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Synthesis and Biological Evaluation of Methylene-Bridged Analogs of the Potent Cannabinoid Receptor Antagonist Rimonabant

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Methylene-bridged analogs of rimonabant were synthesized and evaluated for their activity on CB1 receptors. The pyrazine derivative showed some activity as a CB1 antagonist.

Introduction

The discovery of the cannabinoid receptor-1 (CB1) and the subsequent identification of the endocannabinoids (such as anandamide), as its endogenous ligands has led to the explanation for the well-known effect of Δ9-THC (a CB1 agonist and the active principle from marijuana from *Cannabis sativa* L.) on food intake ("the munchies").[1] The recognition that the endocannabinoid system has an important influence on satiety triggered an intense search for CB1 antagonists and inverse agonists as potential anti-obesity drugs.[2] Currently, rimonabant,[3] a potent CB1 antagonist/inverse agonist (Figure 1) has been launched in Europe for the treatment of obesity. Many analogs of rimonabant are known in which the central pyrazole has been replaced by other (hetero)cyclic systems[4] or even acyclic spacers.[5] The bis(*para*-chlorophenyl) substitution pattern seems to be a prerequisite for high CB1 antagonism and CB1/CB2 selectivity.[6]

Bridging is often introduced in bioactive compounds because a conformational constraint can increase inhibitor activity and selectivity by locking in a bioactive conformation and locking out unwanted conformations.[7] In addition, it has been suggested by Veber et al.[8] that rigid compounds possessing a reduced number of rotatable bonds have a higher probability of having good oral bioavailability. Several bridged analogs of rimonabant, where the phenyl group has been bridged to the pyrazole ring or the pyrazole to the amide substituent, have been described in recent years.[4] Recently, Francisco et al.[9] reported compound **A** (Figure 1), obtained by photocyclization of rimonabant, showing selective binding to the CB1 receptor.

Compounds represented by structure **B** (Figure 1), in which the pyrazole ring of rimonabant has been replaced by a pyridine or pyrazine ring, have been shown to be potent CB1 antagonists.[10–12]

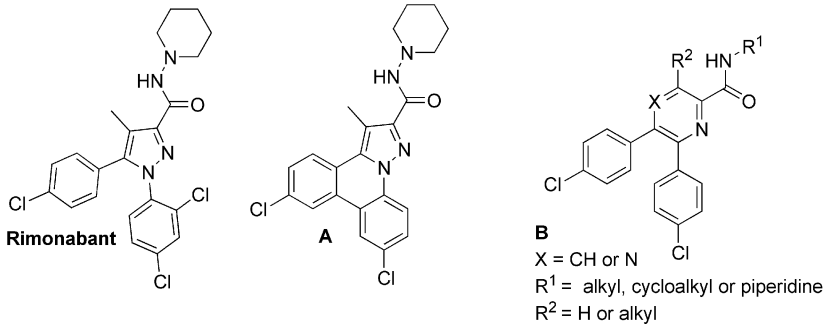

Figure 1. Structures of rimonabant and related CB1 antagonists.

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From our long-standing interest in the preparation of rigid analogs of bioactive molecules,[13,14] we decided to synthesize the compounds **1**–**3** (Figure 2) which may be

considered as methylene-bridged analogs of compounds **B**. In addition, we also prepared compound **4** in order to study the importance of the aromatic substitution pattern.

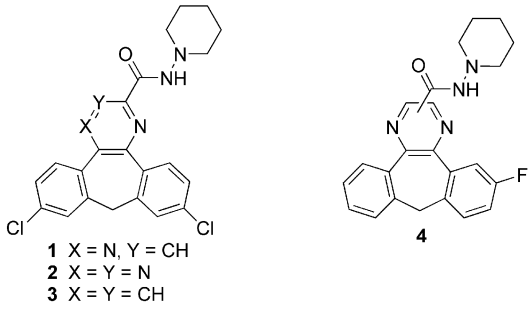


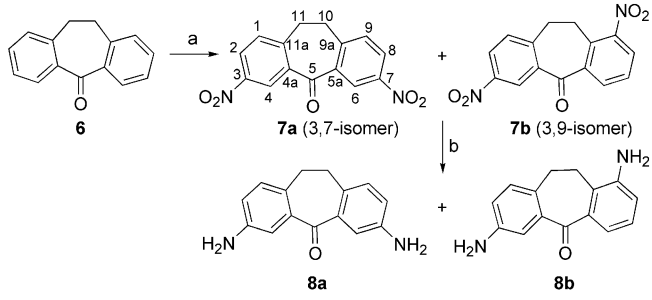
Figure 2. Structures of the desired compounds **1**–**4**.

Results and Discussion

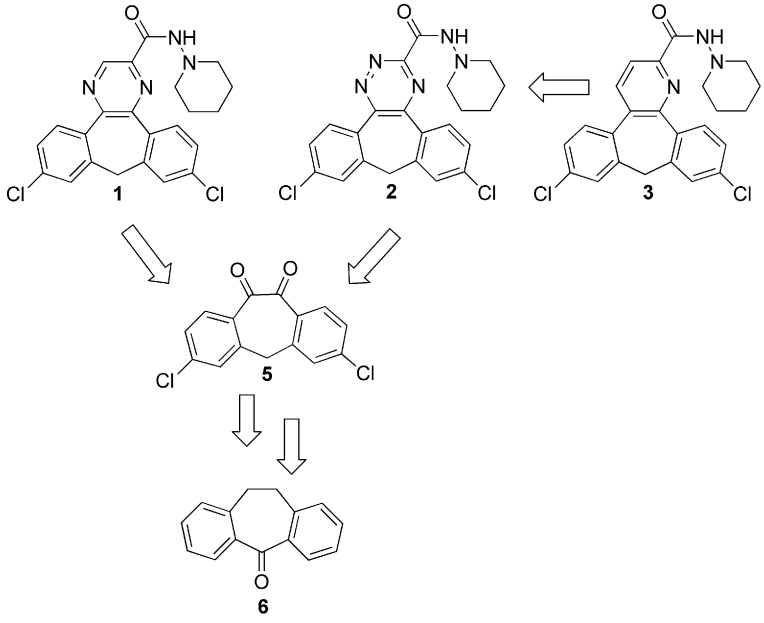
Chemistry

The retrosynthetic pathway for the preparation of the desired heterocycles **1**–**3** with a pyrazine, a 1,2,4-triazine or a pyridine moiety is briefly depicted in Scheme 1. The synthesis of those targets requires the formation of a key intermediate dichloro-substituted tricyclic diketone **5** which upon further cyclocondensation with an appropriate diamine or hydrazide could form a pyrazine and a 1,2,4-triazine, respectively. For the preparation of the pyrazine **4**, a diketone related to **5** will be required. A Diels–Alder reaction of 1,2,4-triazine with 2,5-norbornadiene as a dienophile followed by loss of N_2 might give the pyridine derivative **3**.

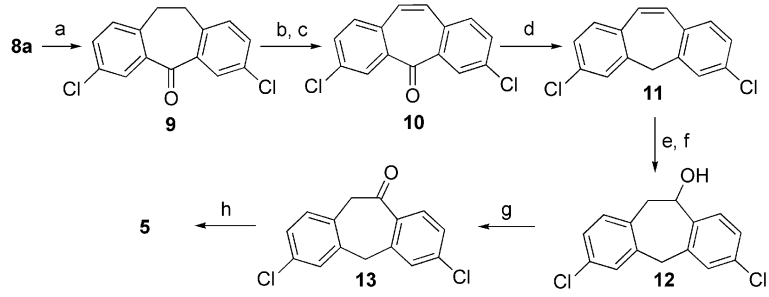
The general method for the synthesis of 1,2-diketone **5** is based on a reported method[15] and is shown in Scheme 2. Nitration of a commercially available dibenzosuberone **6** with fuming HNO_3 at 0 °C using a modified procedure gave a mixture of two isomers **7a** (major) and **7b** (minor). Hydrogenation of crude dinitrodibenzosuberones performed in a Parr apparatus led to the isolation of the corresponding diamino derivatives **8a** and **8b**. The AA′BB′ pattern for the protons of the two methylene groups in the NMR spectrum of **7b** and **8b** indicates that those molecules are not symmetrical, whereas the single peak (4 H) observed for the two methylene groups indicates symmetry in molecules **7a** and **8a**. In order to obtain the desired tricyclic 1,2-diketone **5**, 3,7-diaminodibenzosuberone **8a** was used as a precursor for further steps (Scheme 3). Diazotization of compound **8a** with an aqueous solution of $NaNO_2$ and CuCl in HCl afforded the previously described compound **9** in 30% yield. Dichlorodibenzosuberone **9** upon treatment with NBS and AIBN followed by addition of NaI gave compound **10**. Reduction of the carbonyl group of **10** was performed with Al(*i*PrO)$_3$ at 230 °C under solvent-free conditions to afford



Scheme 2. Reagents and conditions: (a) 100% fuming HNO_3, 0 °C, 4 h; (b) H_2, Pd/C, AcOH, room temp., 38 psi, 8 h.



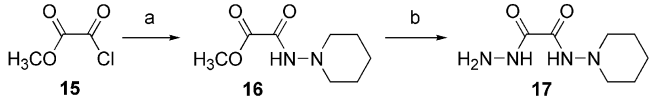
Scheme 1. The retrosynthetic pathway for the preparation of the desired compounds **1**–**3**.



Scheme 3. Reagents and conditions: (a) concd. HCl, aq. $NaNO_2$, CuCl, 0–50 °C, 12 h; (b) NBS, cat. AIBN, CCl_4, reflux, 16 h; (c) dry acetone, NaI, reflux, 3 h; (d) $Al(iPrO)_3$, 230 °C, 14 h; (e) $NaBH_4$, $BF_3{\cdot}Et_2O$, THF, room temp., 20 h; (f) MeOH, 4 N NaOH, 36% H_2O_2, room temp., 3 h; (g) NaOAc, PCC, CH_2Cl_2, room temp., 3 h; (h) SeO_2, AcOH, reflux, 2 h.

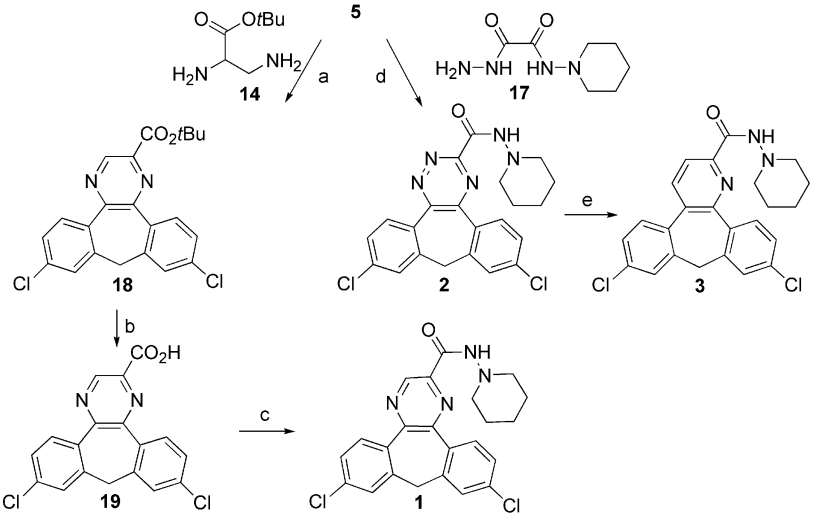
compound **11**. Treatment of this compound with $NaBH_4$ in the presence of $BF_3{\cdot}Et_2O$ in dry THF followed by subsequent addition of sodium hydroxide and hydrogen peroxide afforded alcohol **12**, which was oxidized with PCC to give the monoketone **13**. A second oxidation of compound **13** with SeO_2 in refluxing acetic acid, gave the desired product **5** in good yield. The appearance of a black metal-like powder is indicative of the oxidation in progress.

As mentioned above, the synthetic strategy for the preparation of the desired pyrazine and the 1,2,4-triazine is based on the condensation of 1,2-diketone **5** with an appropriate diamine, or hydrazide precursor, respectively. Well-known procedures were used for the construction of those precursors. The synthesis of *tert*-butyl 2,3-diaminopropionate (**14**), required for the preparation of the pyrazine **1** was described previously.[16] Preparation of the hydrazide intermediate involved the amination of methyl oxalyl chloride (**15**) with 1-aminopiperidine as shown in Scheme 4. Subsequent treatment of the obtained compound **16** with hydrazide hydrate in the presence of methanol and water furnished the desired hydrazide precursor **17**.



Scheme 4. Reagents and conditions: (a) 1-aminopiperidine, Et_3N, CH_2Cl_2, 0 °C, 20 min; (b) EtOH, H_2O, hydrazine hydrate, room temp., 1 h.

The target molecules **1**, **2** and **3** were synthesized according to the reactions shown in Scheme 5. Condensation of the key intermediate **5** with *tert*-butyl 2,3-diaminopropionate (**14**) gave the pyrazine **18** that, after deprotection with HCl in 1,4-dioxane, afforded the corresponding acid **19**. The final compound **1** was obtained from the precursor **19** by coupling the acid with 1-aminopiperidine after activation of the carboxylic acid with TBTU in the presence of DIEA in dry DMF. Similarly, the 1,2-diketone **5** was condensed with the hydrazide **17** to give the 1,2,4-triazine **2**. The synthesis of this compound was performed under microwave irradiation and was completed after 40 min in 30% yield. Diels–Alder reaction with 2,5-norbornadiene –



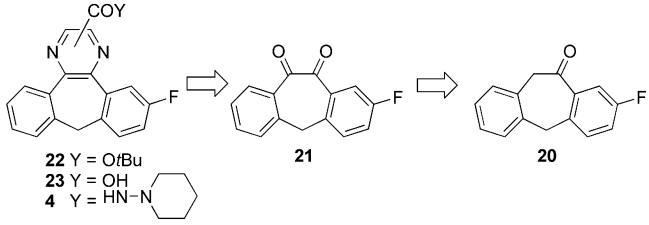
Scheme 5. Reagents and conditions: (a) EtOH, reflux, 20 h; (b) 1,4-dioxane, satd. HCl_g, room temp., 6 h; (c) DIEA, *N*-aminopiperidine, TBTU, room temp., overnight; (d) NH_4OAc, AcOH, microwave irradiation, 40 min, 130 °C, 40W; (e) 2,5-norbornadiene, chlorobenzene, 140 °C, 3 d.

Table 1. Biological activity of target compounds **1**–**4** and rimonabant.

	IC50 agonist-induced GTPγS binding	Inhibition of constitutive GTPγS binding @ 10 μM
1	4400 nM	–37%
2	31% @ 10 μM	–25%
3	14% @ 10 μM	2%
4	27% @ 10 μM	4%
Rimonabant	9 nM	–45%

an acetylene equivalent – in chlorobenzene followed by loss of N_2 converted the triazine-3-carboxamide **2** into the corresponding pyridine **3**.

The synthetic approach for the fourth target compound **4** is depicted in the retrosynthetic Scheme 6. Oxidation of the described compound **20**[17] with SeO_2 (as in the preparation of **5**) yielded the diketone **21**. The latter can be converted into compound **22** by reaction with **14**. The *tert*-butyl ester **22** is then converted into the acid **23** and the final compound **4** in the same way as for **19** and **1**, respectively (Scheme 5).



Scheme 6. The retrosynthetic pathway for the preparation of the desired compound **4**.

Biological Results

The activity of compounds **1**–**4** and rimonabant on the CB1 receptor transfected in HEK-293 cells, was determined at MDS Pharma Services,[18] according to published procedures (Table 1).[19]

As expected, rimonabant proved to be a potent CB1 antagonist (IC50 = 9 nM), which also inhibited constitutive GTPγS binding which is an indication for possible inverse agonist activity. The bridged compound **1** showed some activity (IC50 = 4.4 μM) and potential activity as an inverse agonist, but the pyridine and triazine analogs of **1** were much less active. The monofluoro derivative **4** proved to be without activity as well, showing the importance of the bis *para*-chloro substitution.

Conclusions

As it has been described that the non-bridged analogs of **1** and **3** are low-nM CB1 antagonists,[10–12] we conclude that the bridging fixes the position and orientation of the aromatic rings in an unfavorable conformation. In contrast to bridged Rimonabant A which has a planar conformation,[9] compounds **1**–**4** are probably nonplanar.[20] Introduction of an additional nitrogen atom in **1** to give compound **2**, or removal of one nitrogen atom to give **3**, removed essentially all CB1 antagonist activity. In addition to the unfavorable bridging, there might be subtle differences in SAR between rimonabant (where direct bridging is allowed) and the pyridine/pyrazine/triazine analogs of rimonabant (where bridging with a methylene group leads to compounds with no or very low activity) to explain the observed differences in activity between compounds **1**–**3**.

Experimental Section

General: Commercially available starting materials, reagents and solvents were used as supplied. Reactions were routinely conducted under argon unless otherwise indicated. TLC analyses were performed on Nagel TLC plates SIL G-25 UV_{254}; spots were visualized under 254 nm UV illumination. Purifications on column chromatography were carried out on 70–230 mesh silica gel 60 (E. M. Merck) or chromatotron (Harrison Research). HPLC purification was carried out on a normal phase silica column (Bio-Sil 250 × 10 mm). Mass spectra (EI and CI) were run with a Hewlett–Packard MS-Engine 5989A instrument. Exact mass measurements were performed at a resolution of 10000 with a KRATOS MS50TC instrument. ^{1}H and ^{13}C NMR spectra were measured with a Bruker Avance 300 and a Bruker Avance 400 spectrometer at 25 °C, unless otherwise indicated. Infrared spectra were recorded using KBr pellets or thin films between NaCl plates with a Perkin–Elmer 1600 Series Fourier Transform Spectrometer. Melting points were recorded with a digital melting point apparatus Electrothermal 9200.

3,7-Dinitro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (7a): Chilled fuming HNO_3 (120 mL) was dropwise added to the commercially available dibenzosuberone (14.00 g, 67.30 mmol) in a two-necked flask, at 0 °C over 2 h. The reaction mixture was stirred at 0 °C for further 2 h, and then poured into 1200 mL of water. The white precipitate was collected by filtration, dried and stirred in 120 mL of boiling EtOH. The insoluble product was collected by filtration of the hot mixture. The crude product (18.20 g, 91%) containing 3,7- and 3,9-dinitrodibenzosuberone isomers was used for the next step without further purification. Column chromatography of a small amount of the crude product **7** with EtOAc/heptane (7:93) as an eluent gave compound **7b** as first eluting fraction, and **7a** as second eluting fraction. The spectroscopic data of 3,7-dinitro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**7a**) are in agreement with the published data.[15] M.p. 205.9–207 °C. ^{1}H NMR (DMSO, 300 MHz): δ = 3.37 (s, 4 H, 2 × CH_2), 7.71 (d, J = 8.5 Hz, 2 H, Ar-*H*), 8.38 (dd, J = 8.5, 2.7 Hz, 2 H, Ar-*H*), 8.68 (d, J = 2.7 Hz, 2 H, Ar-*H*) ppm. ^{13}C NMR (DMSO, 75 MHz): δ = 33.8 (2 × *C*H$_2$), 125.4, 126.6, 131.4, (*C*H-Ar), 137.9, 146.8, 148.9 (*C*-Ar), 190.2 (*C*O) ppm. MS (CI): m/z = 299 [M + H].

3,9-Dinitro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (7b): M.p. 204–206.6 °C. ^{1}H NMR (DMSO, 300 MHz): δ = 3.24–3.32 (m, 2 H, CH_2), 3.40–3.45 (m, 2 H, CH_2), 7.64 (t, ^3J = 8.0 Hz, 1 H, Ar-H^7), 7.69 (d, ^3J = 8.5 Hz, 1 H, Ar-H^1), 8.05 (dd, ^3J = 8.0, ^4J = 1.2 Hz, 1 H, Ar-$H^{6\text{ or }8}$), 8.12 (dd, ^3J = 8.0, ^4J = 1.2 Hz, 1 H, Ar-

H$^{6\text{ or }8}$), 8.38 (dd, ^3J = 8.5, ^4J = 2.5 Hz, 1 H, Ar-*H*^{2}), 8.62 (d, ^4J = 2.5 Hz, 1 H, Ar-*H*^{4}) ppm. ^{13}C NMR (DMSO, 75 MHz): δ = 27.8 (*C*H$_2$), 33.5 (*C*H$_2$), 125.2, 127.2, 128.1, 128.4, 132.6, 133.9 (*C*H-Ar), 134.2, 137.8, 141.1, 146.7, 149.7, 149.9 (*C*-Ar), 192.8 (*C*O) ppm. MS (CI): *m*/*z* = 299 [M + H].

3,7-Diamino-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (8a): A solution of the dinitrodibenzosuberone mixture (18.21 g, 61.10 mmol) in AcOH (100 mL) was hydrogenated with 10% Pd/C in a Parr apparatus at a pressure of 38 psi for 8 h. The mixture was filtered through a pad of Celite, and the solids were washed 4 times with EtOAc. After evaporation of the solvents, the crude product was purified by column chromatography using a gradient of CH_2Cl_2/MeOH (99:1 to 95:5). This afforded the desired compound **8a** (second eluting fraction) as yellowish needles (8.00 g, 55%) and **8b** (first eluting fraction, 5.20 g, 36%). The spectroscopic data of 3,7-diamino-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**8a**) are in agreement with the published data.[15] M.p. 163–164.3 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.05 (s, 4 H, 2 × C*H*$_2$), 3.68 (s, 4 H, 2 × N*H*$_2$), 6.77 (dd, ^3J = 8.0, ^4J = 2.5 Hz, 2 H, Ar-*H*), 7.00 (d, ^3J = 8.0 Hz, 2 H, Ar-*H*), 7.30 (d, ^4J = 2.5 Hz, 2 H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 34.9 (*C*H$_2$), 116.7, 119.8, 130.8 (*C*H-Ar), 133.1, 139.5 (*C*-Ar), 145.2 (*C*-NH$_2$), 195 (CO) ppm. IR: $\tilde{\nu}$ = 1598 (C=O) cm^{-1}. MS (CI): *m*/*z* = 239 [M + H]. HRMS: calcd. for $C_{15}H_{14}N_2O$ [M]$^+$ 238.1106; found 238.1095.

3,9-Diamino-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (8b): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.89–2.93 (m, 2 H, C*H*$_2$), 3.09–3.13 (m, 2 H, C*H*$_2$), 3.69 (s, 4 H, 2 × N*H*$_2$), 6.74 (dd, ^3J = 8.0, ^4J = 2.4 Hz, 1 H, Ar-*H*^{2}), 6.86 (dd, ^3J = 7.5, ^4J = 1.4 Hz, 1 H, Ar-*H*$^{6\text{ or }8}$), 6.99 (d, ^4J = 2.4 Hz, 1 H, Ar-*H*^{4}), 7.00 (d, ^3J = 8.0 Hz, 1 H, Ar-*H*^{1}), 7.14 (t, ^3J = 7.5 Hz, 1 H, Ar-*H*^{7}), 7.40 (dd, ^3J = 7.5, ^4J = 1.4 Hz, 1 H, Ar-*H*$^{6\text{ or }8}$) ppm. MS (CI): *m*/*z* = 239 [M + H]. HRMS: calcd. for $C_{15}H_{14}N_2O$ [M]$^+$ 238.1106; found 238.1098.

3,7-Dichloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (9): Concd. HCl (83 mL) was added to 3,7-diamino-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**8a**, 3.00 g, 12.60 mmol), and the flask with reagents was gently heated for 1 h. The reaction mixture was stirred at 55–60 °C for 30 min and then cooled to 0 °C. Then an aqueous solution of $NaNO_2$ (2.27 g in 23 mL of H_2O) was added in one portion. After stirring, an additional portion of pre-cooled concd. HCl (300 mL) was added. The mixture was stirred at 0 °C for 30 min, and then CuCl (2.74 g) – suspended in 200 mL of H_2O – was added in one portion. The reaction mixture was stirred at 0 °C for 10 min and then heated at 50 °C for 12 h to complete the reaction. Upon cooling, the dark brown material that precipitated was collected by filtration and washed well with water. Column chromatography using EtOAc/heptane (1:99) as an eluent gave a pure product as yellow crystals (1.10 g, 30%). The spectroscopic data of compound **9** are in agreement with the published data.[15] M.p. 199–201 °C (ref.[15] 119–121 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.17 (s, 4 H, C*H*$_2$), 7.18 (d, *J* = 8.1 Hz, 2 H, Ar-*H*), 7.40 (dd, *J* = 8.1, 2.2 Hz, 2 H, Ar-*H*), 7.98 (d, *J* = 2.2 Hz, 2 H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 34.6 (2 × *C*H$_2$), 130.9, 131.4, 132.9 (*C*H-Ar), 133.3, 139.6, 140.7 (*C*-Ar), 192.8 (*C*O) ppm. IR: $\tilde{\nu}$ = 1637 (C=O) cm^{-1}. MS (CI): *m*/*z* = 277 [M + H]. HRMS: calcd. for $C_{15}H_{10}Cl_2O$ [M]$^+$ 276.0109; found 276.0108.

3,7-Dichloro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (10): A solution of 3,7-dichlorodibenzosuberone (**9**, 2.52 g, 9.13 mmol), NBS (3.41 g, 19.17 mmol) and a catalytic amount of AIBN in CCl_4 (50 mL) was gently heated to reflux for 16 h. The solvent was evaporated to yield a yellowish precipitate that was dissolved in dry acetone (50 mL). Then NaI (2.99 g, 20.10 mmol) was added, and the reaction mixture was stirred under reflux for 3 h. After that, the mixture was cooled to room temperature, and water (40 mL) and 10% Na_2SO_3 (40 mL) were added. The acetone was evaporated in vacuo to give a white precipitate that was filtered, washed with plenty of water (5 × 70 mL) and ethanol (5 × 30 mL), and dried. The crude product was purified on silica gel with EtOAc/heptane (1:99) as an eluent. 3,7-Dichloro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**10**) was obtained as a yellow solid (1.83 g, 73%). M.p. 193.5–195.1 °C. ^{1}H NMR (DMSO, 300 MHz): δ = 7.30 (s, 2 H, C*H*-olefinic), 7.83 (d, ^3J = 8.4 Hz, 2 H, Ar-*H*^{1,9}), 7.87 (dd, ^3J = 8.4, ^4J = 2.1 Hz, 2 H, Ar-*H*^{2,8}), 8.10 (d, ^4J = 2.1 Hz, 2 H, Ar-*H*^{4,6}) ppm. ^{13}C NMR (DMSO, 75 MHz): δ = 129.5 (2 × *C*H-olefinic), 131.3, 133.0, 134.0 (*C*H-Ar), 133.8, 134.4, 138.8, (*C*-Ar), 189.3 (*C*O) ppm. IR: $\tilde{\nu}$ = 1615 (C=O) cm^{-1}. MS (CI): *m*/*z* = 275 [M + H]. HRMS: calcd. for $C_{15}H_8Cl_2O$ [M]$^+$ 273.9952; found 273.9951.

3,7-Dichloro-5*H*-dibenzo[*a*,*d*]cycloheptene (11): A mixture of 3,7-dichloro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**10**, 0.75 g, 2.75 mmol) and Al(*i*PrO)$_3$ (1.68 g, 8.24 mmol) in a steel bomb was heated at 230 °C overnight. The crude solid material was stirred at room temperature with 2 N HCl for 2 h, followed by extraction with CH_2Cl_2 (3 × 30 mL). The organic layers were combined and dried with $MgSO_4$. Solvent evaporation gave the crude product which was purified by column chromatography using heptane (100%) as an eluent. 3,7-Dichloro-5*H*-dibenzo[*a*,*d*]cycloheptene (**11**) was obtained as yellowish crystals (0.56 g, 79%). M.p. 195–196 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.67 (s, 2 H, C*H*$_2$), 6.99 (s, 2 H, C*H*-olefinic), 7.19–7.23 (m, 4 H, Ar-*H*), 7.31 (br. d, 2 H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 41.3 (*C*H$_2$), 126.9 (2 × *C*H-olefinic), 128.3, 129.7, 131.2 (*C*H-Ar), 133.9, 134.9, 139.2 (*C*-Ar) ppm. MS (CI): *m*/*z* = 261 [M + H]. HRMS: calcd. for $C_{15}H_{10}Cl_2$ [M]$^+$ 260.0159; found 260.0151.

3,7-Dichloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-ol (12): $NaBH_4$ (0.32 g, 8.58 mmol) was added to a solution of 3,7-dichloro-5*H*-dibenzo[*a*,*d*]cycloheptene (**11**, 0.56 g, 2.14 mmol) in dry THF (20 mL). Then BF_3·Et$_2$O (1.40 mL, 10.73 mmol) was added dropwise under argon. The reaction mixture was stirred for 20 h, then the excess of borohydride was decomposed by slow addition of water (10 mL). To that mixture MeOH (5 mL) and 4 N NaOH (5 mL) were added, followed by subsequent addition of 36% H_2O_2 (5 mL). The resulting mixture was stirred at room temperature for 3 h. After evaporation of the solvents, the obtained residue was treated with EtOAc. The organic material was washed 3 times with 20 mL of water, brine (30 mL) and dried with $MgSO_4$. The solvent was evaporated to yield the crude product which was purified by column chromatography using a gradient of EtOAc/heptane (2:98 to 15:85) to afford product **12** as a white powder (0.35 g, 60%). M.p. 146–147.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.62 (br. s, 1 H, O*H*), 3.18 (dd, *J* = 14.6, 7.8 Hz, 1 H, C*H*$_2$-11), 3.47 (dd, *J* = 14.6, 3.7 Hz, 1 H, C*H*$_2$-11), 3.81 (d, *J* = 15.1 Hz, 1 H, C*H*$_2$-5), 4.16 (d, *J* = 15.1 Hz, 1 H, C*H*$_2$-5), 5.08 (dd, *J* = 7.8, 3.7 Hz, 1 H, C*H*OH), 7.16–7.23 (m, 5 H, Ar-*H*), 7.41 (d, *J* = 8.2 Hz, 1 H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 40.2 (*C*H$_2$-5), 40.8 (*C*H$_2$-11), 69.7 (*C*HOH), 127.4, 127.7, 128.8, 129.7, 132.2, 132.4 (*C*H-Ar), 132.9, 133.5, 133.9, 138.5, 139.1, 141.7 (*C*-Ar) ppm. IR: $\tilde{\nu}$ = 3240 (OH) cm^{-1}. MS (CI): *m*/*z* = 279 [M + H]. HRMS: calcd. for $C_{15}H_{12}Cl_2O$ [M]$^+$ 278.0265; found 278.0259.

3,7-Dichloro-5,11-dihydro-10*H*-dibenzo[*a*,*d*]cyclohepten-10-one (13): NaOAc (30.00 mg) was added to a solution of 3,7-dichloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-ol (**12**, 0.58 g, 2.08 mmol) in CH_2Cl_2 (30 mL). After addition of PCC (1.34 g, 6.23 mmol), the reaction mixture was stirred at room temperature for 3 h. Then Et_2O (50 mL) was added, the precipitate was filtered off, and a second portion of Et_2O was added. The filtrate was concentrated

to yield a crude product. Purification on silica gel with EtOAc/heptane (5:95) as an eluent afforded product **13** as white solid (0.37 g, 65%). M.p. 155.5–156.2 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.13 (s, 2 H, CH_2-5), 4.18 (s, 2 H, CH_2-11), 7.20–7.36 (m, 5 H, Ar-*H*), 8.10 (d, ^3J = 8.4 Hz, 1 H, Ar-*H*) ppm. IR: $\tilde{\nu}$ = 1686 (C=O) cm^{-1}. MS (CI): *m*/*z* = 277 [M + H]. HRMS: calcd. for $C_{15}H_{10}Cl_2O$ $[M]^+$ 276.0109; found 276.0112.

3,7-Dichloro-5*H*-dibenzo[*a*,*d*]cycloheptene-10,11-dione (5): SeO_2 (0.18 g, 1.61 mmol) was added to a solution of 3,7-dichloro-5,11-dihydro-10*H*-dibenzo[*a*,*d*]cyclohepten-10-one (**13**, 0.37 g, 1.34 mmol) in AcOH (30 mL), and the reaction mixture was refluxed for 2 h. After evaporation of the AcOH under reduced pressure, the residue was dissolved in EtOAc and the mixture filtered through a pad of Celite. The filtrate was concentrated to furnish a yellowish crude mixture which was purified by column chromatography with EtOAc/heptane (5:95). The desired product **5** was obtained as yellowish solid (0.29 g, 75%). M.p. 210–210.3 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.23 (s, 2 H, CH_2-5), 7.35–7.38 (m, 4 H, Ar-*H*), 7.78 (d, ^3J = 8.7 Hz, 2 H, Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 40.1 (*C*H_2), 128.8, 129.2, 133.6 (*C*H-Ar), 134.1, 140.5, 141.3 (*C*-Ar), 187.8 (*C*O) ppm. MS (CI): *m*/*z* = 291 [M + H]. HRMS: calcd. for $C_{15}H_8Cl_2O_2$ $[M]^+$ 289.9901; found 289.9903.

***tert*-Butyl 2,3-Diaminopropionate (14):** This compound was synthesized according to a reported procedure, the spectroscopic data are in agreement with the data described.[16]

Methyl Oxo(1-piperidinylamino)acetate (16): Methyl oxalyl chloride (1.45 mL, 15.75 mmol) was added to a precooled solution of *N*-aminopiperidine (1.68 mL, 15.00 mmol) and Et_3N (4.20 mL, 30.00 mmol) in CH_2Cl_2 (15 mL). After stirring for 20 min, the crude mixture was extracted 3 times with CH_2Cl_2/H_2O. The organic layers were combined, dried with $MgSO_4$ and the solvents evaporated. Further purification by column chromatography with CH_2Cl_2/EtOAc (95:5) afforded compound **16** as white crystals (1.46 g, 50%). M.p. 100.3–101 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.44 (quint, *J* = 5.6 Hz, 2 H, 4-CH_2-pip), 1.75 (quint, *J* = 5.6 Hz, 4 H, 3,5-CH_2-pip), 2.80 (t, *J* = 5.6 Hz, 4 H, 2,6-CH_2-pip), 3.90 (s, 3 H, OCH_3), 7.78 (s, 1 H, N*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.5 (4-*C*H_2-pip), 25.4 (3,5-*C*H_2-pip), 53.9 (O*C*H_3), 57.1 (2,6-*C*H_2-pip), 153.6 (*C*ONH), 161.6 ($CH_3OCOCONH$) ppm. IR: $\tilde{\nu}$ = 3184 (NH), 1743, 1686 (2 × C=O) cm^{-1}. MS (CI): *m*/*z* = 187 [M + H]. HRMS: calcd. for $C_8H_{14}N_2O_3$ $[M]^+$ 186.1004; found 186.1009.

2-Hydrazino-2-oxo-*N*-(1-piperidinyl)acetamide (17): H_2O (10 mL) and hydrazine hydrate were added (0.17 mL, 5.37 mmol) to a solution of methyl oxo(1-piperidinylamino)acetate (**16**, 1.00 g, 5.37 mmol) in EtOH (30 mL). The reaction mixture was stirred at room temperature for 1 h, and a white precipitate appeared. After filtration, the desired product **17** (0.83 g, 83%) was used as such in the next step. M.p. 242–243.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.46 (quint, *J* = 5.7 Hz, 2 H, 4-CH_2-pip), 1.73 (quint, *J* = 5.7 Hz, 4 H, 3,5-CH_2-pip), 2.80 (t, *J* = 5.7 Hz, 4 H, 2,6-CH_2-pip), 4.31–4.36 (br. s, 4 H, N*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.9 (4-*C*H_2), 25.2 (3,5-*C*H_2-pip), 54.9 (2,6-*C*H_2-pip), 156.7 (*C*OCO-pip), 158.3 (CO*C*ONH-pip) ppm. IR: $\tilde{\nu}$ = 3265 (NH), 1659, 1613 (2 × C=O) cm^{-1}. MS (CI): *m*/*z* = 187 [M + H]. HRMS: calcd. for $C_7H_{14}N_4O_2$ $[M]^+$ 186.1117; found 186.1116.

***tert*-Butyl 7,11-Dichloro-9*H*-1,4-diazatribenzo[*a*,*c*,*e*]cycloheptene-2-carboxylate (18):** A solution of 3,7-dichloro-5*H*-dibenzo[*a*,*d*]cycloheptene-10,11-dione (**5**, 0.15 g, 0.52 mmol) and *tert*-butyl 2,3-diaminopropionate (**14**, 82.50 mg, 0.52 mmol) in EtOH (20 mL) was refluxed for 20 h. After evaporation of the solvent, the crude product was purified by column chromatography using EtOAc/heptane (5:95) to afford the desired compound **18** as a white solid (0.11 g, 50%). M.p. 84.5–85 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.70 [s, 9 H, (CH_3)$_3$], 3.73 (d, *J* = 12.7 Hz, 1 H, CH_2), 3.75 (d, *J* = 12.7 Hz, 1 H, CH_2), 7.35–7.40 (m, 4 H, Ar-*H*), 7.90 (d, ^3J = 8.4 Hz, 1 H, Ar-*H*), 7.98 (d, ^3J = 8.4 Hz, 1 H, Ar-*H*), 9.30 (s, 1 H, pyrazine-*H*) ppm. MS (CI): *m*/*z* = 413 [M + H].

7,11-Dichloro-9*H*-1,4-diazatribenzo[*a*,*c*,*e*]cycloheptene-2-carboxylic Acid (19): 1,4-Dioxane – saturated with $HCl_{(g)}$ (20 mL) – was added to *tert*-butyl 7,11-dichloro-9*H*-1,4-diazatribenzo[*a*,*c*,*e*]cycloheptene-2-carboxylate (**18**, 0.10 g, 0.24 mmol). The reaction mixture was stirred at room temperature under nitrogen for 6 h. The crude product that was obtained after evaporation of the solvent was purified on silica gel using CH_2Cl_2/MeOH (99:1). This afforded the desired compound **19** as a white solid (73.50 mg, 85%). M.p. 200–202.5 °C. ^{1}H NMR (MeOD, 300 MHz): δ = 3.78 (s, 2 H, CH_2), 7.63–7.98 (m, 4 H, Ar-*H*), 7.90–7.98 (m, 2 H, Ar-*H*), 9.40 (s, 1 H, pyrazine-*H*) ppm. Ms (CI) *m*/*z*: 357 [M + H].

7,11-Dichloro-*N*-(1-piperidinyl)-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrazine-2-carboxamide (1): A solution of 7,11-dichloro-9*H*-1,4-diazatribenzo[*a*,*c*,*e*]cycloheptene-2-carboxylic acid (**19**, 50.00 mg, 0.14 mmol) in dry DMF (10 mL) was treated with DIEA (95 μL, 0.57 mmol), *N*-aminopiperidine (27 μL, 0.25 mmol), and TBTU (80.30 mg, 0.25 mmol). The reaction mixture was stirred at room temperature under argon overnight and then treated with brine (30 mL) and extracted 3 times with EtOAc (3 × 30 mL). The organic layers were combined and washed with 1 M HCl, 2% $NaHCO_3$ and brine. After drying with $MgSO_4$, the solvent was evaporated to furnish a crude product which was purified by on a Chromatotron using an eluent gradient of CH_2Cl_2/MeOH (100 to 99:1). Pure target product **1** was obtained as a solid (37.50 mg, 61%). M.p. 195–196.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.50 (quint, *J* = 5.3 Hz, 2 H, 4-CH_2-pip), 1.82 (quint, *J* = 5.3 Hz, 4 H, 3,5-CH_2-pip), 2.97 (t, *J* = 5.3 Hz, 4 H, 2,6-CH_2-pip), 3.74 (d, *J* = 12.6 Hz, 1 H, CH_2), 3.80 (d, *J* = 12.6 Hz, 1 H, CH_2), 7.37–7.42 (m, 4 H, Ar-*H*), 7.83 (d, ^3J = 8.3 Hz, 1 H, Ar-*H*), 7.92 (d, ^3J = 8.3 Hz, 1 H, Ar-*H*), 8.59 (s, 1 H, N*H*-amide), 9.53 (s, 1 H, pyrazine-*H*) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.7 (4-*C*H_2-pip), 25.8 (3,5-*C*H_2-pip), 39.9 (2,6-*C*H_2-pip), 57.4 (Ar-*C*H_2-Ar), 127.3, 127.32, 127.4, 127.5, 131.6, 132.1 (*C*H-Ar), 133.3, 133.6, 136.8, 137.0, 137.1, 142.3, 142.4 (*C*-Ar), 142.5 (*C*H-pyrazine), 147.9, 152.7 (*C*-pyrazine), 159.9 (*C*O) ppm. IR: $\tilde{\nu}$ = 1639 (CO) cm^{-1}. MS (CI): *m*/*z* = 439 [M + H]. HRMS: calcd. for $C_{17}H_{10}N_2Cl_2$ [M – CON – pip]$^+$ 312.0221; found 312.0217.

7,11-Dichloro-*N*-(1-piperidinyl)-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*e*][1,2,4]triazine-3-carboxamide (2): A mixture of 3,7-dichloro-5*H*-dibenzo[*a*,*d*]cycloheptene-10,11-dione (**5**, 0.15 g, 0.53 mmol), hydrazide **17** (98.00 mg, 0.53 mmol) and ammonium acetate (0.20 g, 2.62 mmol) in AcOH was heated in the microwave reactor at 130 °C at a power of 40 W for 40 min. The reaction mixture was then poured into ice/water, and concentrated ammonia was added in small portions. Upon addition of ammonia, a yellow crude compound precipitated. After filtration, the crude compound was purified by HPLC using EtOAc/heptane (70:30) to give the desired product **2** as yellow solid (56.00 mg, 30%). M.p. 222.5–224 °C. ^{1}H NMR ($CDCl_3$/MeOD, 300 MHz): δ = 1.53 (quint, *J* = 5.2 Hz, 2 H, 4-CH_2-pip), 1.82 (quint, *J* = 5.2 Hz, 4 H, 3,5-CH_2-pip), 3.00 (t, *J* = 5.2 Hz, 4 H, 2,6-CH_2-pip), 3.79 (s, 2 H, Ar-CH_2-Ar), 7.42–7.45 (m, 4 H, Ar-*H*), 8.03 (dd, *J* = 6.5, 2.7 Hz, 1 H, Ar-*H*), 8.15 (dd, *J* = 6.5, 2.7 Hz, 1 H, Ar-*H*), 8.87 (s, 1 H, N*H*-amide) ppm. ^{13}C NMR ($CDCl_3$/MeOD, 75 MHz): δ = 23.2 (4-*C*H_2-pip), 25.2 (3,5-*C*H_2-pip), 39.3 (2,6-*C*H_2-pip), 56.9 (Ar-*C*H_2-Ar), 128.29, 128.3, 128.4, 128.5, 132.3, 133.5 (*C*H-Ar), 131.1, 131.7, 138.7, 139.7, 143.3,

143.7, 155.4, 155.7, 156.8 (*C*-Ar), 158.4 (*C*O) ppm. IR: ṽ = 1682 (C=O) cm^{-1}. MS (CI): *m*/*z* = 440 [M + H]. HRMS: calcd. for $C_{22}H_{19}Cl_2N_5O$ $[M]^+$ 439.0967; found 439.0971.

7,11-Dichloro-*N*-(1-piperidinyl)-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*][1,2,4]pyridine-2-carboxamide (3): 2,5-Norbornadiene (0.12 mL) was added to a chlorobenzene (5 mL) solution of carboxamide **2** (50.00 mg, 0.11 mmol) in a steel bomb. The reaction mixture was heated in an oven at 140 °C for 3 d. After evaporation of the solvent, the crude brown residue was purified on silica gel with EtOAc/heptane (50:50) to yield the target compound **3** (24.00 mg, 50%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.50 (quint, *J* = 5.5 Hz, 2 H, 4-CH_2-pip), 1.82 (quint, *J* = 5.5 Hz, 4 H, 3,5-CH_2-pip), 3.00 (t, *J* = 5.5 Hz, 4 H, 2,6-CH_2-pip), 3.65 (d, *J* = 13.6 Hz, 1 H, Ar-CH_2-Ar), 3.69 (d, *J* = 13.6 Hz, 1 H, Ar-CH_2-Ar), 7.31 (dd, ^3J = 8.1, ^4J = 2.1 Hz, 1 H, Ar-*H*), 7.35–7.41 (m, 4 H, Ar-*H*), 7.85 (dd, ^3J = 8.1, ^4J = 1.0 Hz, 1 H, Ar-*H*), 8.07 (d, ^3J = 8.1 Hz, 1 H, pyridine-*H*), 8.31 (d, ^3J = 8.1 Hz, 1 H, pyridine-*H*), 8.90 (br., 1 H, N*H*-amide) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.3 (4-*C*H_2-pip), 25.3 (3,5-*C*H_2-pip), 39.7 (2,6-*C*H_2-pip), 56.9 (Ar-*C*H_2-Ar), 121.1 (*C*H-pyridine), 126.9, 127.3, 127.4, 130.8, 131.5, 133.8 (*C*H-Ar), 135.2, 135.5, 135.9 (*C*-Ar), 136.5 (*C*H-pyridine), 138.8, 142.6, 142.8 (*C*-Ar), 148.9, 152.6, (*C*-pyridine), 160.9 (*C*O) ppm. MS (CI): *m*/*z* = 438 [M + H].

2-Fluoro-5*H*-dibenzo[*a*,*d*]cycloheptene-10,11-dione (21): SeO_2 (2.81 g, 25.30 mmol) was added to a solution of 8-fluoro-5,11-dihydro-10*H*-dibenzo[*a*,*d*]cyclohepten-10-one (**20**, 5.21 g, 23.00 mmol, prepared as described in ref.[17]) in AcOH (45 mL). The reaction mixture was refluxed for 2 h. After the solvent was evaporated under reduced pressure, the residue was redissolved in EtOAc, and selenium was filtered off through a pad of Celite. The crude product was purified by column chromatography using EtOAc/heptane (10:90) to afford the target compound **21** as a yellow powder (3.72 g, 67%). M.p. 154.5–156.6 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.27 (s, 2 H, ArCH_2Ar), 7.19 (td, *J* = 8.6, 2.8 Hz, 1 H, Ar-*H*), 7.32–7.40 (m, 3 H, Ar-*H*), 7.50 (dd, *J* = 7.4, 1.3 Hz, 1 H, Ar-*H*), 7.55 (dd, *J* = 8.6, 2.8 Hz, 1 H, Ar-*H*), 7.83 (dd, *J* = 7.4, 1.3 Hz, 1 H, F-Ar-*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 39.9 (Ar-*C*H_2Ar-F), 117.8 (d, $^2J_{CF}$ = 23.2 Hz, *C*H-Ar-F), 120.6 (d, $^2J_{CF}$ = 21.7 Hz, *C*H-Ar-F), 127.9, 128.5 (*C*H-Ar), 130.6 (d, $^3J_{CF}$ = 7.7 Hz, *C*H-Ar-F), 131.5, 133.8 (*C*H-Ar), 135.2 (*C*-Ar), 136.2 (d, $^4J_{CF}$ = 3.4 Hz, *C*-Ar-F), 136.7 (d, $^3J_{CF}$ = 6.8 Hz, *C*-Ar-F), 139.9 (*C*-Ar), 161.8 (d, $^1J_{CF}$ = 248 Hz, *C*-Ar-F), 188.0, 188.7 (*C*O) ppm. IR: ṽ = 1676 (C=O) cm^{-1}. MS (CI): *m*/*z* = 241 [M + H]. HRMS: calcd. for $C_{15}H_9FO_2$ $[M]^+$ 240.0587; found 240.0578.

***tert*-Butyl-12(6)-fluoro-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrazine-2-carboxylate (22):** A solution of 2-fluoro-5*H*-dibenzo[*a*,*d*]cycloheptene-10,11-dione (**21**, 0.10 g, 0.42 mmol) and *tert*-butyl 2,3-diaminopropionate (**14**, 66.70 mg, 0.42 mmol) in EtOH (20 mL) was stirred under microwave irradiation at 125 °C, *P* = 150 W, *p* = 18 bar for 30 min. After evaporation of the solvent, the crude product was purified by column chromatography using EtOAc/heptane (7:93) to afford the target compound **22** (91.00 mg, 60%) as a yellowish solid containing two isomers. M.p. 83.8–85 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.70 [s, 18 H, 2×(CH_3)$_3$], 3.78 (s, 4 H, 2×ArCH_2Ar), 7.09 (td, *J* ≈ 8.2, 2.6 Hz, 1 H, F-Ar-*H*), 7.13 (td, *J* ≈ 8.2, 2.6 Hz, 1 H, F-Ar-*H*), 7.30–7.49 (m, 8 H, Ar-*H*), 7.67 (dd, *J* = 9.7, 2.6 Hz, 1 H, Ar-*H*), 7.76 (dd, *J* = 9.7, 2.6 Hz, 1 H, Ar-*H*), 7.95 (dd, *J* = 7.3, 1.4 Hz, 1 H, Ar-*H*), 8.04 (dd, *J* = 7.3, 1.4 Hz, 1 H, Ar-*H*), 9.31 (s, 1 H, pyrazine-*H*), 9.34 (s, 1 H, pyrazine-*H*) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.1 [C(*C*H_3)$_3$], 39.4 (Ar-*C*H_2-Ar-F), 83.1, 83.14 [O*C*(CH$_3$)$_3$], 116.9 (d, $^2J_{CF}$ = 21.7 Hz, *C*H-Ar-F), 117.2 (d, $^2J_{CF}$ = 23.3 Hz, *C*H-Ar-F), 117.3 (d, $^2J_{CF}$ = 21.7 Hz, *C*H-Ar-F), 117.4 (d, $^2J_{CF}$ = 23.7 Hz, *C*H-Ar-F), 126.9, 127.1, 127.13, 127.15 (*C*H-Ar), 128.5 (d, $^3J_{CF}$ = 7.9 Hz, *C*H-Ar-F), 128.8 (d, $^3J_{CF}$ = 7.9 Hz, *C*H-Ar-F), 130.3, 130.6, 130.7, 130.9 (*C*H-Ar), 134.9 (*C*-Ar), 136.9 (d, $^3J_{CF}$ = 7.5 Hz, *C*-Ar-F), 137.0 (d, $^3J_{CF}$ = 7.7 Hz, *C*-Ar-F), 137.6 (d, $^4J_{CF}$ = 2.9 Hz, *C*-Ar-F), 138.0 (d, $^4J_{CF}$ = 2.9 Hz, *C*-Ar-F), 141.5, 142.0 (*C*-Ar), 142.4, 142.7 [*C*-$CO_2C(CH_3)_3$], 143.3 (*C*H-pyrazine), 143.7 (*C*H-pyrazine), 149.7 (d, $^4J_{CF}$ = 2.2 Hz, *C*-pyrazine), 150.9 (*C*-pyrazine), 152.2 (d, $^4J_{CF}$ = 2.2 Hz, *C*-pyrazine), 153.4 (*C*-pyrazine), 161.7 (d, $^1J_{CF}$ = 245 Hz, *C*-Ar-F), 161.8 (d, $^1J_{CF}$ = 243 Hz, *C*-Ar-F), 163.0 (2×*C*O) ppm. IR: ṽ = 1711 (C=O) cm^{-1}. MS (CI): *m*/*z* = 363 [M + H]. HRMS: calcd. for $C_{22}H_{19}FN_2O_2$ $[M]^+$ 362.1431; found 362.1427.

12(6)-Fluoro-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrazine-2-carboxylic Acid (23): 1,4-Dioxane – saturated with $HCl_{(g)}$ (20 mL) – was added to *tert*-butyl-12(6)-fluoro-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrazine-2-carboxylate (**22**, 80.00 mg, 0.22 mmol). The reaction mixture was stirred at room temperature under nitrogen for 10 h. Evaporation of 1,4-dioxane afforded the desired compound as a colorless oil. The crude product **23** (59.00 mg, 88%) was verified by mass spectrometry and NMR spectroscopy, and used without purification in the next step. M.p. 210–212 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.78 (s, 4 H, 2×ArCH_2Ar), 7.10–7.20 (m, 2 H, Ar-*H*), 7.35–7.51 (m, 8 H, Ar-*H*), 7.63 (dd, $^3J_{HF}$ = 9.6, $^4J_{HH}$ = 2.3 Hz, 1 H, Ar-*H*), 7.71 (dd, $^3J_{HF}$ = 9.6, $^4J_{HH}$ = 2.3 Hz, 1 H, Ar-*H*), 7.90 (d, *J* = 7.7 Hz, 1 H, Ar-*H*), 7.99 (d, *J* = 7.7 Hz, 1 H, Ar-*H*), 9.52 (s, 1 H, pyrazine-*H*), 9.54 (s, 1 H, pyrazine-*H*) ppm. ^{13}C NMR ($CDCl_3$/MeOD, 100 MHz): δ = 38.7 (Ar-*C*H_2-Ar-F), 116.6 (d, $^2J_{CF}$ = 21.5 Hz, *C*H-Ar-F), 116.7 (d, $^2J_{CF}$ = 21.7 Hz, *C*H-Ar-F), 116.9 (d, $^2J_{CF}$ = 23.5 Hz, *C*H-Ar-F), 117.0 (d, $^2J_{CF}$ = 21.7 Hz, *C*H-Ar-F), 126.6, 126.7 (2×C), 126.9 (*C*H-Ar), 128.3 (d, $^3J_{CF}$ = 7.8 Hz, *C*H-Ar-F), 128.6 (d, $^3J_{CF}$ = 7.8 Hz, *C*H-Ar-F), 130.1, 130.3 (*C*H-Ar), 130.5 (2×C, *C*H-Ar), 134.1, 134.2 (*C*-Ar), 136.18 (d, $^3J_{CF}$ = 6.7 Hz, *C*-Ar-F), 136.2 (d, $^3J_{CF}$ = 6.7 Hz, *C*-Ar-F), 137.5 (d, $^4J_{CF}$ = 3.0 Hz, *C*-Ar-F), 137.9 (d, $^4J_{CF}$ = 3.0 Hz, *C*-Ar-F), 141.4 (*C*H-pyrazine), 141.8 (*C*H-pyrazine), 143.29, 143.33 (*C*-Ar), 143.62, 143.68 (*C*-CO_2H), 149.5 (d, $^4J_{CF}$ = 3.0 Hz, *C*-pyrazine), 150.7 (*C*-pyrazine), 152.2 (d, $^4J_{CF}$ = 3.0 Hz, *C*-pyrazine), 153.4 (*C*-pyrazine), 161.31 (d, $^1J_{CF}$ = 245 Hz, *C*-Ar-F), 161.34 (d, $^1J_{CF}$ = 245 Hz, *C*-Ar-F), 165.90 (*C*O) 165.94 (*C*O) ppm. IR: ṽ = 3209 (OH), 1694 (C=O) cm^{-1}. MS (CI): *m*/*z* = 307 [M + H]. HRMS: calcd. for $C_{18}H_{11}FN_2O_2$ $[M]^+$ 306.0805; found 306.0818.

12(6)-Fluoro-*N*-(1-piperidinyl)-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrazine-2-carboxamide (4): A solution of 12(6)-fluoro-9*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyrazine-2-carboxylic acid (**23**, 60.00 mg, 0.19 mmol) in dry CH_3CN (20 mL) was treated with DIEA (129 μL, 0.78 mmol), *N*-aminopiperidine (26 μL, 0.25 mmol), and TBTU (78.00 mg, 0.25 mmol). The reaction mixture was stirred at room temperature under argon overnight. Then, the reaction mixture was treated with brine (30 mL), EtOAc (30 mL) and extracted 3 times with EtOAc and water. The organic layers were combined and washed with 1 M HCl and 2% $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$, and the solvent was evaporated to furnish the crude product which was purified by column chromatography using a gradient of CH_2Cl_2/MeOH (100 to 99:1). Target product **4** was obtained as a yellowish solid containing two isomers (43.00 mg, 57%). M.p. 208–210 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.50 (quint, *J* = 5.3 Hz, 4 H, 2×4-CH_2-pip), 1.81 (quint, *J* = 5.3 Hz, 8 H, 2×3,5-CH_2-pip), 2.97 (t, *J* = 5.3 Hz, 8 H, 2×2,6-CH_2-pip), 3.79 (s, 2 H, ArCH_2Ar), 3.80 (s, 2 H, ArCH_2Ar), 7.09–7.13 (m, 1 H, Ar-*H*), 7.14–7.16 (m, 1 H, Ar-*H*), 7.32–7.51 (m, 8 H, Ar-*H*), 7.59 (dd, *J* = 9.7, 2.7 Hz, 1 H, Ar-*H*), 7.69 (dd, *J* = 9.7, 2.7 Hz, 1 H, Ar-*H*), 7.88 (dd, *J* = 7.2, 1.4 Hz, 1 H, Ar-*H*), 7.95 (dd, *J* = 7.2, 1.4 Hz, 1 H, Ar-*H*), 8.60 (s, 1 H,

N*H*-amide), 8.64 (s, 1 H, N*H*-amide), 9.52 (s, 1 H, pyrazine-*H*), 9.54 (s, 1 H, pyrazine-*H*) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.3 (4-*C*H_2-pip), 25.4 (3,5-*C*H_2-pip), 39.4 (2,6-*C*H_2-pip), 56.9 (2 × C, Ar-*C*H_2-Ar-F), 116.8 (d, $^2J_{CF}$ = 23.0 Hz, *C*H-Ar-F), 117.1 (d, $^2J_{CF}$ = 21.7 Hz, *C*H-Ar-F), 117.2 (d, $^2J_{CF}$ = 23.0 Hz, *C*H-Ar-F), 117.3 (d, $^2J_{CF}$ = 21.6 Hz, *C*H-Ar-F), 127.0, 127.1, 127.22, 127.23 (*C*H-Ar), 128.5 (d, $^3J_{CF}$ = 8.1 Hz, *C*H-Ar-F), 128.9 (d, $^3J_{CF}$ = 8.1 Hz, *C*H-Ar-F), 130.4, 130.5, 130.6, 130.7 (*C*H-Ar), 134.7, 134.9 (*C*-Ar), 136.9 (d, $^3J_{CF}$ = 6.8 Hz, *C*-Ar-F), 137.1 (d, $^3J_{CF}$ = 6.8 Hz, *C*-Ar-F), 137.7 (d, $^4J_{CF}$ = 3.1 Hz, *C*-Ar-F), 137.9 (d, $^4J_{CF}$ = 3.1 Hz, *C*-Ar-F), 141.7, 141.8 (*C*-Ar), 142.1 (*C*H-pyrazine), 142.5, 142.6 (*C*-Ar), 142.62 (*C*H-pyrazine), 147.8, 149.0 (*C*-Ar), 152.7 (d, ^4J = 2.6 Hz, *C*-pyrazine), 153.9 (*C*-pyrazine), 160.10 (2 × *C*O), 161.7 (d, $^1J_{CF}$ = 245 Hz, *C*-Ar-F), 161.8 (d, $^1J_{CF}$ = 245 Hz, *C*-Ar-F) ppm. IR: $\tilde{\nu}$ = 3448 (NH), 1673 (CO) cm^{-1}. MS (CI): *m*/*z* = 389 [M + H]. HRMS: calcd. for $C_{23}H_{21}FN_4O$ [M]$^+$ 388.1699; found 388.1697.

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