, 2969, 1685, 1627, 1542, 1477; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.47 (t, 2H, *J* = 7Hz), 7.37 (d, 2H, *J* = 8.5Hz), 7.20-7.32 (m, 3H), 7.10-7.17 (m, 3H), 7.04 (t, 1H, *J* = 7.6Hz), 6.91 (d, 1H, *J* = 8.0Hz), 6.82 (brs, 1H), 5.20 (s, 1H), 0.96 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 169.5, 166.4, 142.3, 136.3, 133.6, 132.8, 132.4, 132.4, 131.5, 130.0, 129.7, 129.1, 128.7, 128.4, 128.3, 128.2, 126.5, 63.8, 51.4, 28.1; HRMS (ESI^+) m/z calcd. for $C_{25}H_{23}ClN_2O_2S$ $[M+Na]^+$ 473.1066, found 473.1048.

10-(4-Chlorobenzoyl)-*N*-cyclohexyl-10,11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamide 6c. White Solid (yield 82%); R_f 0.46 (30% EtOAc/PE); mp 170 °C; IR (cm^{-1}) 3299, 2928, 2855, 1670, 1650, 1530, 1477; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46 (d, 2H, *J* = 8Hz), 7.37 (dt, 2H, *J* = 6.7Hz, *J* = 1.6Hz), 7.25-7.30 (m,2H), 7.10-7.17 (m, 3H), 7.05 (t, 1H, *J* = 7Hz), 6.83-6.94 (m, 2H), 5.26 (brs, 1H), 3.47 (m, 1H), 1.54-1.65 (m, 2H), 1.35-1.50 (m, 3H), 1.13-1.21 (m, 3H), 0.93-1.05 (m, 1H), 0.86 (q, 1H, *J* =12Hz), 0.56 (q, 1H, *J* = 16Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 169.5, 166.4, 142.3, 136.3, 133.5, 132.5, 132.4, 132.2, 131.6, 130.2, 129.7, 129.3, 128.8, 128.7, 128.4, 128.2, 126.6, 63.3, 48.1, 32.3, 25.2, 24.4, 24.3. HRMS (ESI^+) m/z calcd. for $C_{27}H_{25}ClN_2O_2S$ $[M+Na]^+$ 499.1223, found 499.1216.

10-(4-Cyanobenzoyl)-*N*-(2,6-dimethylphenyl)-10,11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamide 6d. White solid (yield 85%); R_f 0.50 (30% EtOAc/PE); mp 238 °C; IR (cm^{-1}) 3444, 1687, 1642, 1565, 1412; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43-7.55 (m, 7H), 7.30-7.39 (m, 2H), 7.10-7.18 (m, 2H), 6.95-7.05 (m, 3H), 6.89 (d, 2H, *J* = 4Hz), 6.52 (s, 1H), 1.71 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) δ 168.6, 165.3, 139.5, 134.9, 133.3, 132.7, 131.8, 129.9, 129.5, 129.2, 129.0, 128.8, 128.6, 128.1, 127.6, 126.8, 118.0, 113.8, 63.5, 17.9; HRMS (ESI^+) m/z calcd. for $C_{30}H_{23}N_3O_2S$ $[M+Na]^+$ 512.1409, found 512.1404.

10-(4-Chlorobenzoyl)-*N*-(2,6-dimethylphenyl)-10,11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamide 6e. White solid (yield 80%); R_f 0.60 (30% EtOAc/PE); mp 136 °C; IR (cm^{-1}) 3465, 1641, 1565, 1411; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46-7.53 (m, 3H), 7.37 (dt, 2H, *J* = 8Hz, *J* = 2Hz), 7.27-7.34 (m, 2H), 7.12-7.19 (m, 4H), 6.95-7.06 (m, 3H), 6.90 (d, 2H, *J* = 8Hz), 6.57 (s, 1H), 1.76 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 169.6, 165.6, 142.3, 136.4, 135.0, 133.4, 133.2, 132.9, 132.7, 132.4, 132.1, 132.0, 129.8, 129.7, 129.3, 129.1, 128.7, 128.6, 128.2, 128.1, 127.6, 126.6, 63.0, 17.9; HRMS (ESI^+) m/z calcd. for $C_{29}H_{23}ClN_2O_2S$ $[M+Na]^+$ 521.1066, found 521.1055.

10-Benzoyl-*N*-(2,6-dimethylphenyl)-10,11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamide 6f. Light yellow solid (yield 82%); R_f 0.61 (30% EtOAc/PE); mp 203 °C; IR (cm^{-1}) 3444, 1642, 1565, 1412; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm)7.45-7.54 (m, 3H), 7.43 (dt, 2H, *J* = 6.8Hz, *J* = 1.6Hz), 7.27-7.36 (m, 3H), 7.14-7.21 (m, 3H),

7.08-7.13 (m, 1H), 6.95-7.00 (m, 3H), 6.9 (d, 2H, *J* = 8Hz), 6.62 (s, 1H), 1.75 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 170.6, 165.7, 142.6, 135.0, 133.2, 133.2, 133.1, 132.7, 132.6, 132.2, 132.1, 130.3, 129.8, 129.2, 128.5, 128.3, 128.2, 128.1, 127.9, 127.5, 126.6, 63.4, 18.0; HRMS (ESI$^+$) m/z calcd. for $C_{29}H_{24}N_2O_2S$ [M +Na]$^+$ 487.1456, found 487.4915.

***N*-(2,6-Dimethylphenyl)-10-(2-phenylacetyl)-10, 11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamide 6g.** White solid (yield 78%); R_f 0.55 (30% EtOAc/PE); mp 212 °C; IR (cm^{-1}) 3444, 1642, 1563, 1412; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.54 (dd, 1H, *J* = 6Hz, *J* = 3.28), 7.47 (dd, 1H, *J* = 8Hz, *J* = 4Hz), 7.38-7.44 (m, 2H), 7.32 (dd, 2H, *J* = 8Hz, *J* = 4Hz), 7.26 (dd, 2H, *J* = 8Hz, *J* = 4Hz), 7.15-7.22 (m, 3H), 7.04 (dd, 2H, *J* = 8Hz, *J* = 4Hz), 6.95-7.0 (m, 1H), 6.84-6.92 (m, 3H), 6.45 (s, 1H), 3.54 (d, 2H, *J* = 4Hz), 1.69 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 170.8, 166.0, 141.0, 135.0, 134.7, 134.5, 132.9, 132.9, 132.7, 132.5, 131.7, 130.4, 129.5, 129.4, 129.1, 128.3, 128.1, 127.6, 126.7, 63.5, 40.4, 18.0; HRMS (ESI$^+$) m/z calcd. for $C_{30}H_{26}N_2O_2S$ [M+Na]$^+$ 501.1613, found 501.1607.

***N*-(2,6-Dimethylphenyl)-10-(4-nitrobenzoyl)-10,11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamide 6h.** White solid (yield 70%); R_f 0.51 (30% EtOAc/PE); mp 207 °C; IR (cm^{-1}) 3407, 1686, 1569, 1413; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.05 (d, 2H, *J* = 10Hz), 7.61 (d, 2H, *J* = 5Hz), 7.55 (d, 2H, *J* = 10 Hz), 7.51 (d, 2H, *J* = 5Hz), 7.36 (p, 2H, *J* = 10Hz), 7.13-7.20 (m, 2H), 6.95-7.05 (m, 3H), 6.91 (d, 2H, *J* = 10Hz), 6.54 (s, 1H), 1.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.6, 165.4, 148.5, 141.5, 141.3, 135.0, 133.4, 132.8, 132.7, 132.5, 132.0, 131.9, 130.0, 129.6, 129.3, 129.2, 129.0, 128.9, 127.8, 126.9, 123.6, 123.3, 63.6, 18.0; HRMS (ESI$^+$) m/z calcd. for $C_{29}H_{23}N_3O_4S$ [M+Na]$^+$ 532.1301, found 532.1336.

***N*-Cyclohexyl-10-(4-nitrobenzoyl)-10,11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamide 6i.** White solid (yield 72%); R_f 0.56 (30% EtOAc/PE); mp 198 °C; IR (cm^{-1}) 3430, 1646, 1560, 1412; ^{1}H NMR (500 MHz, $CDCl_3$)δ (ppm) 8.03 (d, 2H, *J* = 5Hz), 7.61 (d, 2H, *J* = 10Hz), 7.49 (t, 2H, *J* = 5Hz), 7.32 (m, 3H), 7.15 (t, 1H, *J* = 5Hz), 7.05 (t, 1H, *J* = 5Hz), 6.95 (brs, 1H), 6.85 (brs, 1H), 5.16 (s, 1H), 3.45 (s, 1H), 1.44 (brs, 2H), 1.36 (brs, 1H), 1.06 -1.27 (m, 4H), 0.94-1.15 (m, 1H), 0.79-0.90 (m, 1H), 0.45-0.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 168.3, 166.0, 148.4, 148.3, 141.5, 141.4, 132.8, 132.8, 132.4, 132.3, 130.2, 129.4, 129.0, 128.9, 128.9, 128.7, 126.8, 123.2, 63.5, 48.1, 32.2, 25.2, 24.3, 24.2; HRMS (ESI$^+$) m/z calcd. for $C_{27}H_{25}N_3O_4S$ [M+Na]$^+$ 510.1463, found 510.1461.

***N*-(*tert*-Butyl)-10-(3,5-dinitrobenzoyl)-10,11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamide 6j.** Yellow solid (yield 70%); R_f 0.55 (30% EtOAc/PE); mp 248-250 °C; IR (cm^{-1}) 3412, 1682, 1543, 1476; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.91 (t, 1H, *J* = 2Hz), 8.62 (d, 2H, *J* = 5Hz), 7.54 (dd, 2H, *J* = 10Hz, *J* = 5Hz), 7.30-7.36 (m, 3H), 7.20 (t, 1H, *J* = 10Hz), 7.09 (t, 1H, *J* = 10Hz), 7.05(d, 1H, *J* =10Hz), 6.76 (s, 1H), 5.08 (s, 1H), 0.95 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 165.7, 165.6, 148.0, 140.9, 138.6, 133.5, 132.5, 132.4, 132.0, 131.0, 130.6, 129.7, 129.6, 129.1, 129.0, 128.4, 127.0, 120.0, 64.2, 51.7, 28.0; HRMS (ESI$^+$) m/z calcd. for $C_{25}H_{22}N_4O_6S$ [M+Na]$^+$ 529.1158, found 529.1173.

***N*-(2,6-Dimethylphenyl)-10-(3,5-dinitrobenzoyl)-10,11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamide 6k.** Light yellow solid (yield 90%); R_f 0.53 (30% EtOAc/PE); mp 149-152 °C; IR (cm^{-1}) 3457, 1663, 1547, 1504, 1412, 1340; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.92 (t, 1H, *J* = 2Hz), 8.63 (d, 2H, *J* = 5Hz), 7.55-7.61 (m, 3H), 7.36-7.43 (m, 2H), 7.22 (t, 1H, *J* = 5Hz), 7.07-7.14 (m, 3H), 7.00 (t, 1H, *J* = 5Hz), 6.91 (d, 2H, *J* =10 Hz), 6.52 (s,1H), 1.71 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm)165.8, 165.0, 148.0, 140.9, 138.5, 134.9, 133.2, 133.0, 132.7, 132.6, 131.7, 131.6, 130.4, 129.8, 129.7, 129.6, 129.2, 128.4, 128.2, 127.8, 127.0, 120.0, 63.8, 17.8; HRMS (ESI$^+$) m/z calcd. for $C_{29}H_{22}N_4O_6S$ [M+Na]$^+$ 577.1158, found 577.1191.

***N*-(tert-Butyl)-10-(4-chlorobenzoyl)-2-nitro-10,11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamide 6l.** Yellow solid (yield 78%); R_f 0.50 (30% EtOAc/PE); mp 156-158 °C; IR (cm^{-1}) 3310, 2965, 2924, 1694, 1627, 1518; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.14 (m, 1H), 8.08 (dd, 1H, *J* = 8Hz, *J* = 4Hz), 7.58 (d, 1H, *J* = 8Hz), 7.50 (dd, 1H, *J* = 8Hz, *J* = 0.8Hz), 7.35 (d, 2H, *J* = 8Hz), 7.21 (dd, 1H, *J* = 8Hz), 7.17 (dt, *J* = 8Hz, *J* = 4Hz), 7.09 (td, 1H, *J* = 8Hz, *J* = 3.4Hz), 6.82 - 6.85 (m, 2H), 5.51 (s, 1H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 169.7, 165.2, 145.5, 141.7, 140.9, 137.1, 134.5, 132.7, 131.7, 131.1, 130.2, 129.9, 129.3, 128.9, 128.8, 128.4, 126.9, 123.0, 63.4, 52.0, 28.3; HRMS (ESI$^+$) m/z calcd. for $C_{25}H_{22}ClN_3O_4S$ [M+Na]$^+$ 518.0917, found 518.0907.

10-(4-Chlorobenzoyl)-*N*-cyclohexyl-2-nitro-10,11-dihydrodibenzo[*b,f*][1,4]thiazepine-11-carboxamide 6m. Light yellow solid (yield 80%); R_f 0.50 (30% EtOAc/PE); mp 227 °C; IR (cm^{-1}) 3316, 2937, 1688, 1640, 1520; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.14 (m, 1H), 8.08 (dd, 1H, *J* = 8Hz, *J* = 4Hz), 7.60 (d, 1H, *J* = 8Hz), 7.50 (dd, 1H, *J* = 8Hz, *J* = 4Hz), 7.37 (dt, 2H, *J* = 8Hz, *J* = 2Hz), 7.18-7.26 (m,1H), 7.18 (dt, 2H, *J* = 8Hz, *J* = 4Hz), 7.10 (td, 1H, *J* = 8Hz, *J* = 4Hz), 6.91 (s, 1H), 6.85 (d, 1H, *J* = 8Hz), 5.63 (d, 1H, *J* = 8Hz), 3.60 (s, 1H), 1.45-1.60 (m, 4H), 0.80-1.24 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 169.8, 165.3, 145.6, 141.8, 140.6, 137.1, 134.1, 132.7, 131.6, 131.0, 130.4, 129.8, 129.7, 129.3, 128.9, 128.4, 126.9, 123.0, 62.8, 48.7, 32.7, 32.5, 25.3, 24.6, 24.5; HRMS (ESI$^+$) m/z calcd. for $C_{27}H_{24}ClN_3O_4S$ [M+Na]$^+$ 544.1074, found 544.1059.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Representative ^{1}H, ^{13}C NMR and HRMS spectra.

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