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Naphthannelated azepinones: synthesis and antitumor activity

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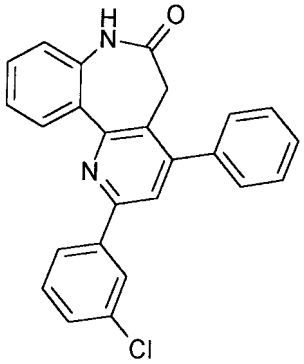
5 *H*-Benzo[*b*]naphth[2,3-*e*]azepine-6,13-diones **4a**, **4b** and 4 *H*-naphtho[2,3-*e*]thieno[3,2-*b*]azepine-5,12-dione (**6**) were prepared by aldol condensation of phthalic dialdehyde (**3**) with the fused azepinediones **2a**, **2b** and **5**, respectively. The Schmidt reaction of naphthacene-5,12-quinone (**7**) yielded 6 *H*-benzo[*e*]naphth[2,3-*b*]azepine-7,12-dione (**10**). Several derivatives of the heterocyclic basic scaffolds **4**, **6** and **10** were prepared by standard procedures, e.g. Grignard reaction, deoxygenation with triethylsilane, and sodium borohydride reduction. Evaluation of the synthesized compounds in the NCl *in vitro* cell line screening revealed a modest antitumor activity without marked cell line selectivity for the majority of the derivatives. The 2-bromo-5 *H*-benzo[*b*]naphth[2,3-*e*]azepin-6(13 *H*)-one (**19**) was the only representative in this series exhibiting a noteworthy growth inhibitory effect for human tumor cells.

1. Introduction

In several recent papers, [1]benzazepines with antitumor activity have been reported, comprising indolo[3,2-*d*]-[1]benzazepin-6-ones [1] and spiro[1-benzazepine-4,1′-cyclohexane]-2,5-diones [2]. 2,4-Diaryl-pyrido[3,2-*d*][1]-benzazepin-6-ones, e.g. **1**, have been shown to exhibit *in vitro* antitumor activity with selectivity for renal cancer cell lines [3, 4]. In order to obtain information about the antiproliferative properties of related ring systems, several benzo[*b*]naphth[2,3-*e*]azepines were synthesized and evaluated in the *in vitro* disease oriented antitumor drug discovery screening of the National Cancer Institute (NCI). Examples of structures with a benzo[*b*]naphth[2,3-*e*]azepine basic scaffold are rare in the literature. One of these entities is the retinoid synergist HX 640, which increases the effect of retinoid acid receptor agonists on cell differentiation [5].



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2. Investigations, results and discussion

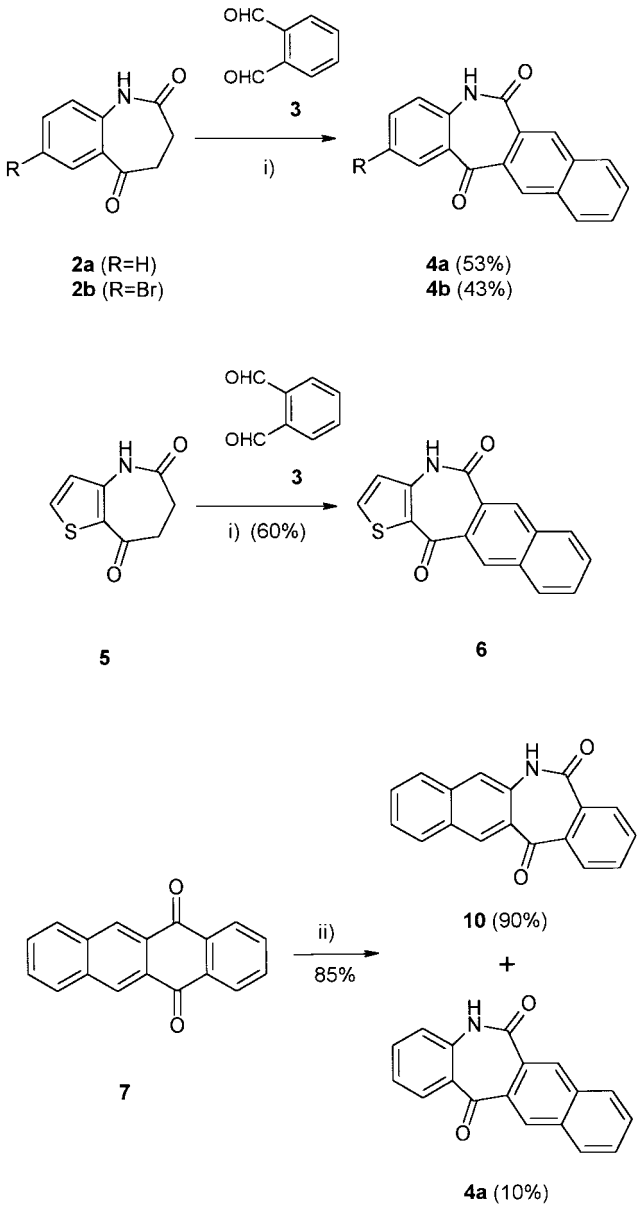
2.1. Chemistry

The use of phthalic dialdehyde (**3**) for the annelation of naphthalene rings to compounds with vicinal C,H-acidic positions has been described in several reports [6–11]. Based on this reaction, a novel synthetic access to the benzo[*b*]naphth[2,3-*e*]azepine scaffold was developed employing the double aldol condensation of phthalic dialdehyde (**3**) with the 1 *H*-[1]benzazepine-2,5(3 *H*, 4 *H*)-diones **2a** and **2b** in the presence of potassium hydroxide in ethanol (Scheme 1). Application of the method on 4 *H*-thieno[3,2-*b*]azepine-5,8(6 *H*, 7 *H*)-dione (**5**) led to 4 *H*-naphtho[2,3-*e*]thieno[3,2-*b*]azepine-5,12-dione (**6**), representing a new heterocyclic ring system (Scheme 1). The 6 *H*-benzo[*e*]naphth[2,3-*b*]azepine-7,12-dione **10**, which is an isomer of the 5 *H*-benzo[*b*]naphth[2,3-*e*]azepine-6,13-dione **4a**, was prepared from naphthacene-5,12-quinone **7** by a Schmidt reaction. Treatment of **7** with sodium azide and concentrated sulfuric acid furnished a mixture of the isomers **4a** and **10** in a ratio of 1 : 9 in favor of the desired product. The ratio of the isomers was calculated from the ^{1}H NMR spectrum of the crude reaction mixture, using for comparison the data of independently prepared **4a**. From the mixture, **10** was isolated and purified by repeated crystallization from ethanol. The synthesis of **10** by an intramolecular Friedel-Crafts reaction from *N*-(2-naphthyl)-phthalimide has been reported earlier [12]. The m.p. given in the literature corresponded to the m.p. of the isolated product **10** of the Schmidt reaction.

Employing standard reaction conditions, several derivatives were prepared from the dioxo compound **4a** (Scheme 2). The reduction of the keto group in **4a** was performed with sodium borohydride in THF furnishing the secondary alcohol **13**. Upon treatment of **4a** with an excess of Grignard reagents in diethyl ether the tertiary alcohols **11a** and **11b** were obtained, from which the hydroxy functions were removed with triethylsilane in trifluoroacetic acid, yielding the compounds **12a** and **12b**. As result of the reaction of the dioxo compound **4a** with triethylsilane in trifluoroacetic acid the methylene compound **14** was obtained. The lactam **14** was converted to the corresponding thiolactam **16** by means of Lawessons reagent in toluene [13]. Deprotonation of lactam **14** or thiolactam **16** with sodium hydride in THF and alkylation with iodomethane furnished the tertiary lactam **15** and the methylthioimidate **17**, respectively.

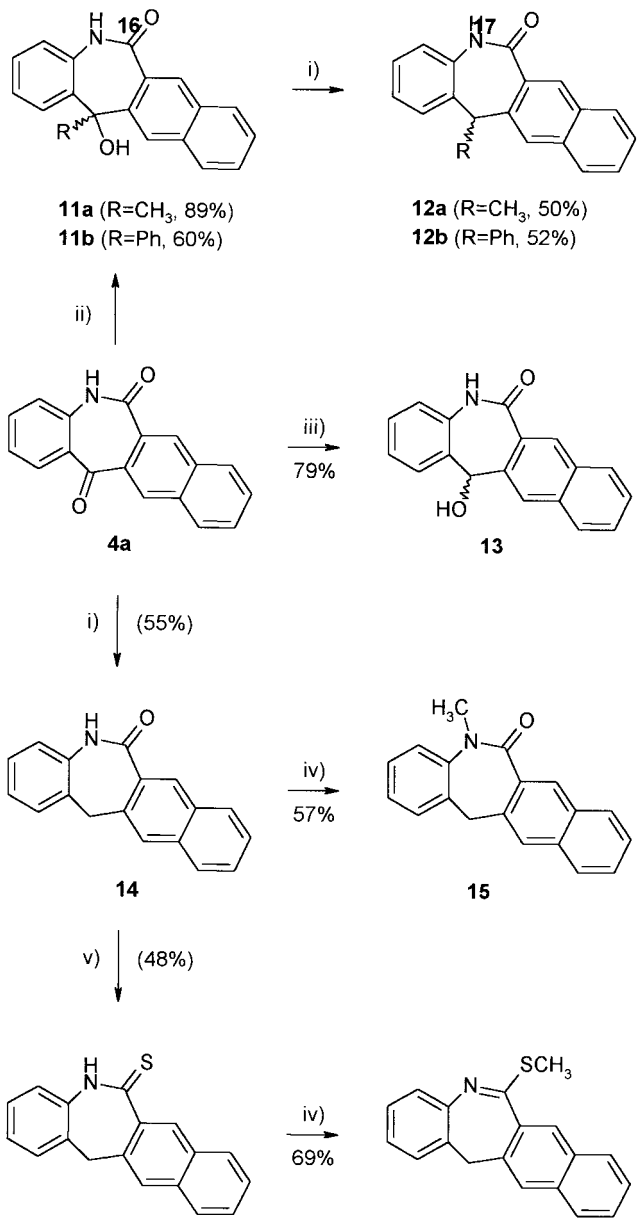
The derivatives **18**–**23** were obtained starting from the dioxo compounds **4b** and **10**, respectively, by application of the methods described above (Scheme 3). In contrast to the benzo analogs **4** and **10**, 4 *H*-naphtho[2,3-*e*]thieno[3,2-*b*]azepine-5,12-dione (**6**) reacted sluggishly with triethylsilane in trifluoroacetic acid. Therefore, the secondary alcohol **24** was treated with the said reagent, furnishing the desired methylene structure **25** in moderate yield. The tertiary lactam **26** was obtained by N-methylation of its sodium salt with iodomethane (Scheme 3).

Scheme 1



i) KOH, EtOH, 25 °C, ii) conc. H_2SO_4, NaN_3, 25 °C

Scheme 2



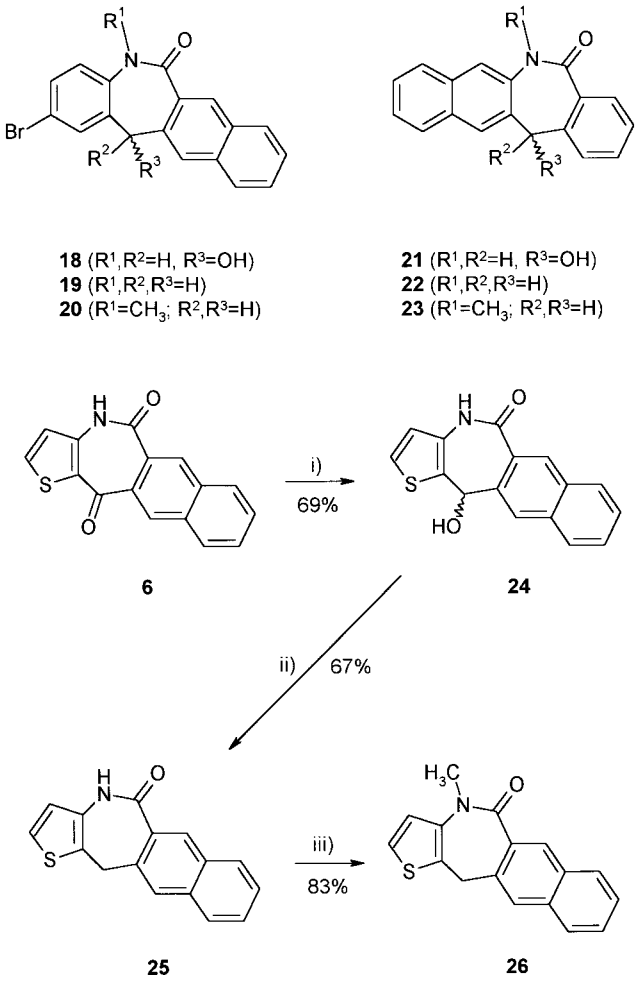
i) $Si(C_2H_5)_3H$, F_3CCOOH, 50–60 °C, ii) RMgBr, diethyl ether, reflux, iii) $NaBH_4$, THF, 25 °C, iv) 1. NaH, THF, reflux, 2. ICH_3, THF, reflux, v) Lawessons reagent, toluene, Δ

2.2. Biological activity

Of the 22 new compounds described in this paper, 18 were tested in the NCI's *in vitro* anti cancer drug discovery screen. The rationale, intentions, applications and technical details of this cell line based screening program have been covered broadly by original articles [14–16] and reviews [17, 18]. As a result of this screening, the antitumor activity of a test compound is reported for each out of 60 tumor cell lines. For every cell line, three parameters are calculated and provided by the NCI: $\log_{10}$ GI_{50} (GI_{50}: molar concentration inhibiting 50% net cell growth), $\log_{10}$ TGI (TGI: molar concentration for total inhibition of net cell growth), and $\log_{10}$ LC_{50} (LC_{50}: molar concentration leading to 50% net cell death). An averaged value on all cell lines, designated as meangraph midpoint (MG_MID), is calculated for each of the three parameters given above. For the calculation of the MG_MID values insensitive cell lines are included with the highest concentration tested. The NCI *in vitro* screening is not only directed to the disclosure of new antitumor compounds with high potency, but also intended for the discovery of compounds with new typical selectivity patterns on the 60 cell lines, because novel selectivity patterns might reflect novel mechanisms of antitumor activity. Selectivity in this context is characterized by a high deviation of the particular cell line parameter compared to the MG_MID value. Furthermore, special interest is dedicated to compounds with a selectivity for one of the nine organ-specific subpanels of the NCI cancer cell panel [17]. For instance, the 2,4-diaryl-pyrido[3,2-*d*][1]benzazepin-6-ones like **1** exhibit antitumor activity with a selectivity for the renal cancer cell line subpanel [3, 4].

In Table 1, the $\log_{10}$ GI_{50} MG_MID values and the $\log_{10}$ GI_{50} values for the renal cancer cell line 786-0 are given for the tested naphthannelated benzazepines and the 2,4-diaryl-pyrido[3,2-*d*][1]benzazepin-6-one **1**. In contrast to the 2,4-diaryl-pyrido[3,2-*d*][1]benzazepin-6-ones a

Scheme 3



i) $NaBH_4$, THF, 25 °C, ii) $Si(C_2H_5)_3H$, F_3CCOOH, 50–60 °C, iii) 1. NaH, THF, reflux, 2. ICH_3, THF, reflux

Table 1: Antitumor activity, expressed as $\log_{10}$ GI_{50}

Compd.	$\log_{10}$ GI_{50} (M)[a]	
	MG_MID[b]	786-0[c]
1	−5.51[d]	−6.01[d]
4a	−4.54	−5.18
4b	−4.09	−4.19
6	−4.01	>−4.00
11a	−4.25	−4.24
12a	−4.66	−4.47
12b	−4.56	−4.52
13	−4.48	−4.26[d]
14	−4.31	−4.64
15	−4.37	−4.43
17	−4.35	−4.39
18	−4.60	−4.77
19	−5.08	−5.53
20	−4.54	−4.75
21	−4.23	>−4.00
23	−4.57	−4.54
24	−4.16	>−4.00
25	−4.42	−4.52[d]
26	−4.61	−4.51

[a] GI_{50} [M]: molar concentration for 50% growth inhibition of tumor cells; [b] Meangraph Midpoint. Parameter giving averaged activity on all cell lines included in the cell line screening; [c] renal cancer cell line; [d] mean values from two test runs

structure-related selectivity for renal cancer cell lines was not found for the naphthannelated benzazepines. Overall, the antitumor potency of the test compounds was not compelling. The majority of the more potent compounds (**12a**, **12b**, **18**, **23**) failed to exhibit a characteristic selectivity pattern in the cell line panel. Only two (**4a** and **19**) of the **18** naphthannelated benzazepines inhibited the growth of 786-0 renal cancer cells in markedly lower concentrations with respect to the MG_MID value. Moreover, the 2-bromo-5 *H*-benzo[*b*]naphth[2,3-*e*]azepin-6(13 *H*)-one **19** was the only derivative exhibiting a noteworthy average growth inhibition, expressed by an IC_{50} value below 10 μM ($\log_{10}$ GI_{50} MG_MID = −5.08). With this entity, a total growth inhibition (TGI) was observed for most of the cell lines in a concentration below 100 μM (data not shown).

In Table 2, the sensitivities of selected cancer cell lines from the NCI *in vitro* antitumor screening panel are compared for **1** and **19**. The selectivity pattern of **19** shows a slight resemblance to the selectivity patterns exhibited by the 2,4-diaryl-pyrido[3,2-*d*][1]benzazepin-6-ones like **1** [3, 4]. Generally, cell lines from the CNS and the renal cancer cell line subpanel tended to be more sensitive to **19** than cell lines from the leukemia and the colon cancer subpanel (data not shown). The cell line SR was the only line from the leukemia subpanel with over average sensitivity to **19**. The lowest GI_{50} values were found for **19** with the cell lines HOP-62 (non-small cell lung cancer) and SK-OV-3 (ovarian cancer). With regard to both *in vitro* antitumor potency and cell line selectivity, **19** was clearly inferior to the 2,4-diaryl-pyrido[3,2-*d*][1]-benzazepin-6-ones. Therefore, the present series of naphthannelated benzazepines will not be pursued further for antitumor activity.

All new compounds described here were also investigated at the NCI for *in vitro* anti-HIV-activity [19]. Of the 22 entities that were tested, three compounds (**13**, **14** and **15**) showed a moderate activity, exhibiting EC_{50} values (EC_{50} = molar concentration for 50% protection of CEM-SS-cells against lysis by HIV) in a range from 4.31×10^{-6} M (compound **14**) to 6.29×10^{-5} M (compound **15**).

Table 2: Comparison of *in vitro* antitumor activity of compounds 1 and 19 for selected cancer cell lines from the NCI *in vitro* screening panel

Cell line	**1**[a, b]	**19**[a, c]
SR[d]	−4.42[c]	−5.25
HOP-62[e]	−5.86	−5.76
HOP-92[e]	−5.87[c]	−5.25
NCI-H460[e]	−5.93	−5.26
COLO 205[f]	−5.18	−4.90
HCT-116[f]	−5.90[c]	−5.27
SW-620[f]	−5.41	−4.89
SF-539[g]	−5.20	−5.02
SNB-75[g]	−5.75	−5.55
LOX IMVI[h]	−5.69	−5.56
UACC-62[h]	−5.52	−4.92
SK-OV-3[i]	−5.73	−6.10
786-0[j]	−6.01	−5.53
ACHN[j]	−5.94	−4.99
RXF 393[j]	−5.67	−5.37
TK-10[j]	−5.83	−5.19
MG_MID[k]	−5.51	−5.08

[a] $\log_{10}$ GI_{50} [M]: $\log_{10}$ of molar concentration for 50% growth inhibition of tumor cells; [b] mean values of two test runs, unless stated otherwise; [c] single results; [d] leukemia; [e] non-small cell lung cancer; [f] colon cancer; [g] cns cancer; [h] melanoma; [i] ovarian cancer; [j] renal cancer; [k] Meangraph Midpoint. Parameter giving the averaged activity on all cell lines included in the cell line screening

3. Experimental

3.1. Apparatus

Melting points were determined on an electric variable heater (Gallenkamp) and are not corrected. IR spectra were recorded using KBr pellets on a Pye-Unicam SP 3-200 S, a Philips PU 9712, or a Perkin Elmer 1660 FTIR spectrometer, respectively. ^{1}H NMR spectra were recorded on a Bruker AMX 400 (400 MHz) or a Bruker DRX 500 (500 MHz), respectively, using tetramethylsilane as internal standard. Elemental analyses were performed in the analytical department of the Institut für Pharmazie, Universität Hamburg. Results obtained were within an error range of $\pm$0.4% with respect to the calculated values (C, H, N, Br, S) with the following exceptions: **12b**, **17**, **24**, **25** (C $\pm$ 0.5%), **11b** (C $\pm$ 0.6%), **16** (C $\pm$ 0.9%). TLC analyses were carried out on fluorescent Polygram Sil G/UV$_{254}$ silica gel plates, using ethyl acetate or toluene/acetone (8 : 2) as eluent. Spots were visualized under 254 nm UV illumination.

3.2. General synthetic procedures

3.2.1. General procedure A for the synthesis of 4a, 4b, and 6

A suspension of the appropriate annelated azepinedione (**2a**, **2b** or **5**) (3.0 mmol) [20] in 9 ml ethanol was stirred with phthalic dialdehyde (**3**) (403 mg, 3.0 mmol) and potassium hydroxide (84 mg, 1.5 mmol) for 5 h at 25 °C. The pH of the mixture was then adjusted to 6 by dropwise addition of glacial acetic acid. A precipitate was formed, which was filtered off with suction, washed with a small amount of cold ethanol and water and recrystallized from toluene/ethanol.

3.2.2. General procedure B for the synthesis of 13, 18, 21, and 24

Sodium borohydride (19 mg, 0.5 mmol) was added to a suspension of the appropriate naphthannelated azepinedione **4a**, **4b**, **6**, or **10** (0.5 mmol) in 10 ml dry THF. The mixture was stirred at 25 °C, and the reaction was monitored by TLC. When the starting material was no longer detectable, glacial acetic acid was added dropwise until the gas evolution ceased. The mixture was concentrated by evaporation. Water (15 ml) was added, and the mixture was stirred for 15 min. A precipitate was formed, which was filtered off, washed with water and hexanes and recrystallized from ethanol.

3.2.3. General procedure C for the synthesis of 14, 19, 22, and 25

A solution of the appropriate starting material (**4a**, **4b**, **10**, or **24**) and triethylsilane in trifluoroacetic acid was stirred at 50–60 °C until the starting material was no longer detectable by TLC. After cooling to room temperature, the mixture was poured into water. The precipitate was filtered off with suction and recrystallized from ethanol.

3.2.4. General procedure D for the synthesis of 15, 20, 23, and 26

A solution of the appropriate secondary lactam **14**, **19**, **22** or **25** in dry THF was refluxed with sodium hydride (60% dispersion in mineral oil) for 45 min. After cooling the mixture to room temperature, iodomethane in THF was added and refluxing was continued for 90 min. Subsequently, the mixture was cooled to room temperature and poured onto crushed ice. The suspension was adjusted to pH 6 by dropwise addition of glacial acetic acid. After stirring for 10 min, the precipitate was filtered off with suction and recrystallized from ethanol.

3.3. Synthesis of the compounds

3.3.1. 5 H-Benzo[b]naphth[2,3-e]azepine-6,13-dione (4a)

Compound **4a** was prepared employing general procedure A starting from **2a** to furnish 53% of colorless needles from ethanol; m.p. 307 °C; IR 3190 cm^{-1} (NH), 1660 cm^{-1} (C=O); ^{1}H NMR (400 MHz, [D$_6$]-DMSO) δ (ppm) = 7.25 (d"t". 1 H, J = 7.6/7.6/1.2 Hz, H arom), 7.37 (d, 1 H, J = 7.6 Hz, H arom.), 7.61 ("t", 1 H, J = 8.6/8.6 Hz, H arom.), 7.74–7.78 (m, 3 H, H arom.), 8.22–8.25 (m, 2 H, H arom.), 8.49 (s, 1 H, H arom.), 8.86 (s, 1 H, H arom.), 11.05 (s, 1 H, NH).
$C_{18}H_{11}NO_2$ (273.3)

3.3.2. 2-Bromo-5 H-benzo[b]naphth[2,3-e]azepine-6,13-dione (4b)

Compound **4b** was prepared employing general procedure A starting from **2b** to furnish 43% colorless crystals from ethanol/toluene, m.p. > 330 °C; IR 3196 cm^{-1} (NH), 1665 cm^{-1} (C=O); ^{1}H NMR (400 MHz, [D$_6$]-DMSO) δ (ppm) = 7.32 (d, 1 H, J = 8.6 Hz, H arom.), 7.74–7.81 (m, 2 H, H arom.), 7.80 (d, 1 H, J = 2.0 Hz, H arom.), 7.87 (d, 1 H, J = 2.0 Hz, H arom.), 8.22–8.29 (m, 2 H, H arom.), 8.50 (s, 1 H, H arom.), 8.87 (s, 1 H, H arom.), 11.14 (s, 1 H, NH).
$C_{18}H_{10}BrNO_2$ (352.2)

3.3.3. 4 H-Naphtho[2,3-e]thieno[3,2-b]azepine-5,12-dione (6)

Compound **6** was prepared employing general procedure A starting from **5** to furnish 60% light yellow crystals from ethanol/toluene, m.p. 348–350 °C (dec.); IR 3180 cm^{-1} (NH), 1660 cm^{-1} (C=O); ^{1}H NMR (400 MHz, [D$_6$]-DMSO) δ (ppm) = 7.11 (d, 1 H, J = 5.1 Hz, H arom.), 7.77–7.82 (m, 2 H, H arom.), 8.05 (d, 1 H, J = 5.6 Hz, H arom.), 8.25–8.32 (m, 2 H, H arom.), 9.02 (s, 1 H, H arom.), 9.22 (s, 1 H, H arom.), 11.77 (s, 1 H, NH).
$C_{16}H_9NO_2S$ (279.3)

3.3.4. 6 H-Benzo[e]naphth[2,3-b]azepine-7,12-dione (10)

To a slurry of 5,12-naphthacenquinone (775 mg; 3 mmol; purchased from Fluka, recrystallized from acetone) in concentrated sulfuric acid (7.5 ml) sodium azide (624 mg, 9.6 mmol) was added in small portions, keeping the temperature of the mixture between 20 and 30 °C. After stirring the mixture at 25 °C for 24 h, it was poured cautiously into a 10% Na_2CO_3-solution. The precipitate was filtered off with suction, washed with water and cold methanol to yield 85% of a raw mixture of the isomers **10** and **4a**. A ^{1}H NMR-evaluation of this mixture revealed a 9 : 1 ratio of the isomers in favor of **10**. Repeated recrystallization from ethanol yielded 10% of compound **10** as light brown needles, m.p. 277–280 °C (dec.) (Lit. [12]: 277.5 °C); IR 3160 cm^{-1} (NH), 1660 cm^{-1} (C=O); ^{1}H NMR (400 MHz, [D$_6$]-DMSO) δ (ppm) = 7.50 (d"t", 1 H, J = 7.6/7.6/1.2 Hz, H arom.), 7.59–7.65 (m, 1 H, H arom.), 7.75 (s, 1 H, H arom.), 7.80–7.84 (m, 3 H, H arom.), 7.89 (d, 1 H, J = 8.6 Hz, H arom.), 8.08 (d, 1 H, J = 8.1 Hz, H arom.), 8.12–8.18 (m, 1 H, H arom.), 8.38 (s, 1 H, H arom.), 11.19 (s, 1 H, NH).
$C_{18}H_{11}NO_2$ (273.3)

3.3.5. (±)-13-Hydroxy-13-methyl-5 H-benzo[b]naphth[2,3-e]azepin-6(13 H)-one (11a)

To a suspension of **4a** (480 mg, 1.76 mmol) in diethyl ether (50 ml) a solution of methyl magnesium bromide in diethyl ether (11 ml of a 3 M solution, $\cong$ 33 mmol) was added dropwise with cooling in an ice bath. The mixture was then stirred for 1 h at 25 °C and subsequently refluxed for 2 h. After cooling to room temperature, crushed ice was added until the gas evolution ceased. The pH was adjusted to 6 by dropwise addition of 10% hydrochloric acid. The organic layer was separated and the water layer was extracted three times with diethyl ether (60 ml, respectively). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness. Recrystallization of the residue from toluene/ethanol yielded 89% of colorless crystals, m.p. 179–180 °C; IR 3390 cm^{-1} (OH), 3180 cm^{-1} (NH), 1635 cm^{-1}, 1620 cm^{-1} (C=O); ^{1}H NMR (400 MHz, [D$_6$]-DMSO) δ (ppm) = 1.80 (s, 2.49 H, CH_3), 2.20 (s, 0.51 H, CH_3), 5.70 (s, 0.17 H, OH), 6.44 (s, 0.83 H, OH), 7.00–7.06 (m, 0.17 H, H arom.), 7.07–7.16 (m, 1.83 H, H arom.), 7.17–7.24 (m, 1 H, H arom.), 7.47 (d, 0.17 H, J = 7.6 Hz, H arom.), 7.50–7.62 (m, 2 H, H arom.), 7.84 (dd, 0.83 H, J = 7.6/1.5 Hz, H arom.), 7.92 (s, 0.17 H, H arom.), 7.95–8.06 (m, 2 H, H arom.), 8.28 (s, 0.83 H, H arom.), 8.31 (s, 0.17 H, H arom.), 8.40 (s, 0.83 H, H arom.), 10.38 (s, 0.17 H, NH), 10.60 (s, 0.83 H, NH). (The double set of signals is due to the existence of two conformers in solution, namely the two forms with a pseudoaxial and pseudoequatorial methyl group, respectively. The signals are split as result of the energetic barrier to the ring inversion.)
$C_{19}H_{15}NO_2$ (289.3)

3.3.6. (±)-13-Hydroxy-13-phenyl-5 H-benzo[b]naphth[2,3-e]azepin-6(13 H)-one (11b)

To a suspension of **4a** (546 mg, 2.0 mmol) in diethyl ether (60 ml) a solution of phenyl magnesium bromide in diethyl ether (6 ml of a 3 M solution, $\cong$ 18 mmol) was added dropwise with cooling in an ice bath. After stirring for 4 h at 25 °C, crushed ice was added until the gas evolution ceased. The pH was adjusted to 6 by dropwise addition of 10% hydrochloric acid. The organic layer was separated and the water layer was extracted three times with diethyl ether (70 ml, respectively). The combined organic layers were dried (Na_2SO_4) and evaporated. Recrystallization of the residue from ethanol yielded 60% of colorless crystals, m.p. 273 °C (dec.); IR 3350 cm^{-1} (OH), 3330 cm^{-1} (OH), 1650 cm^{-1} (C=O); ^{1}H NMR (400 MHz, [D$_6$]-DMSO) δ (ppm) = 6.67 (s, 1 H, OH), 6.79–6.84 (m, 2 H, H arom.), 7.02 (dd, 1 H, J = 7.6/1.5 Hz, H arom.), 7.17–7.29 (m, 5 H, H arom.), 7.54–7.66 (m, 2 H, H arom.), 8.00–8.08 (m, 3 H, H arom.), 8.31 (s, 1 H, H arom.), 8.45 (s, 1 H, H arom.), 10.09 (s, 1 H, NH).
$C_{24}H_{17}NO_2$ (351.4)

3.3.7. (±)-13-Methyl-5 H-benzo[b]naphth[2,3-e]azepin-6(13 H)-one (12a)

A solution of **11a** (203 mg, 0.7 mmol) and triethylsilane (0.3 ml, 1.8 mmol) in trifluoroacetic acid (15 ml) was stirred for 4 h at 50–60 °C. After cooling to room temperature, the mixture was poured into ice water (150 ml). By addition of saturated sodium carbonate solution the resulting suspension was adjusted to pH 6. After stirring for 10 min, the precipitate

was filtered off, washed with water and recrystallized successively from ethanol and toluene to yield 50% colorless crystals, m.p. 201–202 °C; IR 3160 cm^{-1} (NH), 1640 cm^{-1}, 1620 cm^{-1} (C=O); ^1H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 1.54 (d, 1.38 H, J = 7.2 Hz, CH_3), 1.88 (d, 1.62 H, J = 7.2 Hz, CH_3), 4.30 + 4.35 (2 q, comb. 1 H, J = 7.2 Hz, H-13), 7.06 (d"t", 0.54 H, J = 7.1/7.1/1.5 Hz, H arom.), 7.10–7.23 (m, 2.46 H, H arom.), 7.36 (s, 0.54 H, H arom.), 7.37 (s, 0.46 H, H arom.), 7.47–7.62 (m, 2 H, H arom.), 7.83 (s, 0.54 H, H arom.), 7.87 (s, 0.46 H, H arom.), 7.92 (d, 0.46 H, J = 8.2 Hz, H arom.), 7.97 (d, 0.54 H, J = 8.2 Hz, H arom.), 8.00 (d, 0.54 H, J = 8.2 Hz, H arom.), 8.04 (d, 0.46 H, J = 8.2 Hz, H arom.), 8.32 (s, 0.54 H, H arom.), 8.46 (s, 0.46 H, H arom.), 10.52 (s, 0.46 H, NH), 10.58 (s, 0.54 H, NH). (The double set of signals is due to the existence of two conformers in solution, namely the two forms with a pseudoaxial and pseudoequatorial methyl group, respectively. The signals are split as result of the energetic barrier to the ring inversion. Upon recording the ^1H NMR at higher temperatures, e.g. 413 K, coalescence of the methyl signals and of other signals is observed.)
$C_{19}H_{15}NO$ (273.3)

3.3.8. (±)-13-Phenyl-5 H-benzo[b]naphth[2,3-e]azepin-6(13 H)-one (**12b**)

A solution of **11b** (246 mg, 0.7 mmol) and triethylsilane (0.6 ml, 3.6 mmol) in trifluoroacetic acid (15 ml) is stirred for 12 h at 50–60 °C. After cooling to 25 °C, the mixture is poured into ice water (150 ml). By addition of saturated sodium carbonate solution the resulting suspension is adjusted to pH 6. After stirring for 10 min, the precipitate is filtered off, washed with water and hexanes and recrystallized successively from ethanol and toluene to yield 52% colorless needles, m.p. 290 °C; IR 3190 cm^{-1} (NH), 1650 cm^{-1}, 1625 cm^{-1} (C=O); ^1H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 5.64 (s, 1 H, H-13), 6.75 (d, 2 H, J = 7.6 Hz, H arom.), 7.08–7.24 (m, 5 H, H arom.), 7.29 (d"t", 1 H, J = 7.6/7.6/1.5 Hz, H arom.), 7.55–7.67 (m, 3 H, H arom.), 8.00 (d, 1 H, J = 8.1 Hz, H arom.), 8.07 (d, 1 H, J = 8.1 Hz, H arom.), 8.08 (s, 1 H, H arom.), 8.44 (s, 1 H, H arom.), 10.17 (s, 1 H, NH).
$C_{24}H_{17}NO$ (335.4)

3.3.9. (±)-13-Hydroxy-5 H-benzo[b]naphth[2,3-e]azepin-6(13 H)-one (**13**)

Compound **13** was prepared corresponding to general procedure B from **4a** (reaction time 2 h), yielding 79% colorless crystals, m.p. 261–262 °C; IR 3400 cm^{-1} (OH), 3190 cm^{-1} (NH), 1635 cm^{-1}, 1620 cm^{-1} (C=O); ^1H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 5.90 (s, 1 H, H-13), 6.54 (s, 1 H, OH), 7.05–7.24 (m, 3 H, H arom.), 7.52 ("t", 1 H, J = 7.4/7.4 Hz, H arom.), 7.59 ("t", 2 H, J = 6.9/6.9 Hz, H arom.), 8.01 ("t", 2 H, J = 10.1/10.1 Hz, H arom.), 8.10 (s, 1 H, H arom.), 8.33 (s, 1 H, H arom.), 10.52 (s, 1 H, NH).
$C_{18}H_{13}NO_2$ (275.3)

3.3.10. 5 H-Benzo[b]naphth[2,3-e]azepin-6(13 H)-one (**14**)

Compound **14** was prepared according to general procedure C from **4a** (408 mg, 1.5 mmol) and triethylsilane (2.0 ml, 12.6 mmol) in trifluoroacetic acid (30 ml) (reaction time 7 h) to yield 55% colorless needles, m.p. 275 °C; IR 3170 cm^{-1} (NH), 1642, 1622 cm^{-1} (C=O); ^1H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 4.09 (s, 2 H, azepine-CH_2), 7.08 (d"t", 1 H, J = 7.1/7.1/1.5 Hz, H arom.), 7.12–7.22 (m, 2 H, H arom.), 7.39 (d, 1 H, J = 7.6 Hz, H arom.), 7.49–7.55 (m, 1 H, H arom.), 7.56–7.61 (m, 1 H, H arom.), 7.87 (s, 1 H, H arom.), 7.91 (d, 1 H, J = 9.7 Hz, H arom.), 8.02 (d, 1 H, J = 9.7 Hz, H arom.), 8.37 (s, 1 H, H arom.), 10.47 (s, 1 H, NH).
$C_{18}H_{13}NO$ (259.3)

3.3.11. 5-Methyl-5 H-benzo[b]naphth[2,3-e]azepin-6(13 H)-one (**15**)

Compound **15** was prepared according to general procedure D from **14** (104 mg, 0.4 mmol) in THF (7 ml), employing a 60% dispersion of sodium hydride in mineral oil (16 mg ≅ 9.6 mg NaH, 0.4 mmol) and iodomethane (67 mg, 0.47 mmol) in THF (2 ml), to yield 57% colorless crystals from ethanol, m.p. 116 °C; IR 1620 cm^{-1} (C=O); ^1H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 3.56 (s, 3 H, CH_3), 3.92 (d, 1 H, J = 13.2 Hz, X-part of an AX-system, azepine-CH_2), 4.26 (d, 1 H, J = 13.2 Hz, A-part of an AX-system, azepine-CH_2), 7.13 (d"t", 1 H, J = 7.6/7.6/1.0 Hz, H arom.), 7.25 (d"t", 1 H, J = 7.6/7.6/1.5 Hz, H arom.), 7.36–7.41 (m, 2 H, H arom.), 7.46–7.52 (m, 1 H, H arom.), 7.54–7.60 (m, 1 H, H arom.), 7.81 (s, 1 H, H arom.), 7.88 (d, 1 H, J = 8.1 Hz, H arom.), 7.98 (d, 1 H, J = 8.1 Hz, H arom.), 8.29 (s, 1 H, H arom.).
$C_{19}H_{15}NO$ (273.3)

3.3.12. 5 H-Benzo[b]naphth[2,3-e]azepine-6(13 H)-thione (**16**)

A suspension of **14** (194 mg, 0.75 mmol) and Lawessons reagent (175 mg, 0.43 mmol) in toluene (12 ml) was stirred at 100–110 °C for 6.5 h. After chilling the mixture in an ice bath, a precipitate was formed, which was filtered off with suction, washed with ethanol and hexanes and recrystallized from ethanol to yield 48% light yellow, felt-like needles, m.p. 261 °C (dec.); IR 3450 cm^{-1}, 3140 cm^{-1} (NH), 1120 cm^{-1} (C=S); ^1H NMR (500 MHz, [D_6]-DMSO) δ (ppm) = 4.00 (br. s, 1 H, azepine-CH_2), 4.03 (br. s, 1 H, azepine-CH_2), 7.15–7.28 (m, 3 H, H arom.), 7.42 (d, 1 H, J = 7.6 Hz, H arom.), 7.46–7.53 (m, 1 H, H arom.), 7.54–7.60 (m, 1 H, H arom.), 7.79 (s, 1 H, H arom.), 7.88 (d, 1 H, J = 8.2 Hz, H arom.), 7.99 (d, 1 H, J = 8.2 Hz, H arom.), 8.57 (s, 1 H, H arom.), 12.71 (s, 1 H, NH).
$C_{18}H_{13}NS$ (275.4)

3.3.13. 6-Methylthio-13 H-benzo[b]naphth[2,3-e]azepine (**17**)

Compound **17** was prepared according to general procedure D from **16** (83 mg, 0.3 mmol) in THF (6 ml), employing a 60% dispersion of sodium hydride in mineral oil (12 mg ≅ 7.2 mg NaH, 0.3 mmol) and iodomethane (51 mg, 0.36 mmol) in THF (2 ml), to yield 69% cream colored crystals from ethanol, m.p. 157 °C; IR 2950 cm^{-1} (C–H aliph.); ^1H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 2.61 (s, 3 H, CH_3), 3.80 (br. s, 1 H, azepine-CH_2), 3.90 (br. s, 1 H, azepine-CH_2), 7.09 (d"t", 1 H, J = 7.1/7.1/1.5 Hz, H arom.), 7.14–7.24 (m, 2 H, H arom.), 7.34 (dd, 1 H, J = 7.1/1.0 Hz, H arom.), 7.49–7.61 (m, 2 H, H arom.), 7.89 (s, 1 H, H arom.), 7.92 (d, 1 H, J = 8.1 Hz, H arom.), 8.03 (d, 1 H, J = 8.1 Hz, H arom.), 8.30 (s, 1 H, H arom.).
$C_{19}H_{15}NS$ (289.4)

3.3.14. (±)-2-Bromo-13-hydroxy-5 H-benzo[b]naphth[2,3-e]azepin-6(13 H)-one (**18**)

Compound **18** was prepared corresponding to general procedure B from **4b** (reaction time 1 h) to yield 75% colorless needles, m.p. 279 °C; IR 3400 cm^{-1} (OH), 3180 cm^{-1} (NH), 1650 cm^{-1} (C=O); ^1H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 5.90 (s, 1 H, H-13), 6.72 (s, 1 H, OH), 7.08 (d, 1 H, J = 8.1 Hz, H arom.), 7.39 (dd, 1 H, J = 8.1/2.0 Hz, H arom.), 7.50–7.65 (m, 2 H, H arom.), 7.72 (s, 1 H, H arom.), 7.97–8.06 (m, 2 H, H arom.), 8.11 (s, 1 H, H arom.), 8.35 (s, 1 H, H arom.), 10.61 (s, 1 H, NH).
$C_{18}H_{12}BrNO_2$ (354.2)

3.3.15. 2-Bromo-5 H-benzo[b]naphth[2,3-e]azepin-6(13 H)-one (**19**)

Compound **19** was prepared according to general procedure C from **4b** (106 mg, 0.3 mmol) and triethylsilane (0.5 ml, 3.2 mmol) in trifluoroacetic acid (10 ml). After a reaction time of 9 h, the mixture was poured into water (40 ml). The work up led to 52% colorless needles from ethanol, m.p. 315 °C; IR 3150 cm^{-1} (NH), 1660 cm^{-1} (C=O); ^1H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 4.10 (s, 2 H, azepine-CH_2), 7.09 (d, 1 H, J = 9.2 Hz, H arom.), 7.37 (dd, 1 H, J = 8.6/2.5 Hz, H arom.), 7.50–7.56 (m, 1 H, H arom.), 7.57–7.63 (m, 1 H, H arom.), 7.65 (d, 1 H, J = 2.5 Hz, H arom.), 7.87 (s, 1 H, H arom.), 7.92 (d, 1 H, J = 7.1 Hz, H arom.), 8.03 (d, 1 H, J = 9.6 Hz, H arom.), 8.37 (s, 1 H, H arom.), 10.54 (s, 1 H, NH).
$C_{18}H_{12}BrNO$ (338.2)

3.3.16. 2-Bromo-5-methyl-5 H-benzo[b]naphth[2,3-e]azepin-6(13 H)-one (**20**)

Compound **20** was prepared according to general procedure D from **19** (102 mg, 0.3 mmol) and sodium hydride (12 mg 60% dispersion in mineral oil, ≅ 7.2 mg NaH, 0.3 mmol) in THF (7 ml) and iodomethane (57 mg, 0.4 mmol) in THF (2 ml), to yield 54% colorless crystals from ethanol, m.p. 229 °C; IR 1640 cm^{-1}, 1625 cm^{-1} (C=O); ^1H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 3.53 (s, 3 H, CH_3), 3.98 (d, 1 H, J = 13.2 Hz, azepine-CH_2), 4.23 (d, 1 H, J = 13.2 Hz, azepine-CH_2), 7.35 (d, 1 H, J = 8.6 Hz, H arom.), 7.43 (dd, 1 H, J = 8.6/2.5 Hz, H arom.), 7.51 (d"t", 1 H, J = 6.6/6.6/1.0 Hz, H arom.), 7.58 (d"t", 1 H, J = 6.6/6.6/1.0 Hz, H arom.), 7.67 (d, 1 H, J = 2.5 Hz, H arom.), 7.82 (s, 1 H, H arom.), 7.89 (d, 1 H, J = 8.1 Hz, H arom.), 7.99 (d, 1 H, J = 8.1 Hz, H arom.), 8.29 (s, 1 H, H arom.).
$C_{19}H_{14}BrNO$ (352.2)

3.3.17. (±)-12-Hydroxy-6 H-benzo[e]naphth[2,3-b]azepin-7(12 H)-one (**21**)

Compound **21** was prepared corresponding to general procedure B from **10** (reaction time 6 h). Recrystallization from ethanol yielded 59% light brown crystals, m.p. 252 °C; IR 3330 cm^{-1} (OH), 3130 cm^{-1} (NH), 1630 cm^{-1} (C=O); ^1H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 5.91 (s, 1 H, H-13), 6.56 (s, 1 H, OH), 7.28–7.48 (m, 3 H, H arom.), 7.50–7.57 (m, 1 H, H arom.), 7.58 (s, 1 H, H arom.), 7.64–7.76 (m, 2 H, H arom.), 7.79 (d, 1 H, J = 7.6 Hz, H arom.), 7.90 (d, 1 H, J = 7.6 Hz, H arom.), 8.06 (s, 1 H, H arom.), 10.72 (s, 1 H, NH).
$C_{18}H_{13}NO_2$ (275.3)

3.3.18. 6 H-Benzo[e]naphth[2,3-b]azepin-7(12 H)-one (**22**)

A solution of **10** (170 mg, 0.63 mmol) and triethylsilane (0.8 ml, 5.0 mmol) in trifluoroacetic acid (10 ml) was stirred at 50–60 °C for 7 h. Subsequently, the mixture was poured into 50 ml icewater. After stirring

for 10 min, the precipitate was filtered off with suction, washed with water and hexanes and recrystallized from ethanol to yield 44% light brown crystals, m.p. 261 °C; IR 3150 cm^{-1} (NH), 1640 cm^{-1} (C=O); ^{1}H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 4.11 (s, 2 H, azepine-CH_2), 7.33 (d"t", 1 H, J = 7.6/7.6/1.0 Hz, H arom.), 7.37–7.50 (m, 4 H, H arom.), 7.59 (s, 1 H, H arom.), 7.73 (d, 1 H, J = 7.6 Hz, H arom.), 7.78 (d, 1 H, J = 7.6 Hz, H arom.), 7.83 (d, 1 H, J = 7.9 Hz, H arom.), 7.88 (s, 1 H, H arom.), 10.67 (s, 1 H, NH).
$C_{18}H_{13}NO$ (259.3)

3.3.19. 6-Methyl-6 H-benzo[b]naphth[2,3-e]azepin-7(12 H)-one (**23**)

Compound **23** was prepared corresponding to general procedure D from **22** (217 mg, 0.84 mmol) and sodium hydride (36 mg 60% dispersion in mineral oil, ≅21.6 mg NaH, 0.9 mmol) in THF (13 ml) and iodomethane (142 mg, 1.0 mmol) in THF (2 ml), yielding 47% colorless crystals from ethanol, m.p. 170 °C; IR 1640 cm^{-1} (C=O); ^{1}H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 3.64 (s, 3 H, CH_3), 3.96 (d, 1 H, J = 13.2 Hz, azepine-CH_2), 4.25 (d, 1 H, J = 13.2 Hz, azepine-CH_2), 7.28 (d"t", 1 H, J = 7.6/7.6/2.0 Hz, H arom.), 7.37–7.50 (m, 4 H, H arom.), 7.66 (d, 1 H, J = 7.1 Hz, H arom.), 7.81–7.86 (m, 2 H, H arom.), 7.87 (s, 1 H, H arom.), 7.93 (s, 1 H, H arom.).
$C_{19}H_{15}NO$ (273.3)

3.3.20 (±)-12-Hydroxy-4 H-naphtho[2,3-e]thieno[3,2-b]azepin-5(12 H)-one (**24**)

Compound **24** was prepared corresponding to general procedure B (reaction time 16 h), to yield 69% colorless crystals from ethanol, m.p. 254 °C (dec.); IR 3290 cm^{-1} (NH/OH), 1635 cm^{-1}, 1620 cm^{-1} (C=O); ^{1}H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 5.93 (d, 1 H, J = 3.6 Hz, H-13), 6.57 (d, 1 H, J = 3.6 Hz, OH), 6.79 (d, 1 H, J = 5.1 Hz, H arom.), 7.27 (d, 1 H, J = 5.1 Hz, H arom.), 7.53–7.59 (m, 2 H, H arom.), 7.98–8.05 (m, 3 H, H arom.), 8.41 (s, 1 H, H arom.), 10.51 (s, 1 H, NH).
$C_{16}H_{11}NO_2S$ (281.3)

3.3.21. 4 H-Naphtho[2,3-e]thieno[3,2-b]azepin-5(12 H)-one (**25**)

Compound **25** was prepared corresponding to general procedure C from **24** (775 mg, 2.75 mmol) and triethylsilane (0.9 ml, 5.5 mmol) in trifluoroacetic acid (50 ml) (reaction time 8 h), to yield 67% light brown crystals from ethanol, m.p. 288 °C (dec.); IR 3160 cm^{-1} (NH), 1640 cm^{-1}, 1620 cm^{-1} (C=O); ^{1}H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 4.16 (s, 2 H, azepine-CH_2), 6.80 (d, 1 H, J = 5.1 Hz, H arom.), 7.21 (d, 1 H, J = 5.1 Hz, H arom.), 7.52 ("t", 1 H, J = 7.1/7.1 Hz, H arom.), 7.59 ("t", 1 H, J = 7.1/7.1 Hz, H arom., 7.81 (s, 1 H, H arom.), 7.90 (d, 1 H, J = 8.1 Hz, H arom.), 8.02 (d, 1 H, J = 7.6 Hz, H arom.), 8.39 (s, 1 H, H arom.), 10.46 (s, 1 H, NH).
$C_{16}H_{11}NOS$ (265.3)

3.3.22. 4-Methyl-4 H-naphtho[2,3-e]thieno[3,2-b]azepin-5(12 H)-one (**26**)

Compound **26** was prepared corresponding to general procedure D from **25** (80 mg, 0.3 mmol) and sodium hydride (12 mg 60% dispersion in mineral oil, ≅7.2 mg NaH, 0.3 mmol) in THF (6 ml) and iodomethane (50 mg, 0.35 mmol) in THF (1 ml), to yield 83% colorless needles from ethanol, m.p. 190 °C; IR 1610 cm^{-1} (C=O); ^{1}H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 3.49 (s, 3 H, CH_3), 4.16 (s, 2 H, azepine-CH_2), 7.14 (d, 1 H, J = 5.6 Hz, H arom.), 7.28 (d, 1 H, J = 5.6 Hz, H arom.), 7.48–7.61 (m, 2 H, H arom.), 7.77 (s, 1 H, H arom.), 7.88 (d, 1 H, J = 8.1 Hz, H arom.), 7.99 (d, 1 H, J = 8.1 Hz, H arom.), 8.31 (s, 1 H, H arom.).
$C_{17}H_{13}NOS$ (279.3)

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