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A Microwave-Assisted Diastereoselective Multicomponent Reaction To Access Dibenzo[*c*,*e*]azepinones: Synthesis and Biological Evaluation

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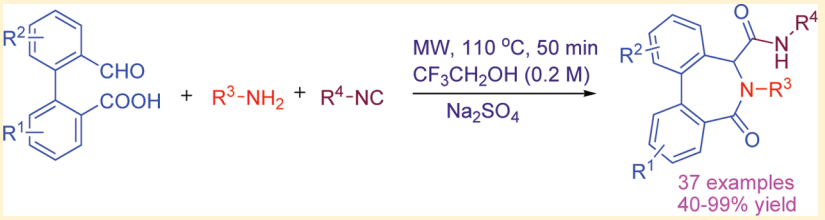
Supporting Information

ABSTRACT:



An unprecedented microwave-assisted multicomponent strategy has been elaborated for the fast, efficient, and diastereoselective generation of the dibenzo[*c*,*e*]azepinone scaffold. The generated compounds were evaluated for their bioactivity.

INTRODUCTION

The structures of small molecules from Nature have been optimized by evolution, and many of them are tailored to interact with larger biomolecules to induce a physiological response.[1] These small natural products represent an invaluable source for the discovery process of new therapeutic agents. Since the active natural product is usually not equipped with advanced biological properties required for a chemotherapeutic agent (e.g., toxicity issues), usually a series of skeletal and stereochemical analogues have to be generated synthetically. Promising strategies for this purpose are diversity-oriented synthesis[2] (DOS) and diverted total synthesis[3] (DTS). Multicomponent reactions[4] (MCRs) are increasingly recognized as valuable tools in the realization of DOS and DTS. Since the pioneering work of Passerini and Ugi, MCRs have become popular tools for diversity generation during drug development.[4g] MCRs are convergent reactions in which three or more starting materials react to form a product, and all or most of the atoms contribute to the newly formed compound.[4] As MCRs have been combined with various cyclization strategies,[5] they often result in the formation of rather complex molecular structures.[6] It has been shown that MCRs can greatly benefit from the use of microwave irradiation in terms of reaction time and yield.[7]

We were interested in the development of the dibenzo[*c*,*e*]azepinone scaffold[8] as it shows interesting structural resemblance with the framework of the γ-secretase inhibitor LY411575, which was developed by Eli Lilly[9] (Figure 1, **I**). The importance of biaryls in biological, synthetic, and materials chemistry has inspired the development of numerous methods for their assembly with control of axial chirality.[10] With this in mind, we were attracted by the retrosynthesis shown in Figure 1, where the key step of our approach consists of a microwave-assisted intramolecular Ugi 4CR of an appropriate biaryl compound bearing the required aldehyde and carboxylic acid moiety. This precursor can easily be assembled applying our previously reported microwave-assisted coupling protocol[11] of an *o*-formyl phenylboronic acid with a suitable methyl *o*-bromo benzoate.

RESULTS AND DISCUSSION

We started our synthesis from the commercially available substituted *o*-bromo benzoates **A1**−**3**. Our goal was to perform the Suzuki−Miyaura cross-coupling reactions with substituted 2-formyl-phenylboronic acids **B1**−**3** (Scheme 1). A mixture of the aryl bromide, boronic acid, and $Pd(PPh_3)_4$ as catalyst was dissolved in 1,4-dioxane/H_2O (1.5:1). To this solution was added Na_2CO_3 as base, and the resulting mixture was irradiated at a ceiling temperature of 120 °C and maximum power of 100 W

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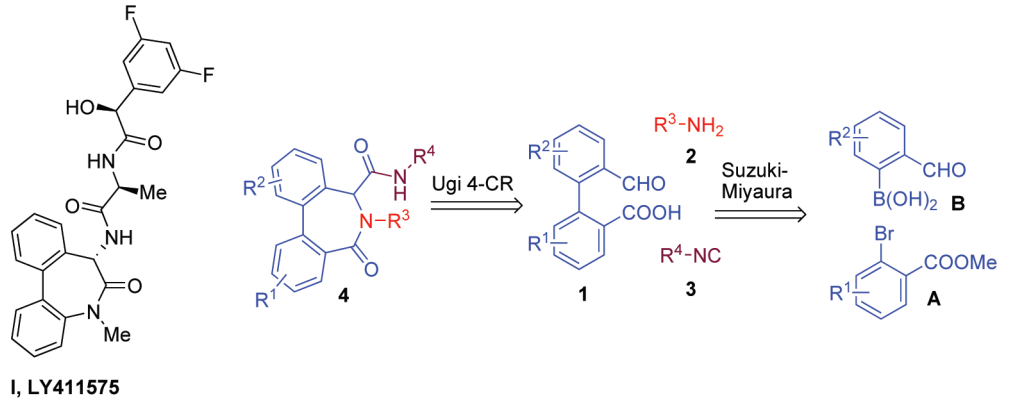
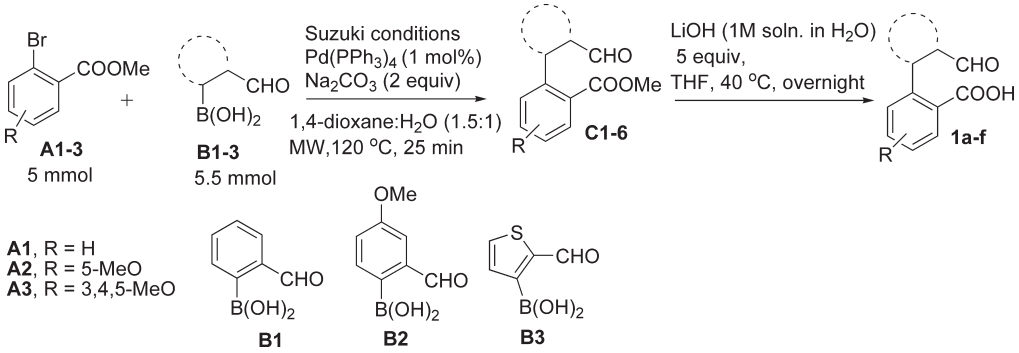


Figure 1. Structure of LY411575 (**I**) and retrosynthesis for the diversity-oriented generation of the dibenzo[*c*,*e*]azepinone scaffold (**4**).

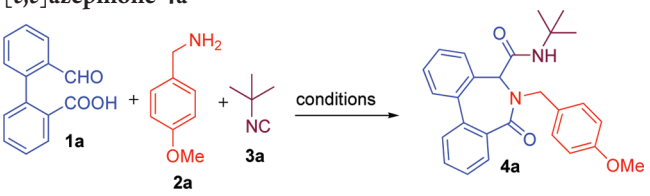
Scheme 1. Synthesis of Functionalized Biaryl Compounds 1a−f



for 25 min. The reactions were found to proceed smoothly, and the resulting biaryl-ester derivatives **C1−6** were purified by column chromatography over silica gel. The corresponding compounds **C1−6** were dissolved in THF, and then LiOH (1 M soln in H_2O) was added to perform the saponification. This mixture was stirred at 40 °C overnight. After standard workup the desired biaryl compounds **1a−f** were obtained in good to excellent yields.

The feasibility of the Ugi 4CR reaction was evaluated applying 2′-formylbiphenyl-2-carboxylic acid (**1a**), *p*-methoxybenzylamine (**2a**), and *tert*-butyl isocyanide (**3a**) (Table 1). In accordance with literature procedures we opted to use MeOH as the solvent in the presence of anhydrous $MgSO_4$.[4b,e] The three components were employed in a (1:1:1) ratio. Gratifyingly, after 48 h of stirring at rt the desired product **4a** could be isolated in 45% yield along with unreacted starting material **1a** (Table 1, entry 1). Therefore, we decided to run the reaction at 60 °C. Although this resulted in a significant increase of the reaction rate (24 h to reach the same conversion), the total yield remained more or less the same (Table 1, entry 2) due to the presence of unreacted starting material **1a** along with some unidentifiable side products. Microwave irradiation has been described as a valuable technique to decrease the reaction time typically accompanied by suppression of side reactions.[7d] When the reaction mixture was irradiated at a ceiling temperature of 80 °C for 30 min, the desired product **4a** was obtained in a moderate yield of 62% (Table 1, entry 3). An increased reaction temperature even in combination with a longer reaction time did not affect the yield

Table 1. Optimization Study for the Synthesis of Dibenzo-[*c*,*e*]azepinone 4a[a]



entry	conditions	yield of **4a** (%)[b]
1	MeOH, rt, 48 h, $MgSO_4$	45[c]
2	MeOH, Δ, 60 °C, 24 h, $MgSO_4$	49[d]
3	MeOH, MW, 80 °C, 30 min, $MgSO_4$	62
4	MeOH, MW, 100 °C, 30 min, $MgSO_4$	64
5	MeOH, MW, 110 °C, 45 min, $MgSO_4$	65
6	**CF_3CH_2OH, MW, 110 °C, 50 min, Na_2SO_4**	**82**
7	CH_2Cl_2, MW, 110 °C, 50 min, Na_2SO_4	78
8	MeCN, MW, 110 °C, 50 min, Na_2SO_4	54

[a] The reactions were run at a 0.2 M concentration of starting material in the indicated solvent. To a solution of **1a** (0.44 mmol) was added amine **2a** (1.0 equiv) along with drying agent. The mixture was allowed to stir for 2 min at rt before isocyanide **3a** (1.0 equiv) was added and then was allowed to react according to the described conditions. For MW conditions, once isocyanide was added, the vial was flushed with argon (2 times) and sealed with a Teflon crimp cap. The mixture was irradiated in a CEM Explorer at the indicated ceiling temperature using a maximum power of 75 W for the stipulated time. [b] Isolated yields (single runs). [c] Unreacted starting material **1a** was detected along with product **4a**. [d] Unreacted starting material **1a** was detected along with some unidentified side product.

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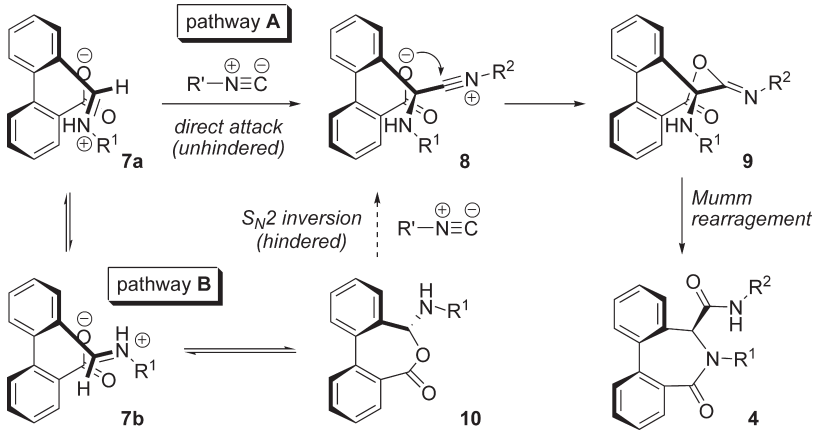
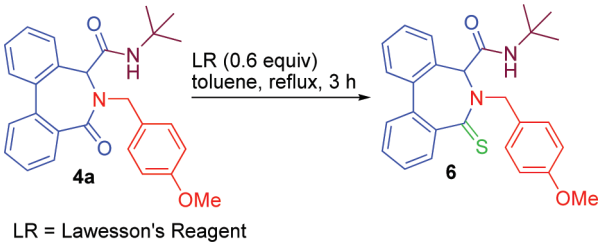
Scheme 2. Tentative Mechanism for the Diastereoselective Formation of Dibenzo[*c*,*e*]azepinones 4



noticeably (Table 1, entries 4 and 5). However, when switching to 2,2,2-trifluoroethanol as solvent at a ceiling temperature of 110 °C using a maximum power of 75 W for 50 min, the corresponding dibenzo[*c*,*e*]azepine-5-carboxamide **4a** was isolated in a good yield of 82% (Table 1, entry 6). Switching the solvent to CH_2Cl_2 resulted in a slightly diminished yield (Table 1, entry 7), and the use of MeCN afforded compound **4a** in a moderate yield of 54% (Table 1, entry 8). Interestingly, according to ^{1}H NMR, compound **4a** was obtained as a single diastereomer.

Having optimized the reaction conditions we evaluated the scope of the procedure. An array of differently substituted biaryl compounds **1a**−**f** were reacted with various amines and isocyanides (Table 2).[12] The corresponding dibenzo[*c*,*e*]azepinones **4b**−**ak** were obtained in good to excellent yields. The reactions were found to proceed well with benzylic amines as well as with a variety of linear and branched aliphatic amines, while a wide range of substituted isocyanide components could also be applied without diminishing the yields. Interestingly, also tryptamine, worked well using the optimized conditions (Table 2, entry 9). The application of phenylhydrazine in this Ugi reaction unexpectedly resulted in the formation of the 6-(phenylamino)-7-(2,2,2-trifluoroethoxy)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepin-5-one **5** (Table 2, entry 13). When the chiral amines (*S*)-(+)-2-phenylglycine methyl ester **2e** and L-leucinol **2p** were used, the corresponding Ugi products **4g** and **4w** were obtained as diastereomeric mixtures (1:1) as was indicated by ^{1}HNMR (Table 2, entry 6 and 23). Both diastereomers of compound **4g** could be separated by column chromatography affording one diastereomer with mp (210−212 °C) whose stereochemistry (a*R*,14*S*,20*S*) was unambiguously deduced by X-ray crystallography. This diastereomer crystallized in the chiral space group $P2_12_12_1$, and hence only one enantiomer is present in the structure.[13] The second diastereomer showed a mp (155−158 °C) but could not be crystallized. Compound **4w** obtained as a mixture was also unequivocally proven by X-ray crystallography. Interestingly, compound **4w** was crystallized in the chiral space group $P2_1$. The asymmetric unit contains two molecules, which are diastereoisomers, related by a noncrystallographic inversion center (90% fit). Moreover, we could also observe an intramolecular H-bonding between the hydroxyl group of (L)-leucinol and the carbonyl group resulting from the isocyanide.

Scheme 3



Interestingly, also α-acidic isocyanides such as TosMIC (entry 5) and 9-isocyanofluorene (entries 17 and 18) are converted to the corresponding Ugi products. Such α-acidic isocyanides often display different reactivity,[14] affording imidazole[15] or imidazoline[16] products.

A tentative mechanism is given in Scheme 2. The primary amine **2** first reacts with the carbonyl compound **1** to give an intermediate iminium ion **7a** after intramolecular protonation by the carboxylic acid moiety. Conformer **7a**, which is plausibly stabilized by favorable electrostatic interaction between the iminium and carboxylate moieties, may undergo direct nucleophilic attack by the isocyanide **3** to give **8** (pathway **A**). Nitrilium ion intermediate **8** then undergoes intramolecular acylation to give **9**.[17] The resulting imino anhydride **9** typically undergoes an irreversible transacylation (Mumm rearrangement)[18] to give the final Ugi 4CR product **4**. The relative stereochemistry of **8** can be deduced from the relative stereochemistry of **4**, which was elucidated by X-ray crystallography (See Supporting Information, Figure 1 and 2). Alternatively, conformer **7b** may be in equilibrium with *N*,*O*-acetal intermediate **10** (pathway **B**) as in the mechanism proposed earlier by Banfi et al.[19] The proposed S_N2 inversion to give **9** (via **8**) would, however, be very hindered in this case. Therefore, we believe the exclusive formation of the observed diastereomer of **4** supports the involvement of pathway **A** rather than pathway **B**.

Having successfully established the methodology for the synthesis of the dibenzo[*c*,*e*]azepinone scaffold, we next explored a possibility for further transformation. We discovered that

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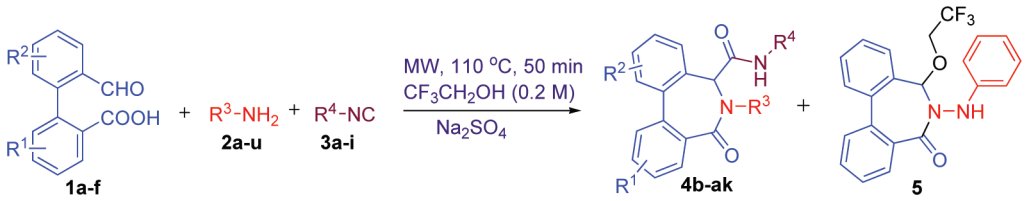
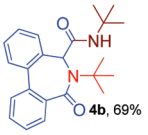
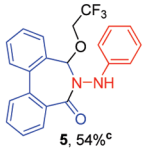
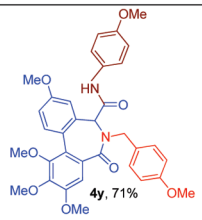
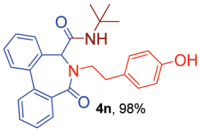
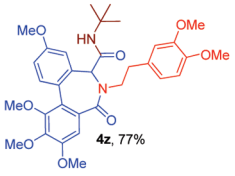
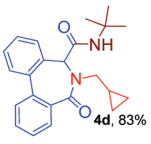
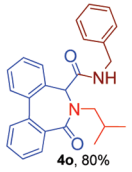
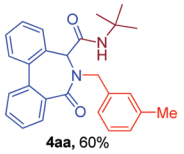
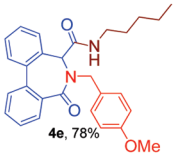
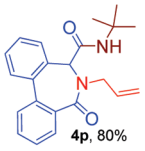
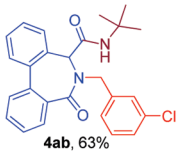
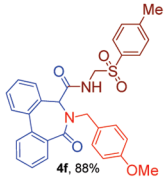
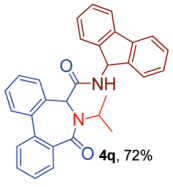
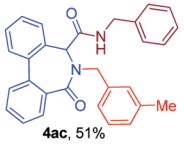
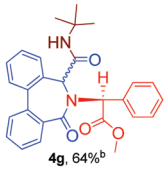
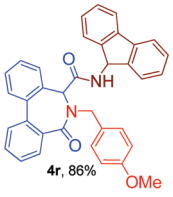
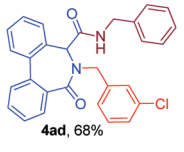
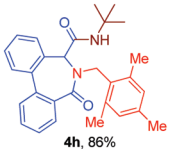
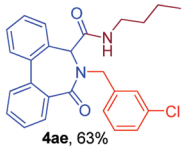
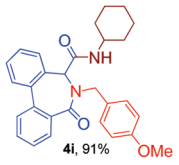
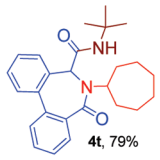
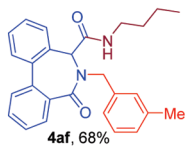
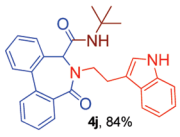
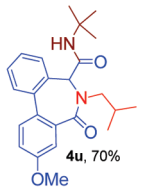
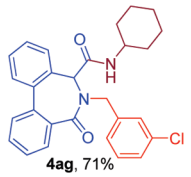
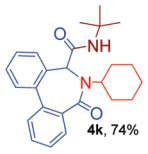
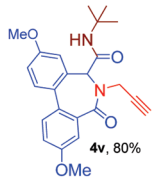
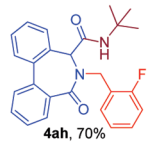
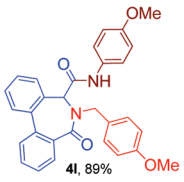
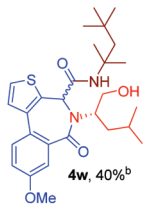
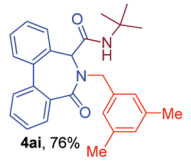
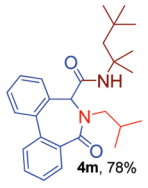
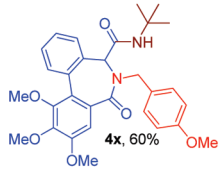
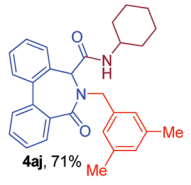
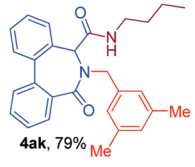
Table 2. Scope of the Optimized Protocol for the Diversity-Oriented Generation of Dibenzo[*c*,*e*]azepinones



entry	product[a]	entry	product[a]	entry	product[a]
1	 **4b**, 69%	13	 **5**, 54%[c]	25	 **4y**, 71%
2	 **4c**, 88%	14	 **4n**, 98%	26	 **4z**, 77%
3	 **4d**, 83%	15	 **4o**, 80%	27	 **4aa**, 60%
4	 **4e**, 78%	16	 **4p**, 80%	28	 **4ab**, 63%
5	 **4f**, 88%	17	 **4q**, 72%	29	 **4ac**, 51%
6	 **4g**, 64%[b]	18	 **4r**, 86%	30	 **4ad**, 68%
7	 **4h**, 86%	19	 **4s**, 76%	31	 **4ae**, 63%

dx.doi.org/10.1021/jo200251q |*J. Org. Chem.* 2011, 76, 2828–2839

Table 2. Continued

entry	product[a]	entry	product[a]	entry	product[a]
8	 **4i**, 91%	20	 **4t**, 79%	32	 **4af**, 68%
9	 **4j**, 84%	21	 **4u**, 70%	33	 **4ag**, 71%
10	 **4k**, 74%	22	 **4v**, 80%	34	 **4ah**, 70%
11	 **4l**, 89%	23	 **4w**, 40%[b]	35	 **4ai**, 76%
12	 **4m**, 78%	24	 **4x**, 60%	36	 **4aj**, 71%
				37	 **4ak**, 79%

[a] Isolated yields (single runs); the compounds were obtained as single diastereomer. [b] Combined yield for the mixture of two diastereomers that is formed (approximate ratio of 1:1). [c] Contrary to all previous results, the unexpected structure **5** was formed, as could be deduced from its ^{1}H and ^{13}C NMR data and X-ray crystal structure; see Supporting Information.

compound **4a**, when reacted with Lawesson's reagent in toluene at reflux temperature for 3 h, was turned into the corresponding thioamide **6** in 67% yield (Scheme 3). It might be clear that a further functionalization of the scaffold is possible via both amide moieties.

Biological Screening Results: Cytotoxicity Study. The **4a**−**z** series of compounds have been evaluated for their inhibitory effect against a wide variety of DNA and RNA viruses in cell culture, but none of them proved inhibitory at subtoxic concentrations. The compounds have also been investigated for their antiproliferative activity against two murine (leukemia L1210 and mammary carcinoma FM3A) and human (lymphocyte CEM and cervix carcinoma HeLa) tumor cell lines. The cytostatic activities (50% inhibitory concentrations) varied between 13 and 828 μM depending the nature of the test compounds. There was in general a fairly good correlation for the cytostatic activities of the compounds between the murine and human tumor cell lines ($r = 0.8991$), and between the murine leukemia L1210 and the FM3A, CEM and HeLa cell lines ($r = 0.911$, 0.9348 and 0.8863, respectively).[12]

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There were three compounds that consistently showed IC_{50} values equal or slightly less than 20 μM against all four tumor cell lines (e.g., **4 h**, **4q**, and **4s**).

Most closely related to **4h** were **4j**, **4n**, **4p**, and **4t**, which differed only in the nature of the substituent at the azepinone ring nitrogen. Their cytostatic activities, however, were substantially lower than **4h**. Therefore, the benzyl moiety should be further substituted with a variety of para, ortho, or meta substituents. The only compound closely related to **4q** was **4r**, which was 3- to 7-fold less cytostatic. When in compound **4s** the nonyl chain was replaced by a propynyl moiety, the cytostatic activity dropped by 10- to 20-fold. It might be interesting to combine potential beneficial substituents in the three lead structures to find out whether superior antiproliferative activity can be achieved. For example, a para, meta, or ortho alkylbenzyl moiety on the N atom of the seven-membered azepinone ring in which the alkyl might represent a butyl, pentyl, or hexyl group might be worth considering for further research. Also, replacing the *tert*-butyl moiety on the amide function by a tricyclic entity such as in **4q** might be synthesized and evaluated.

The compounds **4e** and **4i** display some borderline anti-HIV-1 activity with IC_{50} values of $\geq$12.6 μg/mL (SI $\leq$ 4) and $\geq$21.4 μg/mL (SI $\leq$ 2), respectively. Furthermore both compounds completely lack anti-HIV-2 activity, pointing to a possible NNRTI mode of action. When the anti-HIV activity of compounds **4e** and **4i** was assessed using a typical NNRTI-resistant double (K103N and Y181C) mutant strain, the anti-HIV-1 activity completely disappears, confirming the typical first generation NNRTI mode of action of these compounds. In an attempt to improve on the potency and selectivity of the compounds, the substitution pattern on the benzyl moiety was further explored leading to the synthesis of derivatives **4aa**−**ak** (Table 2) having other substitution patterns than the *p*-methoxy commonly present in **4e** and **4i**. Unfortunately none of the derivatives, **4aa**−**ak**, surpassed the anti-HIV activity of the lead molecules **4e** and **4i**.

In conclusion, we have developed an efficient procedure for the generation of the dibenzo[*c*,*e*]azepinone scaffold via an intramolecular Ugi 4CR of a suitably substituted biaryl compound. Excellent yields, high diastereoselectivities, and tolerance of various groups toward the reaction conditions are the merits of this protocol. It has been demonstrated that the reaction greatly benefits from the use of microwave irradiation. Several lead compounds were discovered with antiproliferative activity against tumor cell lines in the lower micromolar range.

EXPERIMENTAL SECTION

Cytostatic Assays. Murine leukemia L1210, murine mammary carcinoma FM3A, human T-lymphocyte CEM, and human cervix carcinoma (HeLa) cells were suspended at 300,000−500,000 cells/mL of culture medium, and 100 μL of a cell suspension was added to 100 μL of an appropriate dilution of the test compounds in wells of 96-well microtiter plates. After incubation at 37 °C for 2 (L1210, FM3A) or 3 (CEM, HeLa) days, the cell number was determined using a Coulter counter. The IC_{50} was defined as the compound concentration required to inhibit cell proliferation by 50%.

Antiviral Assays. The antiviral assays [except antihuman immunodeficiency virus (HIV) assays] were based on inhibition of virus-induced cytopathicity in HEL [herpes simplex virus type 1 (HSV-1), HSV-2 (G), vaccinia virus, and vesicular stomatitis virus], Vero (parainfluenza-3, reovirus-1, Sindbis, Coxsackie B4, and Punta Toro virus), HeLa (vesicular stomatitis virus, Coxsackie virus B4, and respiratory syncytial virus), CrFK (feline herpes virus (FHV) and feline coronavirus (FIPV)), and MDCK (influenza virus A (H1N1, H3N2) and B) cell cultures. Confluent cell cultures in microtiter 96-well plates were inoculated with 100 cell culture inhibitory dose-50 ($CCID_{50}$) of virus (1 $CCID_{50}$ being the virus dose to infect 50% of the cell cultures) in the presence of varying concentrations (100, 20, 4, ... μg/mL) of the test compounds. Viral cytopathicity was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds.

Evaluation of the antiviral activity of the compounds against HIV in MT-4 cells was performed by using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay as previously described.[20] Stock solutions (10× final concentration) of test compounds were added in 25-μL volumes to two series of triplicate wells to allow the simultaneous evaluation of their effects on mock- and HIV-infected cells at the beginning of each experiment. Serial 5-fold dilutions of test compounds were made directly in flat-bottomed 96-well microtiter trays using a Biomek 3000 robot (Beckman Instruments, Fullerton, CA). Untreated HIV- and mock-infected cell samples were included as controls. An HIV stock (50 μL) at 100 to 300 50% cell culture infectious doses ($CCID_{50}$) or culture medium was added to either the infected or mock-infected wells of the microtiter tray. Mock-infected cells were used to evaluate the effects of the test compound on uninfected cells in order to assess the cytotoxicity of the test compounds. Exponentially growing MT-4 cells were centrifuged for 5 min at 1,000 rpm, and the supernatant was discarded. The MT-4 cells were resuspended at 6×10^5 cells/ml, and 50-μL volumes were transferred into the microtiter tray wells. Five days after infection, the viability of mock- and HIV-infected cells was examined spectrophotometrically by using the MTT assay. The MTT assay is based on the reduction of yellow MTT (Acros Organics, Geel, Belgium) by the mitochondrial dehydrogenase of metabolically active cells to a blue-purple formazan that can be measured spectrophotometrically. The absorbances were read in an eight-channel computer-controlled photometer (Multiscan Ascent reader; Labsystems, Helsinki, Finland) at two wavelengths (540 and 690 nm). All data were calculated by using the median optical density (OD) value of three wells. The 50% cytotoxic concentration (CC_{50}) was defined as the concentration of the test compound that reduced the absorbance (OD at 540 nm [OD_{540}]) of the mock-infected control sample by 50%. The concentration achieving 50% protection against the cytopathic effect of the virus in infected cells was defined as the 50% effective concentration (EC_{50}).

General Remarks for Newly Synthesized Compounds. ^1H and ^{13}C NMR spectra were recorded on 250, 300, 400, and 500 MHz NMR instrument. The ^1H chemical shifts are reported in ppm relative to tetramethylsilane. High-resolution mass spectra were recorded by using ion source temperature 150−250 °C as required. High-resolution electron impact (EI) mass spectra were performed with a resolution of 10000. EI mass spectrometry was carried out with an electron ionization voltage of 70 eV. Fast atom bombardment (FAB) mass spectrometry was carried out using a four-sector mass spectrometer, coupled to a system program (samples were loaded in a matrix solution (3-nitrobenzyl alcohol) onto a stainless steel probe and bombarded with xenon atoms (3 KeV)). For thin layer chromatography, analytical TLC plates SIL G/UV254 and 70−230 mesh silica gel were used. Reagents were used without further purification. Solvents such as cyclohexane, CH_2Cl_2, heptane, and ethyl acetate were distilled prior to use; CH_2Cl_2 was dried under molecular sieves. Melting points are uncorrected.

Microwave Irradiation Experiments. All microwave irradiation experiments were carried out in a dedicated CEM-Explorer and CEM-Discover monomode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W with utilization of the standard absorbance level of 300 W maximum power. The reactions were carried out in 10-mL glass tubes, sealed with a Teflon

septum and placed in the microwave cavity. Initially, microwave irradiation of required watts was used, and the temperature was ramped from room temperature to the desired temperature. Once this was reached the reaction mixture was held at this temperature for the required time. The reaction mixture was continuously stirred during the reaction. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, gas jet cooling rapidly cooled the reaction vessel to ambient temperature.

General Procedure for the Synthesis of Biarylacid (1) by Suzuki−Miyaura Cross-Coupling. Bromoester **A** (5 mmol), *o*-formylphenylboronic acid **B** (5.5 mmol, 1.1 equiv) and tetrakis-(triphenylphosphine)palladium(0) (0.11 mmol, 1 mol %) were suspended in 1,4-dioxane (3 mL) in a 10 mL glass reaction vial containing a stirring bar. To this were added Na_2CO_3 (10 mmol, 2 equiv) and water (2 mL), and the vial was sealed tightly with a Teflon crimp top. The mixture was irradiated for 25 min at a preselected temperature of 120 °C, with an irradiation power of 100 W. After the reaction, the vial was cooled to 40 °C by gas jet cooling. The crude mixture was partitioned between ethyl acetate (25 mL) and brine (25 mL), and the aqueous layer (brine + H_2O) was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried on $MgSO_4$, and solvent was removed under reduced pressure to yield the crude product **C1−6** as yellow oil. Column chromatography [silica gel, 20% ethyl acetate/heptanes] afforded analytically pure product as a colorless or yellow oil. These compounds were further used for hydrolysis of the ester group. To a solution of corresponding ester **C1−6** in THF (25 mL) was added LiOH (1 M soln in H_2O, 5 equiv), and the reaction mixture was heated overnight at 40 °C. The resulting solution was neutralized with 1 N HCl solution until the pH = 7.0 (careful addition of acid and proper check with pH paper). A white hazy solution was obtained at the neutral pH and was extracted with ethyl acetate (100 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to afford the corresponding biaryl acid **1a−f** as a white or yellow solid.

Characterization of Compounds C1−6. *Methyl 2′-Formyl-[1,1′-biphenyl]-2-carboxylate (**C1**).* Colorless oil, 84% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (s, 1H), 8.06−7.99 (m, 2H), 7.62−7.48 (m, 4H), 7.31−7.23 (m, 2H), 3.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 191.6, 167.1, 145.1, 139.3, 133.7, 133.1, 131.6 (× 2), 130.4, 130.0, 128.2, 127.8, 127.3, 52.0. HRMS (EI): calcd for $C_{15}H_{12}O_3$ 240.0786, found 240.0790.

*Methyl 2′-Formyl-4-methoxy-[1,1′-biphenyl]-2-carboxylate (**C2**).* Colorless oil, 98% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.81 (s, 1H), 8.0 (dd, *J* = 8.90 Hz, 1.2 Hz, 1H), 7.58 (dt, *J* = 15.1, 7.45, 1.52 Hz, 1H), 7.55 (d, *J* = 2.45 Hz, 1H), 7.46 (t, *J* = 15.00, 7.51 Hz, 1H), 7.24−7.20 (m, 1H), 7.19 (s, 1H), 7.11 (dd, *J* = 11.13 Hz, 2.69 Hz, 1H), 3.91 (s, 3H), 3.60 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 191.9, 167.1, 159.3, 145.1, 134.2, 133.1, 132.9, 131.6, 131.5, 130.5, 127.7, 127.3, 117.8, 115.0, 55.6, 52.1. HRMS (EI): calcd for $C_{16}H_{14}O_4$ 270.0892, found 270.0895.

*Methyl 2′-Formyl-4,4′-dimethoxybiphenyl-2-carboxylate (**C3**).* HRMS (EI): calcd for $C_{17}H_{16}O_5$ 300.0998, found 300.1004. The compound was used for the hydrolysis without furthur characterization.

*Methyl 2-(2-Formylthiophen-3-yl)-5-methoxybenzoate (**C4**).* Yellow oil, 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.60 (s, 1H), 7.69 (d, *J* = 4.89 Hz, 1H), 7.53 (d, *J* = 2.64 Hz, 1H), 7.29−7.26 (m (merged with chloroform peak), 1H), 7.11 (dd, *J* = 2.64, 8.47 Hz, 1H), 7.04 (d, *J* = 4.89 Hz, 1H), 3.90 (s, 3H), 3.69 (s, 3H). HRMS (EI): calcd for $C_{14}H_{12}O_4S$ 276.0456, found 276.0459.

*Methyl 2′-Formyl-4,5,6-trimethoxy-[1,1′-biphenyl]-2-carboxylate (**C5**).* Yellow oil, 54% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.82 (s, 1H), 8.01 (d, *J* = 6.60 Hz, 1H), 7.59 (dt, *J* = 1.32, 7.53 Hz, 1H), 7.49 (t, *J* = 7.53 Hz, 1H), 7.37 (s, 1H), 7.18 (d, *J* = 7.17 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.53 (s, 3H), 3.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 192.0, 166.8, 153.0, 151.4, 145.4, 140.6, 134.2, 133.1, 130.7, 127.7, 127.3, 127.0, 125.7, 109.4, 61.0, 60.7, 56.1, 52.0. HRMS (EI): calcd for $C_{18}H_{18}O_6$ 330.1103, found 330.1106.

*Methyl 2′-Formyl-4,4′,5,6-tetramethoxy-[1,1′-biphenyl]-2-carboxylate (**C6**).* Yellow viscous oil, 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.75 (s, 1H), 7.52 (d, *J* = 2.64 Hz, 1H), 7.35 (s, 1H), 7.15 (dd, *J* = 2.64, 8.49 Hz, 1H), 7.09 (d, *J* = 8.46 Hz, 1H), 3.96 (s, 3H), 3.95 (m, 6H), 3.90 (s, 3H), 3.57 (s, 3H), 3.51 (s, 3H). HRMS (EI): calcd for $C_{19}H_{20}O_7$ 360.1209, found 360.1211.

Characterization of Compounds 1a−f. *2′-Formylbiphenyl-2-carboxylic Acid (**1a**)*[1]. The characteristic data of the compound were in accordance with the one reported in the literature.

*2′-Formyl-4-methoxybiphenyl-2-carboxylic Acid (**1b**).* White solid mp 179−181 °C in 99% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.97−7.94 (d, *J* = 7.65 Hz, 2H), 7.60−7.44 (m, 3H), 7.22−7.14 (m, 3H), 3.89 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 192.0, 171.1, 159.4, 144.8, 134.2, 133.3, 133.2, 132.4, 130.6, 130.2, 127.8, 127.6, 118.9, 115.6, 55.7. HRMS (EI): calcd for $C_{15}H_{12}O_4$ 256.0736, found 256.0737.

*2′-Formyl-4,4′-dimethoxybiphenyl-2-carboxylic Acid (**1c**).* Yellow solid mp 164−166 °C in 97% yield. ^{1}H NMR (300 MHz, DMSO): δ 12.80 (bs, 1H), 9.67 (s, 1H), 7.58 (bs, 1H), 7.41−7.22 (m, 5H), 3.85 (s, 6H). ^{13}C NMR (75 MHz, DMSO): 167.9, 158.6, 158.4, 134.6, 133.3, 133.1, 132.1, 131.5, 131.4, 129.8, 128.8, 128.6, 120.0, 116.9, 114.4, 109.8, 55.4 (× 2). HRMS (EI): calcd for $C_{16}H_{14}O_5$ 286.0841, found 286.0845.

*2-(2-Formylthiophen-3-yl)-5-methoxybenzoic Acid (**1d**).* White solid mp 158−160 °C in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.61 (s, 1H), 7.69−7.68 (d, *J* = 3.78 Hz, 1H), 7.64 (s, 1H), 7.30 (s, 1H), 7.18−7.15 (m, 1H), 7.04−7.05 (d, 1H), 3.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 183.7, 171.1, 159.9, 150.2, 139.0, 133.4, 133.1, 131.4, 130.7, 127.7, 118.8, 116.3, 55.8. HRMS (EI): calcd for $C_{13}H_{10}O_4S$ 262.0300, found 262.0302.

*2′-Formyl-4,5,6-trimethoxybiphenyl-2-carboxylic Acid (**1e**).* White solid mp 142−144 °C in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.99 (d, *J* = 7.53 Hz, 1H), 7.60−7.54 (dt, *J* = 1.29, 7.44 Hz, 1H), 7.48 (t, *J* = 7.53 Hz, 1H), 7.17 (d, *J* = 7.53 Hz, 1H), 3.96−3.95 (m, 6H), 3.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 192.1, 171.1, 153.0, 151.6, 146.3, 140.3, 134.2, 133.2, 130.8, 128.1, 127.8, 127.6, 124.2, 110.3, 61.1, 60.8, 56.3. HRMS (EI): calcd for $C_{17}H_{16}O_6$ 316.0947, found 316.0948.

*2′-Formyl-4,4′,5,6-tetramethoxybiphenyl-2-carboxylic Acid (**1f**).* White solid mp 132−134 °C in 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73 (s, 1H), 7.49−7.43 (m, 2H), 7.15−7.07 (m, 2H), 3.95−3.91 (m, 9H), 3.49 (s, 3H). HRMS (EI): calcd for $C_{18}H_{18}O_7$ 346.1053, found 346.1056.

General Procedure for Intermolecular U4CR Reaction for the Synthesis of the Dibenzo[*c*,*e*]azepinone Ring System. In a microwave vial equipped with a magnetic stir bar, biaryl acid **1a−f** (100 mg, 1.0 equiv) was dissolved in 3 mL of 2,2,2-trifluoroethanol along with Na_2SO_4 (0.25 g). Then the corresponding amine **2a−u** (1.0 equiv) was added, and the mixture was allowed to stir for 5 min at room temperature. After a light yellow solution is obtained the corresponding isocyanide **3a−i** (1.0 equiv) was added, and the vial was flushed with nitrogen (3 times) and sealed with Teflon crimp. Then it was irradiated with CEM-Explorer or CEM-Discover microwave for 50 min at a ceiling temperature of 110 °C. After the completion of the reaction the mixture was allowed to cool to room temperature with external gas jet cooling (∼ 2 min). The resulting mixture was diluted with EtOAc and was extracted with brine solution. The organic layer was separated, the aqueous layer (brine + water) was extracted with EtOAc (2 × 10 mL), and combined organic layers were dried on Na_2SO_4, evaporated to give crude mixture, loaded on a silica gel column, and eluted with (20% ethyl acetate/heptane mixture) or (20% ethyl acetate/cyclohexane mixture) to afford the desired dibenzo[*c*,*e*]azepinone scaffold (**4a−ak**) and **5**.

Characterization of Compounds 4a−ak and 5. *N-tert-Butyl-6-(4-methoxybenzyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4a**).* White solid mp 168−170 °C in 82% yield. ^{1}H

NMR (250 MHz, $CDCl_3$): δ 7.95 (d, J = 7.5 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.51−7.42 (m, 4H), 7.31 (t, J = 8.6 Hz, 3H), 7.01 (d, J = 7.4 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 5.16 (d, J = 14.2 Hz, 1H), 5.04 (s, 1H), 4.75 (s, 1H), 4.52 (d, J = 14.3 Hz, 1H), 3.81 (s, 3H), 0.75 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.5, 166.8, 159.6, 137.5, 137.4, 136.9, 134.6, 131.1, 130.9, 130.4 (× 2), 129.5, 129.4, 129.3, 129.1, 128.7, 128.1 (× 2), 114.4, 65.8, 55.4, 51.9, 51.0, 27.8, 26.9. HRMS (FAB): calcd for $C_{27}H_{29}O_3N_2$ (MH^+) 429.2173, found 429.2166.

*N,6-Di-tert-butyl-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4b**).* White solid mp 143−145 °C in 69% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, J = 7.5 Hz, 1H), 7.64 (dd, J = 1.1, 7.7 Hz, 1H), 7.5 (dd, J = 1.4, 7.6 Hz, 1H), 7.47−7.44 (m, 2H), 7.41−7.39 (m, 2H), 7.35 (dd, J = 1.2, 7.5 Hz, 1H), 5.27 (s, 1H), 5.17 (s, 1H), 1.59 (s, 9H), 0.86 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 169.1, 167.8, 138.6, 137.4 (× 2), 135.5, 131.2, 130.4, 129.3, 129.2, 129.0, 128.3, 128.0, 127.6, 62.6, 59.7, 51.0, 29.1, 27.9. HRMS (FAB): calcd for $C_{23}H_{29}O_2N_2$ (MH^+) 366.2224, found 365.2215.

*N-tert-Butyl-6-isobutyl-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4c**).* White solid mp 128−130 °C in 88% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 7.1 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.49−7.48 (m, 3H), 7.43−7.37 (m, 2H), 7.33 (d, J = 6.3 Hz, 1H), 5.18 (s, 1H), 4.72 (s, 1H), 3.65 (dd, J = 7.7, 13.15, 1H), 3.50 (dd, J = 7.1, 13.5, 1H), 2.03 (septet, J = 6.8 Hz, 1H), 1.01 (d, J = 6.65 Hz, 3H), 0.87 (s, 9H), 0.76 (d, J = 6.65 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.8, 166.9, 137.7, 137.6, 136.4, 131.1, 129.8, 129.6, 129.5, 128.5, 128.4, 67.7, 57.5, 51.3, 28.1, 28.0, 27.0, 20.6, 19.8. HRMS (FAB): calcd for $C_{23}H_{29}O_2N_2$ (MH^+) 365.2224, found 365.2223.

*N-tert-Butyl-6-(cyclopropylmethyl)-7-oxo-6,7-dihydro-5H-dibenzo-[c,e]azepine-5-carboxamide (**4d**).* Colorless Oil in 83% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, J = 7.85 Hz, 1H), 7.60 (d, J = 7.4 Hz, 1H), 7.52−7.51 (m, 2H), 7.45−7.43 (m, 2H), 7.39−7.36 (m, 2H), 5.64 (s, 1H), 4.93 (s, 1H), 3.77 (dd, J = 7.7, 14.1, 1H), 3.47 (dd, J = 6.6, 14.1, 1H), 1.12−1.18 (m, 1H), 0.91 (s, 9H), 0.61−0.58 (m, 2H), 0.48−0.45 (m, 1H), 0.39−0.37 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.4, 167.1, 137.7, 137.5, 136.7, 134.8, 131.0, 129., 129.5, 129.3, 128.7, 128.1, 128.1, 66.9, 53.4, 51.1, 28.0, 26.9, 10.3, 4.1, 4.0. HRMS (FAB): calcd for $C_{23}H_{27}O_2N_2$ (MH^+) 363.2067, found 363.2077.

*6-(4-Methoxybenzyl)-7-oxo-N-pentyl-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4e**).* White solid mp 158−160 °C in 78% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 7.7 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.51−7.41 (m, 4H), 7.30−7.27 (m, 3H), 6.93 (d, J = 6.6 Hz, 1H), 6.85 (d, J = 8.65 Hz, 2H), 5.17 (t, J = 5.35 Hz, 1H), 5.01 (d, J = 14.5 Hz, 1H), 4.76 (s, 1H), 4.73 (d, J = 14.5 Hz, 1H), 3.80 (s, 3H), 2.75−2.72 (m, 1H), 2.60−2.57 (m, 1H), 1.10−1.09 (m, 2H), 0.86−0.84 (m, 4H), 0.79 (t, J = 7.5 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 167.6, 159.4, 137.7, 137.0, 136.4, 134.6, 131.0, 130.9, 130.3, 129.5, 129.4, 129.3, 128.9, 128.5, 128.1 (× 2), 114.2, 65.0, 55.3, 51.8, 39.6, 28.7 (× 2), 26.9, 22.1, 13.8. HRMS (FAB): calcd for $C_{28}H_{31}O_3N_2$ (MH^+) 443.2329, found 443.2345.

*6-(4-Methoxybenzyl)-7-oxo-N-(tosylmethyl)-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4f**).* Colorless oil 88% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.90 (dd, J = 1.9, 8.0 Hz, 1H), 7.57 (d, J = 6.7 Hz, 1H), 7.49−7.38 (m, 6H), 7.30−7.19 (m, 6H), 6.93 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 6.6 Hz, 1H), 5.99 (t, J = 6.7 Hz, 1H), 4.89 (d, J = 14.4 Hz, 1H), 4.68 (d, J = 14.5 Hz, 1H), 4.57 (s, 1H), 4.06 (d, J = 6.8 Hz, 2H), 3.84 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.6, 167.8, 159.7, 145.5, 137.7, 136.2, 135.7, 134.2, 133.8, 131.4, 130.8, 130.4, 130.0, 129.9, 129.8, 129.2, 128.6, 128.5 (× 2), 128.4, 128.3, 114.6, 64.2, 60.2, 55.5, 51.4, 30.2, 27.0 (× 2), 21.8, 14.3. HRMS (FAB): calcd for $C_{31}H_{29}O_5N_2S$ (MH^+) 541.1792, found 541.1790.

Two diastereoisomers separated for **4g**:

*1st Diastereoisomer: (S)-Methyl 2-((S)-5-(tert-Butylcarbamoyl)-7-oxo-5H-dibenzo[c,e]azepin-6(7H)-yl)-2-phenylacetate (**4g**).* (Confirmed by X-ray crystallography) White solid mp 210−214 °C in 64% combined yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (bs, 1H), 7.91 (d, J = 7.55 Hz, 1H), 7.54−7.45 (m, 7H), 7.34−7.31 (m, 1H), 7.25−7.20 (d, J = 7.55 Hz, 2H), 7.08−7.05 (dt, J = 1.25, 7.47 Hz, 1H), 6.17 (s, 1H), 6.07 (d, J = 7.6 Hz, 1H), 4.64 (s, 1H), 3.87 (s, 3H), 1.01 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 173.3, 169.3, 167.8, 138.7, 137.8, 137.4, 133.3, 132.4, 131.6, 130.4, 130.0, 129.7, 129.2, 129.1, 128.9, 128.6, 127.8, 127.7, 62.1, 53.1, 51.1, 28.1, 27.0. HRMS (FAB): calcd for $C_{28}H_{29}O_4N_2$ (MH^+) 457.2122, found 457.2123. $[\alpha]^{20}_D$ = +55.9 (c 0.294, $CHCl_3$)

*2nd Diastereoisomer: (S)-Methyl 2-((R)-5-(tert-Butylcarbamoyl)-7-oxo-5H-dibenzo[c,e]azepin-6(7H)-yl)-2-phenylacetate (**4g**).* (Structure assumed from X-ray crystallographic data of first diastereoisomer) Light pink solid mp 155−158 °C in 64% combined yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 15.1 Hz, 1H), 7.59−7.33 (m, 11H), 7.24 (d, J = 14.8 Hz, 1H), 6.28 (s, 1H), 5.56 (bs, 1H), 4.92 (s, 1H), 3.65 (s, 3H), 0.77 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 170.0, 168.9, 166.7, 137.9, 137.2 (× 2), 134.1, 131.4, 130.7, 129.7, 129.4, 129.2, 129.1, 129.0, 129.0, 128.0 (× 2), 64.5, 64.4, 52.5, 51.0, 27.8. HRMS (FAB): calcd for $C_{28}H_{29}O_4N_2$ 457.2122, found 457.21236. $[\alpha]^{20}_D$ = −34.3 (c 0.396, $CHCl_3$)

*N-tert-Butyl-7-oxo-6-(2,4,6-trimethylbenzyl)-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4h**).* White solid mp 70−72 °C in 86% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, J = 7.1 Hz, 1H), 7.58 (d, J = 6.7 Hz, 1H), 7.54−7.42 (m, 4H), 7.20−7.17 (m, 1H), 6.89 (s, 2H), 6.43 (d, J = 6.6 Hz, 1H), 5.19 (d, J = 14.5 Hz, 1H), 5.00 (s, 1H), 4.87 (d, J = 14.5 Hz, 1H), 4.48 (s, 1H), 2.34 (s, 3H), 2.18 (s, 6H), 0.82 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.4, 167.3, 138.7, 138.0, 137.4, 137.3, 136.5, 135.0, 131.2, 130.9, 129.5, 129.4, 129.3, 129.2, 128.4, 128.2, 127.9, 62.9, 51.1, 45.1, 27.9, 26.9, 21.0, 19.9. HRMS (FAB): calcd for $C_{29}H_{33}O_2N_2$ (MH^+) 441.2537, found 441.2555.

*N-Cyclohexyl-6-(4-methoxybenzyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4i**).* White solid mp 164−166 °C in 91% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 7.4 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.52−7.41 (m, 4H), 7.33−7.28 (m, 3H), 6.99 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 5.14 (d, J = 14.3 Hz, 1H), 4.99 (d, J = 8.3 Hz, 1H), 4.76 (s, 1H), 4.57 (d, J = 14.3 Hz, 1H), 3.81 (s, 3H), 3.19−3.17 (m, 1H), 1.50−1.30 (m, 3H), 1.23−0.95 (m, 5H), 0.57−0.44 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.6, 166.7, 159.6, 137.8, 137.1, 136.7, 134.5, 131.2, 131.0, 130.4, 129.6, 129.4 (× 2), 128.6, 128.2, 114.5, 65.3, 55.4, 51.8, 48.0, 32.4, 32.3, 27.0, 25.4, 24.6. HRMS (FAB): calcd for $C_{29}H_{31}O_3N_2$ (MH^+) 455.2329, found 455.2342.

*6-(2-(1H-Indol-3-yl)ethyl)-N-tert-butyl-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4j**).* White solid mp 185−187 °C in 84% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (bs, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.58 (d, J = 6.6 Hz, 1H), 7.50−7.41 (m, 4H), 7.34 (t, J = 7.55 Hz, 2H), 7.22−7.15 (m, 4H), 5.18 (s, 1H), 4.78 (s, 1H), 4.48−4.42 (m, 1H), 3.88−3.83 (m, 1H), 3.31−3.24 (m, 1H), 3.16−3.11 (m, 1H), 0.61 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.8, 167.0, 137.7, 137.4, 136.6, 135.1, 131.1, 130.6, 129.6 (× 2), 129.4, 128.7, 128.3, 128.2, 127.5, 122.2, 122.1, 119.5, 118.6, 112.2, 111.4, 67.6, 50.9, 49.3, 46.3, 27.6, 24.1, 11.7. HRMS (FAB): calcd for $C_{29}H_{30}O_2N_3$ (MH^+) 452.2333, found 451.2349.

*N-tert-Butyl-6-cyclohexyl-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4k**).* White solid mp 75−77 °C in 74% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.49−7.42 (m, 4H), 7.40−7.38 (m, 2H), 5.26 (s, 1H), 4.93 (s, 1H), 4.82−4.77 (m, 1H), 1.98 (m, 1H), 1.91 (m, 1H), 1.77 (m, 1H), 1.68 (m, 2H), 1.52 −1.46 (m, 4H), 1.40−1.37 (m, 2H), 1.17−1.14 (m, 1H), 0.86 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.2, 167.6, 139.0, 137.7, 136.4, 135.5, 131.2, 130.9, 129.6, 129.5, 129.3, 128.6, 128.3, 128.2, 61.4, 55.1, 51.3, 32.0, 31.3, 28.1, 26.0, 25.8, 25.7. HRMS (FAB): calcd for $C_{25}H_{31}O_2N_2$ (MH^+) 391.2371, found 391.2383.

*6-(4-Methoxybenzyl)-N-(4-methoxyphenyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4l**).* White solid mp 217−219 °C

in 89% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 7.4 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.52−7.50 (m, 3H), 7.42−7.40 (m, 3H), 7.36 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 7.4 Hz, 1H), 6.93 (d, J = 8.6 Hz, 2H), 6.72 (s, 1H), 6.65 (d, J = 9.1 Hz, 2H), 6.59 (d, J = 9.1 Hz, 2H), 5.23 (d, J = 14.5 Hz, 1H), 4.93 (s, 1H), 4.62 (d, J = 14.3 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.7, 166.2, 159., 156.8, 137.9, 136.8, 136.6, 134.4, 131.3, 130.9, 130.5, 129.7 (× 2), 129.6, 129.4, 129.0, 128.6, 128.4, 128.3, 122.4, 114.6, 113.9, 65.4, 55.5 (× 2), 51.7. HRMS (FAB): calcd for $C_{30}H_{27}O_4N_2$ (MH^+) 479.1965, found 479.1981.

6-Isobutyl-7-oxo-N-(2,4,4-trimethylpentan-2-yl)-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (***4m***). Colorless oil in 78% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.50−7.38 (m, 5H), 7.35 (d, J = 6.6 Hz, 1H), 5.26 (s, 1H), 4.67 (s, 1H), 3.73 (dd, J = 8.0, 13.5, 1H), 3.41 (dd, J = 6.9, 13.4, 1H), 2.02 (septet, J = 7.1 Hz, 1H), 1.30 (d, J = 15 Hz, 1H), 1.21 (d, J = 14.9 Hz, 1H), 1.01−0.99 (m, 6H), 0.77−0.74 (m, 15H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.6, 166.3, 137.6 (× 2), 136.0, 135.5, 131.2, 130.8, 129.7, 129.6, 129.4, 128.4, 128.3 (× 2), 67.8, 57.6, 55.3, 52.9, 31.4, 31.2, 27.9, 27.4, 20.5, 19.7. HRMS (FAB): calcd for $C_{27}H_{37}O_2N_2$ (MH^+) 421.2850, found 421.2860.

N-tert-Butyl-6-(4-hydroxyphenethyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (***4n***). White solid mp 107−109 °C in 98% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, J = 7.4 Hz, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.51−7.50 (m, 3H), 7.45−7.38 (m, 3H), 7.27 (d, J = 7.4 Hz, 1H), 7.01 (d, J = 6.95 Hz, 2H), 6.72 (d, J = 8.2 Hz, 2H), 5.12 (s, 1H), 4.79 (s, 1H), 4.06−4.01 (m, 1H), 3.92−3.86 (m, 1H), 3.00−2.94 (m, 1H), 2.91−2.86 (m, 1H), 0.82 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.8, 166.9, 155.1, 137.5 (× 2), 136.5, 134.9, 131.2, 131.0, 129.8 (× 2), 129.7, 129.6, 128.7, 128.6, 128.4, 115.7, 67.9, 52.0, 51.4, 33.6, 28.0. HRMS (FAB): calcd for $C_{27}H_{29}O_3N_2$ 429.2173, found 429.2182.

N-Benzyl-6-isobutyl-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (***4o***). White solid mp 158−160 °C in 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, J = 6.45 Hz, 1H), 7.63 (d, J = 7.55 Hz, 1H), 7.53−7.38 (m, 6H), 7.21−7.19 (m, 3H), 6.78 (d, J = 6.00 Hz, 2H), 5.58 (t, J = 5.2 Hz, 1H), 4.85 (s, 1H), 4.15−4.12 (m, 1H), 3.94−3.90 (m, 1H), 3.76−3.71 (m, 1H), 3.50−3.46 (m, 1H), 2.08−2.03 (m, 1H), 1.03 (d, J = 6.60 Hz, 3H), 0.76 (d, J = 6.60 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.6, 167.9, 137.8, 137.4, 137.0, 135.7, 135.1, 131.1, 130.9, 129.9, 129.8, 129.5, 128.6, 128.4 (× 2), 128.3, 127.7, 127.4, 67.2, 57.5, 43.8, 27.9, 20.5, 19.7. HRMS (FAB): calcd for $C_{26}H_{27}O_2N_2$ (MH^+) 399.2067, found 399.2060.

6-Allyl-N-tert-butyl-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (***4p***). White solid mp 120−122 °C in 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.52−7.48 (m, 3H), 7.46−7.42 (m, 1H), 7.38 (dt, J = 1.2, 6.9 Hz, 1H), 7.30 (d, J = 6.5 Hz, 1H), 5.90−5.83 (m, 1H), 5.35 (dd, J = 1.4, 17.0, 1H), 5.29 (dd, J = 2.2, 9.4, 1H), 5.16 (s, 1H), 4.79 (s, 1H), 4.39 (d, J = 5.3 Hz, 2H), 0.86 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.3, 166.9, 137.7, 137.3, 136.5, 135.0, 133.4, 129.8, 129.6, 128.6, 128.4, 128.3, 119.5, 65.7, 52.1, 51.3, 28.0. HRMS (FAB): calcd for $C_{22}H_{25}O_2N_2$ (MH^+) 349.1911, found 349.1912.

N-(9H-Fluoren-9-yl)-6-isopropyl-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (***4q***). White solid mp 238−240 °C in 72% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 7.9 Hz, 1H), 7.61−7.59 (m, 3H), 7.56−7.53 (m, 1H), 7.48−7.42 (m, 4H), 7.39 (d, J = 7.4 Hz, 1H), 7.36−7.33 (m, 2H), 7.20−7.14 (m, 2H), 7.03 (d, J = 7.5 Hz, 1H), 6.74 (d, J = 7.4 Hz, 1H), 5.84 (d, J = 8.8 Hz, 1H), 5.65 (d, J = 8.7 Hz, 1H), 5.28−5.22 (m, 1H), 5.14 (s, 1H), 1.43 (d, J = 6.8 Hz, 3H), 1.20 (d, J = 6.7 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 169.4, 167.9, 143.4, 140.3, 140.2, 137.7, 135.7, 135.2, 131.4, 131.1, 129.8, 129.6, 128.6, 128.5, 128.4 (× 2), 127.7 (× 2), 125.1, 125.0, 119.7, 60.4, 54.9, 46.7, 21.3, 20.3. HRMS (FAB): calcd for $C_{31}H_{27}O_2N_2$ (MH^+) 459.2067, found 459.2058.

N-(9H-Fluoren-9-yl)-6-(4-methoxybenzyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (***4r***). White solid mp 108−110 °C in 86% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 6.7 Hz, 1H), 7.61−7.58 (m, 4H), 7.52−7.45 (m, 3H), 7.35−7.29 (m, 3H), 7.25 (d, J = 8.6 Hz, 2H), 7.17−7.14 (m, 2H), 7.05 (d, J = 7.6 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.73 (d, J = 8.7 Hz, 2H), 6.66 (d, J = 7.55 Hz, 1H), 5.69 (d, J = 8.6 Hz, 1H), 5.49 (d, J = 8.7 Hz, 1H), 5.13 (d, J = 14.5 Hz, 1H), 4.99 (s, 1H), 4.63 (d, J = 14.3 Hz, 1H), 3.77 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.8, 168.3, 159.4, 143.3, 143.1, 140.2, 140.1, 137.5, 136.5, 136.3, 134.3, 1314, 131.2, 130.2, 129.8, 129.5, 129.4, 128.6, 128.5 (× 2), 128.4, 128.2, 127.5 (× 2), 125.2, 125.0, 119.6, 114.3, 65.2, 55.1, 54.6, 51.8. HRMS (FAB): calcd for $C_{36}H_{29}O_3N_2$ 537.2173, found 537.2057.

N-tert-Butyl-3,9-dimethoxy-6-nonyl-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (***4s***). Brownish Oil in 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 11.5 Hz, 1H), 7.41 (d, J = 3.52 Hz, 1H), 7.34 (d, J = 11.5 Hz, 1H), 7.06−6.98 (m, 2H), 6.88 (d, J = 3.52 Hz, 1H), 5.18 (s, 1H), 4.65 (s, 1H), 3.87−3.86 (m, 6H), 3.75−3.65 (m, 2H), 1.67−1.65 (m, 2H), 1.2 (bs, 12H), 0.90−0.80 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): 168.1, 166.8, 159.1, 159.0, 138.3, 135.7, 130.5, 129.7, 129.6, 129.0, 118.8, 115.2, 114.3, 113.6, 67.4, 55.5, 55.4, 51.2, 50.3, 31.8, 29.4, 29.3, 29.2, 28.2, 27.9, 26.8, 22.6, 14.1. HRMS (EI): calcd for $C_{30}H_{42}O_4N_2$ 494.3145, found 494.3149.

N-tert-Butyl-6-cycloheptyl-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (***4t***). White solid mp 72−74 °C in 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, J = 7.35 Hz, 1H), 7.60 (d, J = 7.56 Hz, 1H), 7.48−7.38 (m, 6H), 5.19 (s, 1H), 4.90 (m, 2H), 1.67−1.52 (m, 12H), 0.85 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 167.7, 167.5, 139.0, 137.6, 135.5, 131.1, 130.8, 129.6, 129.5, 129.3, 128.5, 128.3, 128.2, 62.1, 57.4, 51.2, 35.5, 33.9, 33.1, 28.0, 27.6, 27.3, 26.5, 25.4, 25.0. HRMS (EI): calcd for $C_{26}H_{32}O_2N_2$ 404.2464, found 404.2470.

N-tert-Butyl-6-isobutyl-9-methoxy-7-oxo-6,7-dihydro-5H-dibenzo-[c,e]azepine-5-carboxamide (***4u***). White solid mp 201−203 °C in 70% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J = 7.4 Hz, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.44(d, J = 2.6 Hz, 1H), 7.40−7.34 (m, 3H), 7.07 (dd, J = 2.8, 8.6 Hz, 1H), 5.15 (s, 1H), 4.71 (s, 1H), 3.87 (s, 3H), 3.64 (dd, J = 7.7, 13.5 Hz, 1H), 3.49 (dd, J = 7.2, 13.4 Hz, 1H), 2.06−2.00 (m, 1H), 1.02 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.77 (d, J = 6.6 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.5, 167.0, 159.7, 137.4, 137.1, 136.5, 130.0, 129.6, 129.4 (× 2), 129.2, 127.8, 119.0, 113.9, 67.7, 57.6, 55.7, 51.3, 28.1, 28.0, 27.0, 20.6, 19.8. HRMS (FAB): calcd for $C_{24}H_{31}O_3N_2$ (MH^+) 395.2329, found 395.2314.

N-tert-Butyl-3,9-dimethoxy-7-oxo-6-(prop-2-ynyl)-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (***4v***). White solid mp 170−172 °C in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.6 Hz, 2H), 7.09−6.98 (m, 2H), 6.93 (d, J = 2.5 Hz, 1H), 5.47 (s, 1H), 5.01 (s, 1H), 4.83 (d, J = 17.7 Hz, 1H), 4.39 (d, J = 19.9 Hz, 1H), 3.87−3.86 (m, 6H), 2.38 (s, 1H), 0.93 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.0, 166.7, 159.2, 159.0, 137.6, 134.6, 130.0, 129.9, 129.7, 119.3, 115.5, 114.6, 113.8, 78.7, 73.6, 65.8, 55.7, 55.5, 51.4, 38.1, 28.1. HRMS (EI): calcd for $C_{24}H_{26}O_4N_2$ 406.1893, found 406.1895.

5-(1-Hydroxy-4-methylpentan-2-yl)-8-methoxy-6-oxo-N-(2,4,4-trimethylpentan-2-yl)-5,6-dihydro-4H-benzo[c]thieno[3,2-e]azepine-4-carboxamide (***4w***). (Mixture of two diastereoisomers) White crystalline solid (mixture of diastereomers) in 40% combined yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55−7.52 (m, 2H), 7.35−7.33 (m, 6H), 7.07−7.04 (m, 2H), 5.55 (s, 1H), 5.39 (s, 1H), 5.35−5.21 (m, 2H), 4.93 (bs, 2H), 4.68 (bm, 1H), 4.51−4.46 (m, 1H), 3.87−3.86 (m, 6H), 3.77−3.70 (m, 2H), 3.65−3.51 (m, 2H), 2.14−2.09 (m, 1H), 1.44−1.39 (m, 3H), 1.35−1.10 (m, 4H), 1.05- 0.90 (m, 9H), 0.85−0.65 (m, 35H). ^{13}C NMR (100 MHz, $CDCl_3$): 169.5, 168.6, 168.0, 167.6, 159.4, 159.3, 139.4, 138.8, 136.9, 136.8, 133.6, 133.5, 128.0, 127.9, 127.4, 127.3, 125.9, 125.8, 124.7, 124.5, 119.4, 119.3, 115.6, 115.2, 63.8, 63.2, 55.9, 55.8, 55.7 (× 2), 53.3 (× 2), 53.1, 38.0, 37.8, 31.4, 31.3, 31.2, 27.6, 27.5, 27.4, 27.3, 25.0, 24.7, 23.2, 23.1, 22.4, 22.0. HRMS (EI): calcd for $C_{28}H_{40}O_4N_2S$ 500.2709, found 500.2713.

N-tert-Butyl-9,10,11-trimethoxy-6-(4-methoxybenzyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (***4x***). Colorless oil in

60% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.74 (d, J = 7.7 Hz, 1H), 7.40−7.33 (m, 3H), 7.22 (s, 1H), 7.08 (d, J = 6.4 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 5.30 (d, J = 14.2 Hz, 1H), 5.17 (s, 1H), 4.68 (s, 1H), 4.23 (d, J = 14.2 Hz, 1H), 3.94−3.92 (m, 6H), 3.81 (s, 3H), 3.52 (s, 3H), 0.82 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 168.1, 166.7, 159.8, 153.2, 150.9, 145.2, 137.7, 132.7, 131.9, 130.9, 130.4, 129.2, 129.1, 128.0, 127.6, 125.3, 114.7, 108.7, 66.4, 61.3, 60.7, 56.3, 55.5, 51.8, 50.9, 28.1. HRMS (EI): calcd for $C_{30}H_{34}O_6N_2$ 518.2417, found 518.2424.

3,9,10,11-Tetramethoxy-6-(4-methoxybenzyl)-N-(4-methoxyphenyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4y**). White solid mp 215−218 °C in 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69−7.64 (m, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.19 (s, 1H), 6.95−6.89 (m, 2H), 6.81 (s, 1H), 6.73 (d, J = 9.0 Hz, 2H), 6.65 (d, J = 9.0 Hz, 2H), 6.49 (s, 1H), 5.06 (d, J = 14.3 Hz, 1H), 4.76 (s, 1H), 4.64 (d, J = 14.3 Hz, 1H), 3.83−3.79 (m, 12H), 3.69 (s, 3H), 3.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 168.3, 165.9, 159.7, 159.0, 156.7, 152.9, 150.2, 144.9, 138.4, 133.4, 132.2, 132.1, 130.7, 130.5, 129.9, 128.9, 128.6, 128.5, 125.2, 124.3, 121.9, 114.5, 114.3, 114.0, 113.8, 108.9, 65.6, 60.9, 60.6, 56.1, 55.4 (× 2), 55.3, 51.6. HRMS (EI): calcd for $C_{34}H_{34}O_8N_2$ 598.2315, found 598.2319.

N-tert-Butyl-6-(3,4-dimethoxyphenethyl)-3,9,10,11-tetramethoxy-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4z**). (∼9:1 mixture of rotamers) Yellow solid mp 65−67 °C in 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69−7.64 (m, 2H), 7.56−7.44 (m, 2H), 7.15 (s, 1H), 6.94 (dd, J = 2.28, 8.68 Hz, 1H), 6.80 (m, 2H), 5.28 (s, 1H), 4.63 (s, 1H), 4.21−4.15 (m, 1H), 3.91 (s, 6H), 3.86 (s, 9H), 3.70−3.63 (m, 1H), 3.56 (s, 3H), 3.06−2.90 (m, 2H), 0.89 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 168.5, 166.7, 159.1, 152.9, 150.6, 149.3, 147.9, 145.1, 139.2, 133.2, 132.2, 132.1, 132.0, 131.9, 131.0, 130.9, 128.6, 128.5, 124.8, 124.5, 120.6, 115.2, 113.1, 112.0, 111.7, 108.6, 68.1, 61.1, 60.6, 56.2, 56.0 (× 2), 55.4, 51.1, 51.0, 34.0, 28.1. HRMS (EI): calcd for $C_{33}H_{40}O_8N_2$ 592.2785, found 592.2784.

N-tert-Butyl-6-(3-methylbenzyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4aa**). White solid mp 123−125 °C in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 7.5 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.51−7.50 (m, 2H), 7.47−7.42 (m, 2H), 7.30−7.20 (m, 3H), 7.17−7.13 (m, 2H), 7.01 (d, J = 7.3 Hz, 1H), 5.21 (d, J = 14.3 Hz, 1H), 5.07 (bs, 1H), 4.75 (s, 1H), 4.53 (d, J = 14.1 Hz, 1H), 2.30 (s, 3H), 0.74 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.5, 166.8, 138.8, 137.4, 137.2, 136.9, 136.8, 134.4, 131.1 130.7, 129.7, 129.5, 129.4, 129.2, 129.1, 129.0, 128.9, 128.7, 128.0 (× 2), 126.2, 65.9, 52.3, 50.9, 27.7, 21.3. HRMS (EI): calcd for $C_{27}H_{28}O_2N_2$ 412.2151, found 412.2151.

N-tert-Butyl-6-(3-chlorobenzyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4ab**). White solid mp 69−71 °C in 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 7.5 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.53−7.45 (m, 4H), 7.31−7.24 (m, 5H), 6.96 (d, J = 7.5 Hz, 1H), 5.01−4.98 (m, 2H), 4.83 (d, J = 14.6 Hz, 1H), 4.69 (s, 1H), 0.78 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.7, 166.4, 139.0, 137.4, 137.0, 136.6, 134.7, 134.3, 131.2, 130.9, 130.1, 129.7, 129.5, 129.4, 128.8, 128.6, 128.2 (× 2), 128.1, 127.0, 66.2, 52.2, 51.1, 27.8. HRMS (EI): calcd for $C_{26}H_{25}ClO_2N_2$ 432.1605, found 432.1604.

N-Benzyl-6-(3-methylbenzyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]-azepine-5-carboxamide (**4ac**). White solid mp 165−167 °C in 51% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.51−7.40 (m, 4H), 7.27−7.06 (m, 8H), 6.91 (d, J = 7.5 Hz, 1H), 6.70 (d, J = 7.04 Hz, 2H), 5.01 (bs, 1H), 5.00 (d, J = 14.3 Hz, 1H), 4.82−4.79 (m, 2H), 3.95 (dd, J = 6.0, 14.6 Hz, 1H), 3.79 (dd, J = 5.3, 14.6 Hz, 1H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.6, 167.7, 138.7, 137.6, 137.1, 136.6, 136.5, 136.3, 134.2, 131.2, 129.6, 129.4 (× 2), 128.8, 128.5, 128.2, 128.0, 127.6, 127.3, 126.0, 65.2, 52.3, 43.7, 21.2. HRMS (EI): calcd for $C_{30}H_{26}O_2N_2$ 446.1994, found 446.1995.

N-Benzyl-6-(3-chlorobenzyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4ad**). White solid mp 184−187 °C in 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (dd, J = 1.2, 7.4 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.51−7.39 (m, 4H), 7.29−7.15 (m, 8H), 6.90 (d, J = 7.0 Hz, 1H), 6.71−6.69 (m, 2H), 5.40 (bs, 1H), 5.06 (d, J = 14.8 Hz, 1H), 4.82 (d, J = 14.8 Hz, 1H), 4.77 (s, 1H), 4.04 (dd, J = 6.5, 14.6 Hz, 1H), 3.82 (dd, J = 5.2, 14.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.7, 167.5, 138.7, 137.6, 137.1, 136.3, 136.0, 134.5, 134.2, 131.2, 131.1, 129.8 (× 2), 129.3, 128.7, 128.5, 128.4, 128.3, 128.0, 127.6, 127.4, 126.8, 65.7, 52.2, 43.8. HRMS (EI): calcd for $C_{29}H_{23}ClO_2N_2$ 466.1448, found 466.1438.

N-Butyl-6-(3-chlorobenzyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4ae**). White solid mp 164−166 °C in 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.3 Hz, 1H), 7.53−7.43 (m, 4H), 7.30−7.21 (m, 5H), 6.90 (d, J = 7.1 Hz, 1H), 5.12 (bs, 1H), 5.04 (d, J = 14.8 Hz, 1H), 4.84 (d, J = 14.8 Hz, 1H), 4.71 (s, 1H), 2.88−2.80 (m, 1H), 2.66−2.58 (m, 1H), 0.94−0.81 (m, 4H), 0.72 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.7, 167.3, 138.8, 137.6, 136.6, 136.1, 134.5, 134.4, 131.1, 131.0, 130.0, 129.7 (× 2), 129.3, 128.7, 128.4, 128.3, 128.2, 128.0, 126.9, 65.7, 52.2, 39.3, 31.2, 19.7, 13.6. HRMS (EI) calcd for $C_{26}H_{25}ClO_2N_2$: 432.1605, found 432.1604.

N-Butyl-6-(3-methylbenzyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4af**). White solid mp 145−147 °C in 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.3 Hz, 1H), 7.52−7.41 (m, 4H), 7.28−7.26 (m(peak merged wih chloroform peak), 1H), 7.21 (d, J = 7.9 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.12−7.10 (m, 2H) 6.90 (d, J = 7.0 Hz, 1H), 5.17 (bs, 1H), 5.00 (d, J = 14.8 Hz, 1H), 4.81 (d, J = 14.8 Hz, 1H), 4.75 (s, 1H), 2.79−2.70 (m, 1H), 2.65−2.57 (m, 1H), 2.28 (s, 3H), 0.94−0.81 (m, 4H), 0.72 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.6, 167.6, 138.6, 137.6, 136.9, 136.6, 136.5, 134.4, 131.1, 130.8, 129., 129.5, 129.3, 128.7, 128.5, 128.1, 128.0, 126.0, 65.2, 52.4, 39.2, 31.1, 21.3, 19.7, 13.6. HRMS (EI): calcd for $C_{27}H_{28}O_2N_2$ 412.2151, found 412.2150.

N-Cyclohexyl-6-(3-chlorobenzyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4ag**). White solid mp 171−173 °C in 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 7.3 Hz, 1H), 7.54−7.42 (m, 4H), 7.32−7.25 (m(peak merged wih chloroform peak), 5H), 6.96 (d, J = 7.0 Hz, 1H), 4.98−4.95 (m, 2H), 4.87 (d, J = 14.8 Hz, 1H), 4.70 (s, 1H), 3.27−3.19 (m, 1H), 1.46−1.30 (m, 4H), 1.12−0.93 (m, 4H), 0.67−0.57 (m, 1H), 0.50−0.40 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.7, 166.3, 138.9, 137.6, 136.7, 136.3, 134.6, 134.3, 131.2, 131.0, 130.1, 129.7, 129.6, 129.3, 128.8, 128.5, 128.3, 128.2, 128.1, 127.0, 65.7, 52.1, 48.1, 32.3 (× 2), 25.2, 24.5 (× 2). HRMS (EI): calcd for $C_{28}H_{27}ClO_2N_2$ 458.1761, found 458.1759.

N-tert-Butyl-6-(2-fluorobenzyl)-7-oxo-6,7-dihydro-5H-dibenzo-[c,e]azepine-5-carboxamide (**4ah**). White solid mp 62−64 °C in 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 7.5 Hz, 1H), 7.58 (d, J = 7.3 Hz, 1H), 7.52−7.42 (m, 5H), 7.33−7.29 (m, 2H), 7.14−7.07 (m, 3H), 5.29 (d, J = 14.6 Hz, 1H), 5.20 (bs, 1H), 4.81 (s, 1H), 4.69 (d, J = 14.6 Hz, 1H), 0.77 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.6, 166.7, 162.8, 159.6, 137.3, 137.2, 136.7, 134.5, 132.0, 131.9, 131.2, 130.6, 130.1, 130.0, 129.6, 129.4, 129.3, 128.7, 128.1 (× 2), 124.9, 124.8, 123.9, 123.7, 115.7, 115.4, 66.2, 51.0, 45.8 (× 2), 27.7. HRMS (EI): calcd for $C_{26}H_{25}FO_2N_2$ 416.1900, found 416.1894.

N-tert-Butyl-6-(3,5-dimethylbenzyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4ai**). White solid mp 183−186 °C in 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, J = 7.5 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.52−7.41 (m, 4H), 7.33−7.28 (m, 1H), 7.04 (d, J = 7.4 Hz, 1H), 6.99−6.96 (m, 3H), 5.25 (d, J = 14.1 Hz, 1H), 5.11 (bs, 1H), 4.76 (s, 1H), 4.40 (d, J = 14.1 Hz, 1H), 2.28 (s, 6H), 0.74 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.5, 166.9, 138.7, 137.4, 137.7, 136.9, 136.7, 134.4, 131.1, 130.7, 129.7, 29.5 (× 2), 129.1, 128.7, 128.0, 127.9, 126.9, 65.8, 52.2, 50.8, 27.7, 21.2. HRMS (EI): calcd for $C_{28}H_{30}O_2N_2$ 426.2307, found 426.2313.

N-Cyclohexyl-6-(3,5-dimethylbenzyl)-7-oxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**4aj**). White solid mp 223−226 °C

in 71% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 7.0 Hz, 1H), 7.51−7.39 (m, 4H), 7.33−7.27 (m, 1H), 7.00−6.95 (m, 4H), 5.16 (d, J = 14.3 Hz, 1H), 5.09 (d, J = 8.5 Hz, 1H), 4.76 (s, 1H), 4.52 (d, J = 14.3 Hz, 1H), 3.23−3.10 (m, 1H), 2.28 (s, 6H), 1.45−1.42 (m, 2H), 1.23−0.93 (m, 6H), 0.60−0.40 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.6, 166.7, 138.7, 137.6, 137.0, 136.8, 136.6, 134.3, 131.1, 130.8, 129.7, 129.5, 129.4, 129.2, 128.6, 128.0, 127.9, 126.8, 65.2, 52.1, 47.8, 32.3, 32.2, 25.3, 24.5, 21.2. HRMS (EI): calcd for $C_{30}H_{32}O_2N_2$ 452.2464, found 452.2467.

*N-Butyl-6-(3,5-dimethylbenzyl)-7-oxo-6,7-dihydro-5H-dibenzo-[c,e]azepine-5-carboxamide (**4ak**).* White solid mp 188−191 °C in 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, J = 7.3 Hz, 1H), 7.60 (d, J = 7.0 Hz, 1H), 7.51−7.40 (m, 4H), 7.30−7.26 (m(peak merged wih chloroform peak), 1H), 6.93−6.90 (m, 4H), 5.22 (bs, 1H), 5.00 (d, J = 14.5 Hz, 1H), 4.76−4.70 (m, 2H), 2.79−2.68 (m, 1H), 2.67−2.56 (m, 1H), 2.26 (s, 6H), 0.95−0.80 (m, 4H), 0.73 (t, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.6, 167.7, 138.5, 137.6, 137.0, 136.6, 136.5, 134.4, 131.1, 130.8, 129.6, 129.5, 129.4, 129.3, 128.5, 128.1, 127.9, 126.8, 65.1, 52.3, 39.2, 31.1, 21.2, 19.7, 13.6. HRMS (EI): calcd for $C_{28}H_{30}O_2N_2$ 426.2307, found:426. 2309.

*6-(Phenylamino)-7-(3,3,3-trifluoropropanoyl)-6,7-dihydro-5H-dibenzo[c,e]azepin-5-one (**5**).* Yellow oil in 54% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.0, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.63−7.58 (m, 3H), 7.50−7.45 (m, 2H), 7.38 (d, J = 7.5 Hz, 1H), 7.15 (t, J = 15.0, 7.5 Hz, 2H), 7.14, (s, 1H), 6.90 (t, J = 14.9, 7.4 Hz, 1H), 6.66 (d, J = 7.9, 1H), 5.88 (s, 1H), 3.76−3.66 (dp, J = 37.7 Hz, 16.1 Hz, 4.56 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 167.6, 147.0, 137.1, 136.7, 135.5, 132.1, 131.7, 130.7, 130.6, 130.4, 129.3, 128.8, 128.3, 128.2, 128.0, 122.0, 114.2, 96.7, 65.2, 64.8. ^{19}F NMR (376 MHz, $CDCl_3$): 64.06. (HRMS (EI): calcd for $C_{23}H_{17}F_3O_2N_2$ 410.1242, found 410.1250.

Thionation of Compound 4a To Give Corresponding Compound 6. To a solution of compound **4a** (43 mg, 0.1 mmol) in 3 mL of dry toluene was added Lawesson's reagent (25 mg, 0.06 mmol). The resulting solution was heated at reflux under conventional heating until all the starting material was consumed (as determined by TLC and mass analysis, ∼3.0 h). The solvent was evaporated, and the crude reaction mixture was applied to silica gel column chromatography. The corresponding product was isolated with EtOAC/heptane (2:8) solvent system to afford as yellow solid.

*N-tert-Butyl-6-(4-methoxybenzyl)-7-thioxo-6,7-dihydro-5H-dibenzo[c,e]azepine-5-carboxamide (**6**).* Yellow solid mp 186−188 °C in 67% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, J = 7.53 Hz, 1H), 7.64 (d, J = 7.53 Hz, 1H), 7.50−7.30 (m, 7H), 6.97−6.87 (m, 3H), 5.94 (d, J = 14.31 Hz, 1H), 5.10−5.04 (m, 2H), 4.83 (s, 1H), 3.82 (s, 3H), 0.77 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 198.5, 165.1, 159.9, 141.1, 137.6, 136.0, 133.7, 130.5 (× 2), 129.9, 129.3 (× 2), 128.4, 128.3, 127.8, 127.7, 114.5, 69.1, 59.6, 55.5, 51.3, 28.0. HRMS (EI): calcd for $C_{27}H_{28}O_2N_2S$ 444.1871, found 444.1879.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental protocols, spectroscopic data for all newly synthesized compounds, biological screening protocols and results, crystallographic data for compound **4g**, **4w**, and **5** in CIF format, and copies of ^{1}HNMR and ^{13}CNMR of all newly synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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