Design, Synthesis, and Biological Evaluation of Phenylamino-Substituted 6,11-Dihydro-dibenzo[*b,e*]oxepin-11-ones and Dibenzo[*a,d*]cycloheptan-5-ones: Novel p38 MAP Kinase Inhibitors

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The pathogenesis of chronic inflammatory diseases is promoted by various pro-inflammatory cytokines. p38 MAP kinase seems to be a valid target as it controls proinflammatory cytokine levels on both transcriptional and translational levels. Starting from benzophenone-type inhibitors, a rigidisation strategy lead to 3-amino-6,11-dihydro-dibenzo[*b,e*]thiepin-11-one, phenylamino-substituted 6,11-dihydro-dibenzo-[*b,e*]oxepin-11-ones, and dibenzo[*a,d*]cyclohepten-5-ones. Synthesis, p38 inhibition, and CYP-inhibition of selected compounds are described.

Introduction

First generation compounds like the pyridinyl-imidazole **2** (SB-203580)[1,2] (Figure 1) targeted the kinase's binding site for its cosubstrate ATP.[3] Compound **2**-type compounds are fully competitive with ATP, occupying essentially the same molecular interaction sites as ATP itself at the binding site of the kinase.[4,5] Both pyridinyl and imidazol rings are known to bind to cytochrome P-450 (CYP-450) enzymes, implicating hepatotoxicity as well as drug−drug interaction potential. Thus, there is a continuous need for structurally novel inhibitors that overcome the intrinsic problems of the common diaryl-substituted heterocyclic compounds. More recently developed second generation p38 MAP kinase[6] inhibitors differ insofar as they do not directly compete with ATP for its binding site; they are exemplified by the pyrazolyl-urea derivatives like **4** (BIRB-796;[7] Figure 1) and the 4-phenylamino-diarylketones **3** (LEO;[8,9] Figure 1). For **4**, Regan et al.[10−12] described a novel binding mode based on an X-ray structure.

In this study, we describe the synthesis and biological testing of novel 3-amino-6,11-dihydro-dibenzo[*b,e*]thiepin-11-ones, **26**, *N*-substituted 3- and 8-amino-6,11-dihydro-dibenzo[*b,e*]oxepin-11-ones, **27** and **28**, 2-amino-10,11-dihydro-dibenzo[*a,d*]cyclohepten-5-ones, **29**, and 2-amino-dibenzo-[*a,d*]cyclohepten-5-ones, **30**. Kinase structures are quite flexible as they undergo substantial conformational changes during activation. Together with flexible inhibitor structures, there is considerable room for induced fits that may reduce the selectivity of the compounds. Therefore, the aim of our work was to design very rigid structures. SAR from benzophenone derivates make it obvious that inhibitory potency is related to limited ability of rotation due to steric hindrance. In consequence, we proposed to fix the torsion angle between the two phenyl rings by introduction of condensed ring systems. To keep the molecular geometry and the spatial conformation similar to those of the benzophenones, we chose the moieties ethano, etheno, methylenoxy, and methylsulfanyl as linkers.

Chemistry

Synthesis of the scaffolds 3-amino-6,11-dihydro-dibenzo[*b,e*]-thiepin-11-one, **8c**, 3-amino-6,11-dihydrodibenzo[*b,e*]oxepin-11-one, **8b**, 3-fluoro-6,11-dihydrodibenzo[*b,e*]oxepin-11-one, **8a** (Scheme 1), and 8-amino-6,11-dihydrodibenzo[*b,e*]oxepin-11-one, **14** (Scheme 2), were performed via either **7c**, **7b**, **7a**, or **12** in a modified synthetic pathway according to Kluge et al.[13]

Preparation of the scaffold 2-amino-dibenzosuberone **23** and the corresponding 2-fluoro-dibenzosuberenone **24** (Scheme 3) was derived from a modified synthesis according to Eicher et al.[14] and Kluge et al.

Coupling of the resulting ketones with any respective residues was carried out with the suitable fluoronitrobenzene or amino compound using sodium hydride and a polar aprotic solvent or by melting the reactants in the absence of reagents or solvent (Scheme 4). Any resulting nitro compound was reduced to the corresponding amine by the use of tin and HCl or tin(II)-chloride-dihydrate.

Biological Testing

All compounds were primarily screened in an isolated p38α kinase assay.[15] CYP interactions were investigated by BD-Gentest Corp.[16]

Results and Discussion

From the results of p38 MAP kinase enzyme assays,[15] summarized in Table 1, we deduced several SARs. Any *ortho*-

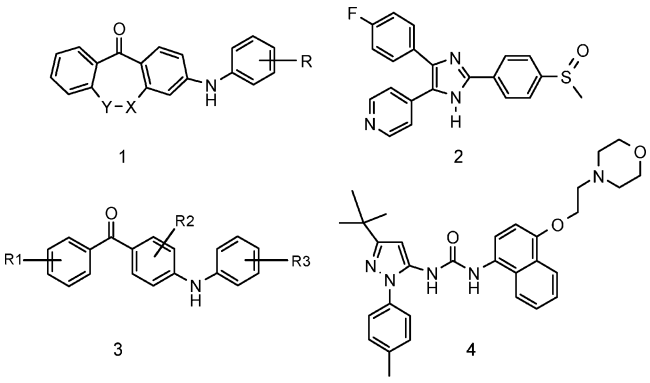

Figure 1. MAP kinase p38 inhibitors.

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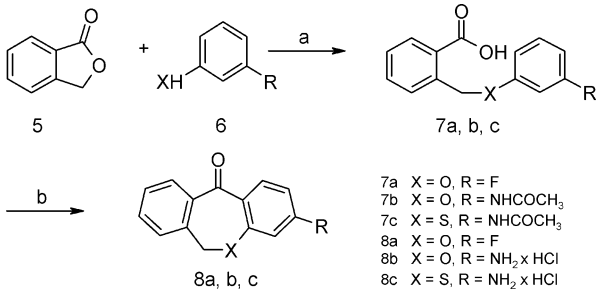
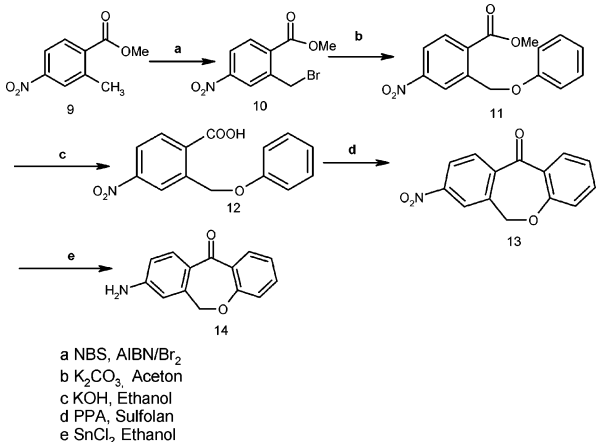
Scheme 1. Preparation of 6,11-Dihydrodibenzo[*b*,*e*]oxepin-11-one Derivates[a]



[a] Reagents: (a) NaH, DMF; (b) PPA, sulfolan.

Scheme 2. Preparation of 8-Amino-6,11-dihydrodibenzo[*b*,*e*]oxepin-11-one[a]

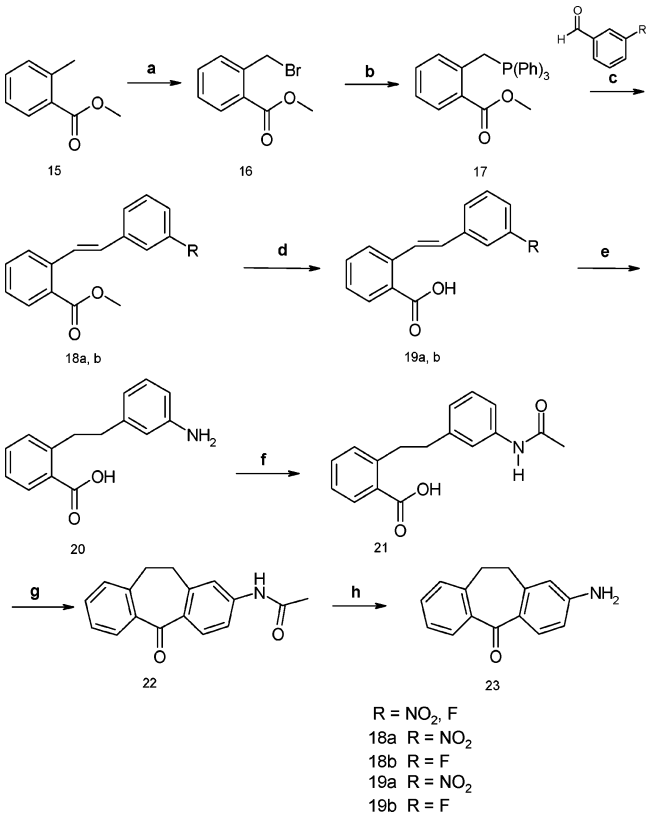


[a] Reagents: (a) NBS, AIBN/Br_2; (b) K_2CO_3, acetone; (c) KOH, ethanol; (d) PPA, sulfolan; (e) $SnCl_2$, ethanol.

anilino-substituted 2-aminodibenz[*a*,*d*]epines inhibited p38 MAP kinase with medium to good IC_{50} values ranging from ~1 μM **30b** to 0.1 μM **29b**. Interestingly, **28d**, the isomeric structure to **27i**, resulted in almost total loss in activity. Moving the amino substituent to either the *meta*- or the *para*-position led to reduced activity (cf. **27i** vs **27k** and **27j** and, correspondingly, cf. **29b** vs **29d**); note that even the potency of *ortho*-anilino compound **27n** deteriorated due to the 4-amino substituent. Because other 4-substituents are less detrimental, steric reasons cannot fully explain the reduction in inhibitor potency; hydrogen bond donor/acceptor functions of the amino group might be responsible. Comparing **27l** to **27j** and **27n**, it is surprising that inhibitory activity of the *para*-compounds is improved by the introduction of fluorine instead of an amino group in position 2. Consequently, we replaced the 4-amino substituent of **27n** with fluorine, leading to the potent p38 kinase inhibitor **27a** (IC_{50} = 0.239 μM). Subsequently, the other 2,4-dihalogen substituted compounds **27b** and **27c** were investigated and found to lose activity as the size of the halogen increased. The combination of the substitution patterns of both **27a** and **27i** led us finally to the best inhibitor in this series. Compound **27m** gave an IC_{50} of 38 nM, surpassing both reference compounds **2** and **3** (Figure 1).

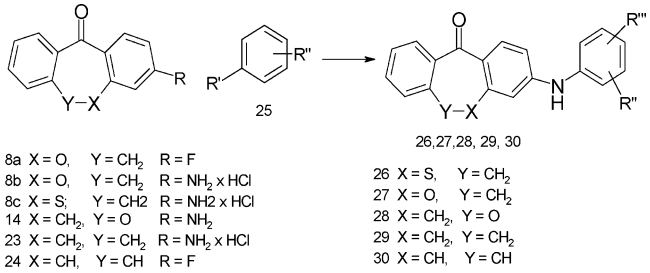
For further investigations, we selected **29b** as a candidate with good activity in p38 enzyme assay and first in vivo experiments (data not shown). The second target activity in the development of novel p38 inhibitors was CYP interaction. Concerning this parameter, compound **29b** was only slightly superior to **2**. The most relevant isoenzyme, 2D6, was only inhibited by 42%, whereas **2** inhibited this same enzyme variant by 73%. (Table 2).

Scheme 3. Preparation of 2-Amino-dibenzosuberone[a]



[a] Reagents and conditions: (a) NBS, AIBN, $CHCl_3$, reflux; (b) $P(Ph)_3$, acetone, reflux; (c) NaOMe, MeOH, reflux; (d) NaOH (20%), MeOH, reflux; (e) H_2 (4 bar), Pd/C, ethyl acetate, rt; (f) acetic anhydride, rt; (g) PPA, sulfolan, reflux; (h) HCl (20%), reflux.

Scheme 4. Coupling of the Ketones with Respective Residues



In summary, our 3-phenylamino-dibenzo[*a*,*d*]thiepin-11-ones, 3-phenylamino-dibenzo[*b*,*e*]oxepin-11-ones, and 2-phenylamino-dibenzosuberones represent a structurally novel class of p38 MAP kinase inhibitors that have good activities.

Experimental Section

General. All commercially available reagents and solvents are used without further purification. Melting points were determined with a Büchi melting point B-545, IR data were determined with a Perkin-Elmer Spectrum One (ATR Technik), and ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) were determined with a Bruker Advance 200 using TMS as internal standard. The chemical shifts are reported in ppm.

For the preparation of the 3-fluoro or 3- or 8-amino-6,11-dihydrodibenzo[*b*,*e*]oxepin-11-one and -thiepinone templates and of the 2-aminodibenzosuberones and 2-aminodibenzosuberenones, we used the method published by Kluge et al.

2-(3-Fluoro-phenoxymethyl)-benzoic Acid (7a). Yield 48.5%; mp 90−92 °C. **2-(3-Acetylamino-phenoxymethyl)-benzoic Acid (7b).** Yield 50.0%; mp 200−202 °C. **2-(3-Acetylamino-phenylsulfanylmethyl)-benzoic Acid (7c).** Mp 161−163 °C. **2-Bromo-**

Table 1. Inhibitory Activity in MAP Kinase p38 Alpha Enzyme Assay

cmpd	Y−X	R	IC_{50} μmol/L	*n*	SEM
26b	CH_2EnDash−S−	2-NH_2	0.196	3	0.051
27a	CH_2−O−	2,4-di-F	0.239	3	0.036
27b	CH_2−O−	2,4-di-Cl	3.021	3	0.224
27c	CH_2−O−	2,4-di-Br	>5	3	
27i	CH_2−O−	2-NH_2	0.303	6	0.072
27j	CH_2−O−	4-NH_2	>5	3	
27k	CH_2−O−	3-NH_2	1.219	2	0.027
27l	CH_2−O−	2-F, 4-NH_2	1.316	3	0.185
27m	CH_2−O−	2-NH_2, 4-F	0.038	3	0.016
27n	CH_2−O−	2,4-di-NH_2	>5	3	
28d	O−CH_2	2-NH_2	3.060	1	
29b	CH_2−CH_2	2-NH_2	0.104	9	0.018
29d	CH_2−CH_2	4-NH_2	1.171	3	0.096
30b	CH=CH	2-NH_2	1.056	3	0.066
2			0.068	44	0.008
3	$R^1 = CH_3$ $R^2 = Cl$	2-NH_2	0.190	3	0.065
4			0.089	6	0.038

Table 2. Inhibitory Activity on CYP-450 Isozymes[a]

	2C19	2D6	3A4
2	92%	73%	77%
29b	53%	42%	70%

[a]As tested by BDGentest Corp.[16] Values are reported as % inhibition at a concentration of 10 μM.

methyl-4-nitro-benzoic Acid Methyl Ester (10). Yield 75.1%. **4-Nitro-2-phenoxymethyl-benzoic Acid Methyl Ester (11).** Yield 46.0%; mp 112 °C. **4-Nitro-2-phenoxymethyl-benzoic Acid (12).** Yield 67.7%; mp 180 °C. **2-Bromomethyl-benzoic Acid Methyl Ester (16).** The crude product was used in the next step without further purification. **(2-Methoxycarbonylbenzyl)-triphenylphosphoniumbromide (17).** Yield 60.5%; mp 234 °C. **2-[(*E*/*Z*)-2-(3-Nitro-phenyl)-vinyl]-benzoic Acid Methyl Ester (18a).** Yield 78.1%; mp 66.5 °C. **2-[(*E*/*Z*)-2-(3-Fluoro-phenyl)-vinyl]-benzoic Acid Methyl Ester (18b).** Yield 79.1%. **2-[(*E*/*Z*)-2-(3-Nitro-phenyl)-vinyl]-benzoic Acid (19a).** Yield 80.0%; mp 164−166 °C. **2-[(*E*/*Z*)-2-(3-Fluoro-phenyl)-vinyl]-benzoic Acid (19b).** Yield 52.9%; mp 113 °C. **2-[2-(3-Acetylamino-phenyl)-ethyl]-benzoic Acid (21).** Yield 78.9%; mp 145−148 °C. **3-Fluoro-6,11-dihydro-dibenzo[*b*,*e*]oxepin-11-one (8a).** Yield 53.2%; mp 79−81 °C. **8-Nitro-6*H*-dibenzo[*b*,*e*]oxepin-11-one (13).** Yield 90.0%; mp 175 °C. **2-Fluoro-dibenzo[*a*,*d*]cyclohepten-5-one (24).** Yield 40.7%; mp 120 °C. **3-Amino-6,11-dihydro-dibenzo[*b*,*e*]oxepin-11-one Hydrochloride (8b).** Yield 89.0%. **3-Amino-6,11-dihydro-dibenzo[*b*,*e*]thiepin-11-one Hydrochloride (8c).** Yield 86.7%; mp 204−206 °C. **2-Amino-10,11-dihydro-dibenzo[*a*,*d*]cyclohepten-5-one Hydrochloride (23).** Yield 91.9%; mp 219 °C. **3-(2,4-Difluoro-phenylamino)-6,11-dihydro-dibenzo[*b*,*e*]oxepin-11-one (27a).** 2,4-Difluoroaniline (0.46 g; 3.6 mmol) was given to a suspension of 0.30 g (6.9 mmol) NaH (55%) in 7.5 mL of DMF in small portions. After the gas formation was completed, 0.82 g (3.60 mmol) **8a** were added, and the mixture was stirred at about 160 °C for 15 h. After cooling down to room temperature, 50 mL of ice water was added, and the mixture was acidified with HCl (20%). The deposit was filtered and purified by column chromatography (SiO_2 60, DCM/MeOH 95 + 5) to yield 6.8%; mp 158.6 °C; ^{1}H NMR ($CDCl_3$) δ 8.30−8.17 (m, 2H), 7.95 (d, 1H), 7.78−7.70 (m, 1H), 7.59−7.29 (m, 2H), 6.98−6.81 (m, 2H), 6.67−6.62 (m, 1H), 6.48 (s, 1H), 5.93 (s, 1H), 5.16 (s, 2H); IR 3307 cm^{-1} (N−H); IR (ATR, cm^{-1}) 1667, 1629, 1588, 1575, 1552, 1523, 1500, 1479, 1457, 1436, 1376, 1360, 1348, 1329, 1307, 1288, 1261, 1231, 1219, 1181, 1157, 1142, 1121, 1097, 1062, 1028, 965, 926, 849, 827, 761, 720, 711, 704; Anal. ($C_{20}H_{13}F_2NO_2$) C, H, N.

A Similar Procedure Was Used to Prepare the Following Compounds: 3-(2,4-Dichloro-phenylamino)-6,11-dihydro-dibenzo[*b*,*e*]oxepin-11-one (27b). Yield 3.1%; mp 155.6 °C; ^{1}H NMR ($CDCl_3$) δ 8.37−8.19 (m, 1H), 8.00−7.89 (m, 1H), 7.61−7.32 (m, 5H), 7.29−7.17 (m, 1H), 6.81−6.74 (m, 1H), 6.70−6.64 (m, 1H), 6.27 (s, 1H), 5.19 (s, 2H); IR 1589 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$) δ 188.73, 162.95, 148.45, 140.45, 136.06, 135.31, 134.12, 132.29, 129.65, 129.51, 129.14, 127.59 (2C), 127.16, 125.01, 120.54, 119.24, 111.68, 105.20, 73.60; IR (ATR) (cm^{-1}) 1589, 1573, 1514, 1468, 1326, 1298, 1278, 1253, 1121, 1100, 758, 703; Anal. ($C_{20}H_{13}Cl_2NO_2$) C, H, N.

3-(2,4-Dibromo-phenylamino)-6,11-dihydro-dibenzo[*b*,*e*]oxepin-11-one (27c). Yield 8.0%; mp 157.2−159.2 °C; ^{1}H NMR ($CDCl_3$) δ 8.31−8.20 (m, 1H), 7.98−7.89 (m, 1H), 7.86−7.69 (m, 1H), 7.60−7.29 (m, 5H), 6.88−6.75 (m, 1H), 6.70−6.62 (m, 1H), 6.26 (s, 1H), 5.19 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 188.74, 162.95, 148.36, 140.44, 137.74, 135.31 (2C), 134.13, 132.30, 131.15, 129.50, 129.14, 127.59, 120.89, 119.32, 115.47, 114.86, 111.75, 105.34, 73.60; IR (ATR, cm^{-1}) 1634, 1602, 1586, 1561, 1463, 1329, 1301, 1276, 1252, 1121, 1049, 818, 759, 702, 686; Anal. ($C_{20}H_{13}Br_2NO_2$) C, H, N.

3-(2-Nitro-phenylamino)-6,11-dihydro-dibenzo[*b*,*e*]oxepin-11-one (27d). Yield 43.7%. **3-(4-Nitro-phenylamino)-6,11-dihydro-dibenzo[*b*,*e*]oxepin-11-one (27e).** Yield 95.0%. **3-(3-Nitro-phenylamino)-6,11-dihydro-dibenzo[*b*,*e*]oxepin-11-one (27f).** Yield 92.3%. **3-(2,4-Dinitro-phenylamino)-6,11-dihydro-dibenzo[*b*,*e*]-oxepin-11-one (27g)**. Yield 84.0%. **3-(2-Fluoro-4-nitro-phenylamino)-6,11-dihydro-dibenzo[*b*,*e*]oxepin-11-one (27h).** Yield 57.5%. **2-(2-Nitro-phenylamino)-dibenzo[*a*,*d*]cyclohepten-5-one (30a).** The crude product was used in the next step without further purification. **8-(2-Nitrophenylamino)-6*H*-dibenzo[*b*,*e*]oxepin-11-one (28a).** Compound **14** (0.30 g, 1.3 mmol) was given to a suspension of 0.10 g (4.2 mmol) NaH (55%) in 10 mL of DMF in small portions. After the gas formation was completed, 0.20 g (1.4 mmol) 2-fluoronitrobenzene were added, and the mixture was stirred at 0 °C for 1 h. A 10 mL portion of ice water was added, and the deposit was filtered and washed to yield 0.30 g (65.13%) of **28a**, mp 217 °C.

A Similar Procedure Was Used to Prepare the Following: 3-(2-Nitro-phenylamino)-6,11-dihydro-dibenzo[*b*,*e*]thiepin-11-one (26a). Yield 43.7%; mp 186−188 °C. **8-(2-Fluoro-4-nitro-phenylamino)-6*H*-dibenzo[*b*,*e*]oxepin-11-one (28b).** Yield 78.8%; mp 239 °C. **8-(4-Nitrophenylamino)-6*H*-dibenzo[*b*,*e*]oxepin-11-one (28 c).** Yield 51.6%; mp 280 °C. **2-(2-Nitro-phenylamino)-10,11-dihydro-dibenzo[*a*,*d*]cyclohepten-5-one (29a).** The crude product was used in the next step without further purification. **2-(4-Nitro-phenylamino)-10,11-dihydro-dibenzo[*a*,*d*]cyclohepten-5-one (29c).** The crude product was used in the next step without further purification. **3-(2-Amino-phenylamino)-6,11-dihydro-dibenzo[*b*,*e*]oxepin-11-one (27i).** Compound **27d** (0.75 g, 2.17 mmol) is dissolved in 4 mL of EtOH and 2.45 g (10.9 mmol) of tin(II)-chloride-dihydrate and stirred for 2 h at 70 °C. After cooling down to room temperature, 20 mL of ice water was added, and the mixture was alkalized with NaOH (20%). The aqueous phase was extracted with EtOAc, the organic layer was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2 60, DCM/MeOH 95:5) to yield 135 mg (15%) **27i**; mp 122−124 °C; ^{1}H NMR (DMSO-d_6) δ 8.16 (s, 1H), 7.96 (d, 1H), 7.79 (d, 1H), 7.60−7.46 (m, 3H), 7.01−6.93 (m, 2H), 6.78 (d, 1H), 6.62−6.49 (m, 2H), 6.08 (s, 1H), 5.15 (s, 2H), 4.86 (s, 2H); IR (ATR, cm^{-1}) 3335 (N−H), 1587, 1559, 1498, 1459, 1297, 1276, 1253, 1229, 1154, 1118, 746; Anal. ($C_{20}H_{16}N_2O_2$) C, H, N.

A Similar Procedure Was Used to Prepare the Following Compounds: 3-(2-Amino-phenylamino)-6,11-dihydro-dibenzo-[*b*,*e*]thiepin-11-one (26b). Mp 195 °C; ^{1}H NMR (DMSO-δ_6) δ 8.09−8.03 (d, 1H), 7.51−7.44 (m, 4H), 7.00−6.76 (m, 6H), 4.86 (br s, 2H), 4.12 (s, 2H); IR (ATR, cm^{-1}) 2923 (N−H), 2853, 1615, 1583, 1564, 1497, 1479, 1457, 1275, 1238, 1136, 735; Anal. ($C_{20}H_{16}N_2OS$) C, H, N: calcd, 72.26, 4.85, 8.43; found, 70.75, 5.09, 7.11. C, H, N: calcd, 72.26, 4.85, 8.43; found, 70.75, 5.09, 7.11. No satisfactory EA even after recrystallization from EtOH/toluene. LC-MS: TSQ quantum, 92% purity; LCQDuo, 95% purity.

3-(4-Amino-phenylamino)-6,11-dihydro-dibenzo[*b*,*e*]oxepin-11-one (27j). Yield 20.3%; mp 131−133 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (d, 1H), 7.97−7.92 (m, 1H), 7.51−7.43 (m, 2H), 7.33−7.25

(m, 1H), 7.03−7.97 (m, 2H), 6.70−6.65 (m, 2H), 6.52 (dd, 1H), 6.33 (d, 1H), 5.92 (s, 1H), 5.12 (s, 2H), 3.56 (s, 2H). IR (ATR, cm^{-1}) 1626, 1589, 1564, 1510, 1329, 1301, 1277, 1256, 1156, 1120, 826. Anal. ($C_{20}H_{16}N_2O_2$) C, H, N.

3-(3-Amino-phenylamino)-6,11-dihydro-dibenzo[*b,e*]oxepin-11-one (27k). Yield 7.8%; mp 150 °C; ^{1}H NMR ($CDCl_3$) δ 8.19 (d, 1H), 7.95 (dd, 1H), 7.80−7.71 (m, 1H), 7.53−7.46 (m, 2H), 7.36−7.32 (m, 1H), 7.18−7.06 (m, 1H), 6.73−6.36 (m, 4H), 6.09 (s, 2H), 5.16 (s, 2H), 4.68 (s, 1H); IR (ATR, cm^{-1}) 1585, 1569, 1490, 1459, 1297, 1276, 1254, 1230, 1156, 1121, 759, 701; Anal. ($C_{20}H_{16}N_2O_2$) C, H, N.

3-(4-Amino-2-fluoro-phenylamino)-6,11-dihydro-dibenzo[*b,e*]-oxepin-11-one (27l). Yield 20.4%; mp 123−125 °C; ^{1}H NMR ($CDCl_3$) δ 8.16 (d, 1H), 7.94 (d, 1H), 7.51−7.43 (m, 2H), 7.33−7.25 (m, 1H), 7.10 (t, 2H), 6.55−6.42 (m, 2H), 6.30 (d, 1H), 5.74 (s, 1H), 5.13 (s, 2H), 3.77 (s, 2H); IR (ATR, cm^{-1}) 1624, 1589, 1564, 1517, 1494, 1299, 1277, 1229, 1155, 1120; Anal. ($C_{20}H_{15}FN_2O_2$) C, H, N.

3-(2-Amino-4-fluoro-phenylamino)-6,11-dihydro-dibenzo[*b,e*]-oxepin-11-one (27m). Yield 26.0%; mp 182.6 °C; ^{1}H NMR ($CDCl_3$) δ 8.16 (d, 1H), 7.93 (d, 1H), 7.52−7.39 (m, 2H), 7.31 (d, 1H), 7.09−7.01 (m, 1H), 6.54−6.39 (m, 3H), 6.11 (s, 1H), 5.59 (s, 1H), 5.12 (s, 2H), 3.2 (ws, 2H); IR (ATR, cm^{-1}) 1631, 1600, 1549, 1506, 1303, 1271, 1232, 1156, 1121, 825, 755; Anal. ($C_{20}H_{15}FN_2O_2$) C, H, N.

3-(2,4-Diamino-phenylamino)-6,11-dihydro-dibenzo[*b,e*]oxepin-11-one (27n). Yield 4.9%; mp 191.8 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (d, 1H), 7.94 (d, 1H), 7.57−7.40 (m, 2H), 7.36−7.23 (m, 1H), 6.87 (d, 1H), 6.44 (d, 1H), 6.20−6.05 (m, 3H), 5.50 (s, 1H), 5.12 (s, 2H), 3.68 (s, 4H); IR (ATR, cm^{-1}) 1622, 1590, 1563, 1514, 1468, 1384, 1300, 1276, 1255, 1235, 1155, 1119, 922, 758, 700; Anal. ($C_{20}H_{17}N_3O_2$) C, H, N: calcd, 72.49, 5.17, 12.68; found, 71.03, 4.35, 11.53. LC-MS: TSQ quantum, 96% purity; LCQDuo, 90% purity.

8-(2-Aminophenylamino)-6,11-dihydrodibenzo[*b,e*]oxepin-11-one (28d). The product was purified by column chromatography (LiChroprep RP-18, ACN/H_2O 6:4) to yield 0.16 g (50.0%) **28d**; mp 231 °C; IR (ATR, cm^{-1}) 1591, 1577, 1546, 1301, 1245, 1208, 767, 736.

2-(2-Amino-phenylamino)-10,11-dihydro-dibenzo[*a,d*]cyclo-hepten-5-one (29b). Yield 10.7%; mp 153 °C; IR (ATR, cm^{-1}) 1599, 1581, 1566, 1499, 1290, 1279, 1258, 1111, 750, 694; Anal. ($C_{21}H_{18}N_2O$) C, H, N.

2-(4-Amino-phenylamino)-10,11-dihydro-dibenzo[*a,d*]cyclo-hepten-5-one (29d). Yield 5.5%; mp 217 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (d, 1H), 8.02 (d, 1H), 7.31−7.41 (m, 2H), 7.19 (d, 1H), 7.04 (d, 2H), 6.69−6.75 (m, 3H), 6.55 (d, 1H), 5.81 (s, 1H), 3.66 (d, 2H), 3.06−3.16 (m, 4H); IR (ATR, cm^{-1}) 1582, 1562, 1506, 1295, 1281, 1211, 1109, 825, 758; Anal. ($C_{21}H_{18}N_2O$) C, H, N.

2-(2-Amino-phenylamino)-dibenzo[*a,d*]cyclohepten-5-one (30b). Yield 7.2%; mp 232 °C; ^{1}H NMR (DMSO-d_6) δ 8.19 (d, 1H), 8.03−8.09 (m, 2H), 7.67−7.70 (m, 2H), 7.57−7.61 (m, 1H), 7.10 (d, 1H), 7.02 (d, 2H), 6.88−6.94 (m, 2H), 6.75−6.82 (m, 2H), 6.61 (t, 1H), 4.88 (s, 2H); IR (ATR, cm^{-1}) 1596, 1571, 1558, 1497, 1370, 1304, 1257, 1226, 806, 751, 735; Anal. ($C_{21}H_{16}N_2O$) C, H, N.

Inhibitory activity on CYP-450 isozymes was determined by BDGentest Corp.[16] Values are reported as % inhibition at a concentration of 10 μM.

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Supporting Information Available: Synthetic procedures, purity data of test compounds, routine spectroscopic data, and IR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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