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SYNTHESIS OF NAPHTHO[2,3-*b*]- AND NAPHTHO[1,2-*b*]-FUSED THIENO[2,3-*d*][1]BENZOXEPINS AND THIENO[2,3-*d*][1]-BENZOTHIEPINS

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Abstract – Synthesis of four novel classes of structurally related fused hetero-pentacyclic compounds, naphtho[2,3-*b*]thieno[2,3-*d*][1]benzothiepins (**Ia**), naphtho[1,2-*b*]thieno[2,3-*d*][1]benzothiepins (**IIa**), naphtho[2,3-*b*]thieno-[2,3-*d*][1]benzoxepins (**Ib**,**c**) and naphtho[1,2-*b*]thieno[2,3-*d*][1]benzoxepins (**IIb**,**c**), is described. The key intermediates were the tetracyclic ketones, benzo[*b*]-naphtho[*f*]-fused thiepinones **1a**,**b** and oxepinones **1c-f**, formed by intramolecular cyclization of the corresponding 2-naphthalenylthio- (**2a**,**b**) and 2-naphthalenyloxy-substituted (**2c-f**) phenylacetic acid derivatives. Reaction of ketones **1a-f** with Vilsmeier reagent provided *β*-chlorovinyl aldehydes **10a-f** that readily cyclized with ethyl 2-mercaptoacetate to form thieno[2,3-*d*]-fused derivatives of benzo-naphtho-thiepins **11a**,**b** and benzo-naphtho-oxepins **11c-f**. Reduction of ester group of **11a-f** afforded final hydroxymethyl derivatives **12a-f**.

INTRODUCTION

As a part of our research program on various heterocyclic dibenzo[*e,h*]azulenes as prospective anti-inflammatory drugs, we recently reported on the synthesis, properties, structure determination and preliminary biological results of dibenzoxepino[4,5]- and dibenzothiepino[4,5]-fused five-membered heterocycles: furan,[1] pyrrole,[2] thiophene[3] and imidazole.[4] Preliminary data revealed potential of these

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polycyclic compounds to act as anti-inflammatory agents. In order to study importance of the additional benzo- or cyclohexano-ring condensed to dibenzo[*b*,*f*]thieno[2,3-*d*]oxepin or dibenzo[*b*,*f*]thieno[2,3-*d*]thiepin scaffold for anti-inflammatory activity, we have directed our syntheses to novel polycondensed benzothiepin and benzoxepin analogs with [1,2]- or [2,3]-fused naphthalene moiety and [2,3]-fused thiophene ring (**I**, **II**, Figure 1). Herein we report the synthesis and structural characterization of the target hetero-pentacyclic derivatives of benzothiepins **Ia** and **IIa** and benzoxepins **Ib**,**c** and **IIb**,**c** as well as intermediates for the preparation thereof.

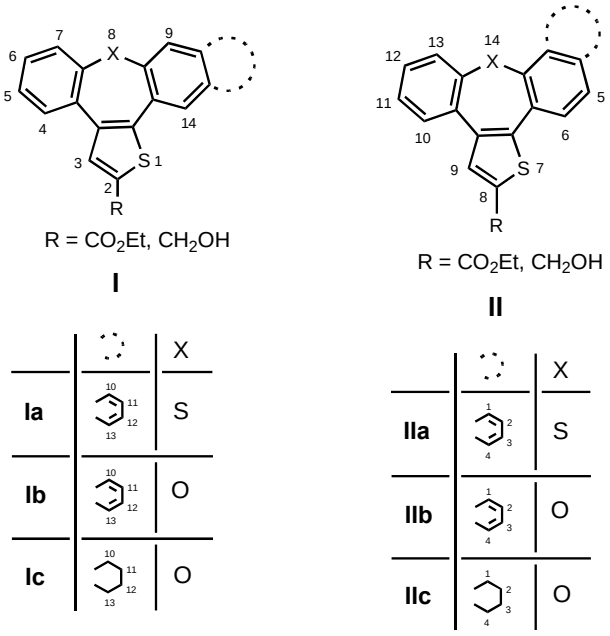
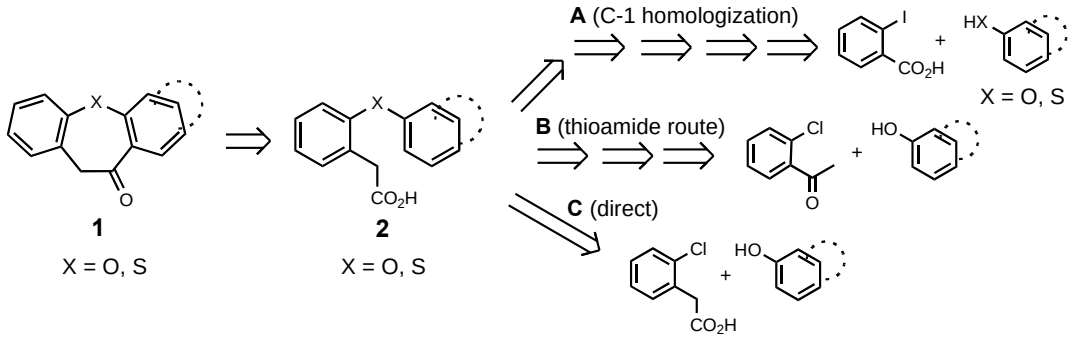


Figure 1. Synthesized final compounds and numbering according to IUPAC

RESULTS AND DISCUSSION

In the synthesis of dibenzo[*b*,*f*]thieno[2,3-*d*]oxepins and dibenzo[*b*,*f*]thieno[2,3-*d*]thiepins with an additional condensed benzo- or cyclohexano-ring an analogy of the procedure employed for the parent dibenzo[*b*,*f*]thieno[2,3-*d*]oxepins and dibenzo[*b*,*f*]thieno[2,3-*d*]thiepins was used.[5-7] Starting *α*- and *β*-naphthalenols and naphthalenethiols as well as *α*- and *β*-tetrahydronaphthalenols enabled synthesis of a series of structurally related final compounds, which were along with their precursors thoroughly spectroscopically characterized. Furthermore, distinctions in reactivity and/or properties of oxygen *versus* sulfur analogs were noticed and will be discussed when appropriate.

Tetracyclic ketones **1**, possessing an active methylene group and subject to further transformation into intermediate functionalized for thiophene annulation, were obtained by cyclo-dehydration of 2-substituted derivatives of phenylacetic acids **2**. Depending on the starting (thio)naphthol, acids **2** can be prepared following one of three available routes: C-1 homologation (route A), thioamide route (route B) or direct condensation (route C) (Scheme 1).

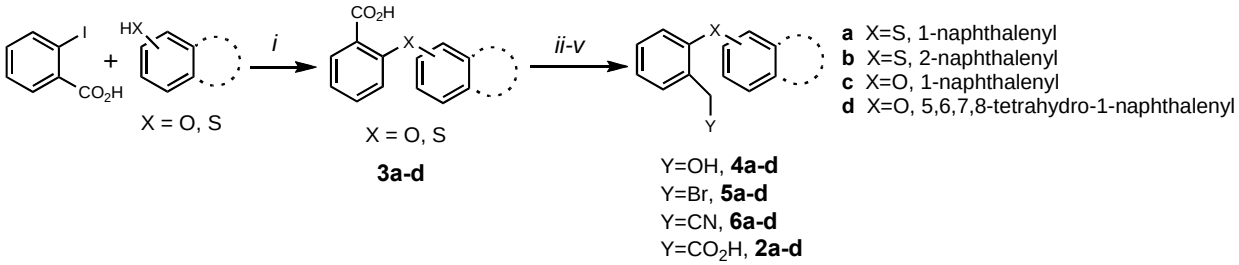


Scheme 1. Retro-synthetic sequence to tetracyclic ketones **1**

As the main synthetic method emerged route A, by which naphthalenylthio-derivatives (**2a-b**) and 1-naphthalenyloxy-derivatives (**2c-d**) of phenylacetic acid were prepared. This method comprises introducing cyanide ion into 2-substituted benzoic acid derivative, following published methods for synthesis of analogous tricyclic ketones, 11*H*-dibenzo[*b,f*]oxepin-10-one and 11*H*-dibenzo[*b,f*]thiepin-10-one.[8-19] Although a similar route towards the formation of naphthalenylthio-derivatives (**a** and **b**) including ketones **1a-b** was previously reported,[20,21] poor spectroscopic or structural analysis had been performed, for some compounds only by melting point and IR spectrum.

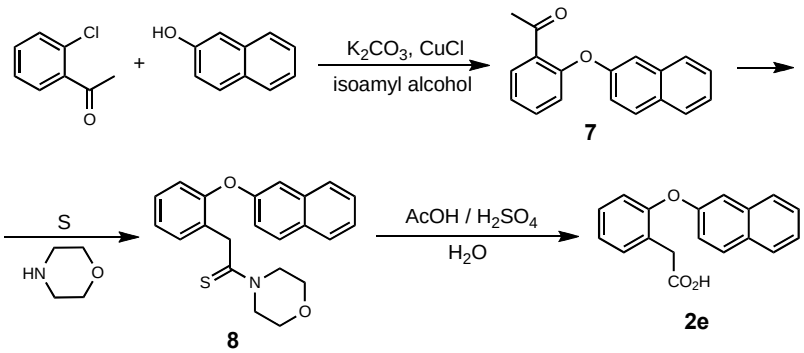
Route A proceeds as depicted in Scheme 2. When dealing with sulfur analogs, the synthesis starts with copper catalyzed Ullmann type reaction of thionaphthol and 2-iodobenzoic acid in aqueous potassium hydroxide affording products in high yields (86% for 1-naphthalenyl (**3a**) and 98% for 2-naphthalenyl (**3b**) derivative). On the other hand, Ullmann type coupling for oxygen analogs requires harsher conditions, potassium carbonate in nitrobenzene or xylene at 140 °C with copper catalysis, and results with lower yields (49% for 1-naphthalenyl (**3c**) and 77% for 5,6,7,8-tetrahydro-1-naphthalenyl (**3d**) derivative). 2-Substituted benzoic acid derivatives **3a-d** were subsequently reduced with lithium aluminum hydride in ether to corresponding alcohols **4a-d** (55-95%) and then brominated to facilitate substitution with cyanide. Bromination instead of chlorination is a main modification of the published procedure.[8,10-17,19-21] Comparing with chlorination procedure, bromination appeared more feasible due to shorter reaction time, complete consumption of reactant, more pure products and introducing a better leaving group for nucleophilic displacement. Sulfur analogs **4a-b** were brominated by refluxing in 47% hydrobromic acid in almost quantitative yield (99% for **5a** and 96% for **5b**), while oxygen analogs **4c-d** were subjected to milder conditions with phosphorus tribromide in dichloromethane at 0 °C thus providing bromides **5c-d** with excellent yields (81% for **5c** and 92% for **5d**). Substitution of bromides **5a-d** by reaction with sodium cyanide in refluxing 96% ethanol afforded nitriles **6a-d**. However, partial solvolysis with ethanol occurred giving as a by-product ethyl ether of the corresponding 2-substituted benzyl alcohols, lowering the yields

(66-86%). Formation of analogous by-product was already reported for similar compounds.[13] Homologation procedure ended with hydrolysis of nitriles **6a-d** in alkaline medium. Nitriles **a**, **b** and **d** were converted smoothly to corresponding phenylacetic acids **2** (71-88%), while hydrolysis of analog **c** stopped at intermediary amide to the extent of 40-50% even after prolonged reaction time. The same issue was already noticed for similar compound.[22] Nevertheless, unreacted amide was easily separable during work-up.



Scheme 2. Route A for synthesis of 2-substituted derivatives of phenylacetic acids **2a-d**. Reagents and conditions: *i*, X=S: Cu, KOH/H_2O, reflux, 8 h; X=O: K_2CO_3, Cu, nitrobenzene or xylene, 140 °C, 1 h; *ii*, $LiAlH_4$, diethyl ether, r.t., 4 h; *iii*, X=S: 47% HBr, reflux, 2 h; X=O: PBr_3, CH_2Cl_2, 0 °C, 30 min; *iv*, NaCN, 96% EtOH, reflux, 4 h; *v*, KOH/H_2O, EtOH, reflux, 15 h, then conc. HCl

In order to shorten multistep reaction path for preparation of phenylacetic acids **2**, three-step synthesis (route B) was employed which includes conversion of 2-substituted acetophenone to a thioamide with the same number of C-atoms (Scheme 3), according to the previously described procedure for analogous tricyclic compounds.[8,23] Starting 2-chloroacetophenone and 2-naphthol were coupled in an Ullmann type reaction in the presence of copper(I) catalyst and potassium carbonate in isoamyl alcohol to yield 2-substituted acetophenone **7** (78%). Subjecting compound **7** to sulfur in boiling morpholine gave thioamide **8**,[24] that was hydrolyzed in acidic conditions to the expected 2-substituted phenylacetic acid **2e** (52% from **7**).

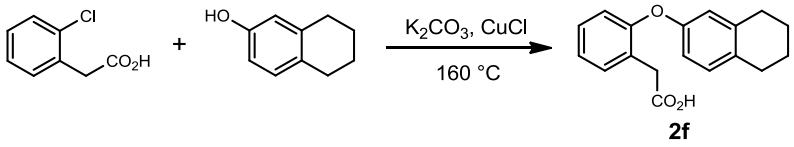


Scheme 3. Thioamide route (route B) for synthesis of 2-substituted phenylacetic acid **2e**

An attempt to perform analogous reaction with 1-naphthol was encountered with side-reactions and

difficulties during isolation and resulted in formation of only minor amount of the corresponding acid **2c**. Substantial reduction of the yield due to formation of the α-oxo by-product was previously described for similar compounds.[25] Hence the method B, although attractive due to reduced number of reaction steps, proved less effective for the synthesis of 2-naphthalenyl phenylacetic acids.

Condensation of 2-chlorophenylacetic acid with a suitable naphthol (route C) represents the shortest and the most effective method for synthesis of 2-substituted phenylacetic acids **2**. Variation of Ullmann type reaction between 2-halophenylacetic acid (halo is chloro, bromo or iodo) and (substituted) phenol [*cf*. refs 26-28], as employed in route C, is scarcely applied due to low reactivity of aryl halides, particularly aryl chlorides, under the common reaction conditions used for nucleophilic aromatic substitution, unless they are activated by the presence of electron withdrawing substituents. Dry heating of 5,6,7,8-tetrahydro-2-naphthalenol and 2-chlorophenylacetic acid with potassium carbonate and copper(I) catalyst at 160 °C affords the expected acid **2f** in a high yield (89%) (Scheme 4). Addition of xylene enables azeotropic distillation of water, shifting the equilibrium to the right and enhancing the yield. Analogous reactions in preparation of **2c** and **2d** failed, or yielded minor quantity of the expected product. Acid **2f** can be efficiently prepared by C-1 homologation too. Therefore, the one-step route C is the optimized procedure for synthesis of **2f**.

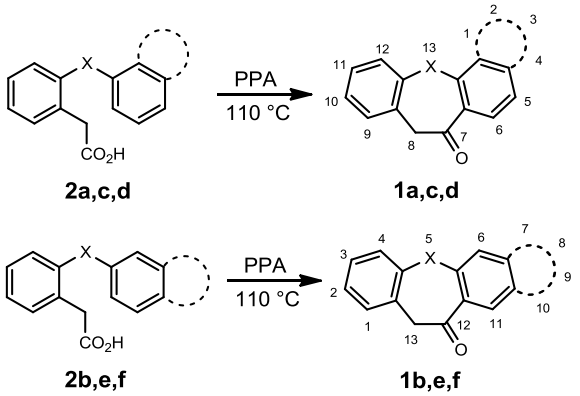


2f

Scheme 4. Synthesis of the acid **2f** by direct condensation (route C)

Spectroscopic and analytical data for compounds **2a-f**, **3a-d**, **4a-d**, **5a-d** and **6a-d** can be found in Tables 1 and 2.

Acids **2a-f** were cyclized to corresponding tetracyclic ketones **1a-f** in a high yield using an excess of polyphosphoric acid (PPA) at 110 °C (Scheme 5).



2a,c,d **1a,c,d**

2b,e,f **1b,e,f**

	X	
a	S	
b	S	
c	O	
d	O	
e	O	
f	O	

Scheme 5. Synthesis of ketones **1** by cyclodehydration of acids **2** and numbering of the two isomers according to IUPAC

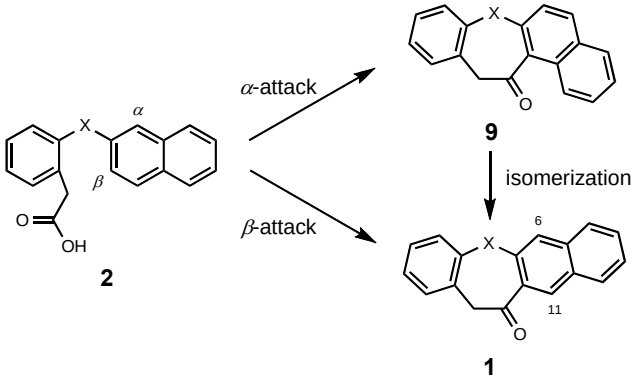
Table 1. Analytical and spectroscopic data of intermediates **2-6**

compound	formula (M_r)	yield %	found / % (requires) C	H	S or N	MS *m/z*	IR, [a] as KBr pastille, [b] as film, ν/cm^{-1}
2a[20]	$C_{18}H_{14}O_2S$ (294.37)	86	-	-	-	317 $[M+Na]^+$	[a] 3300-2700 (broad, COOH), 1709 (C=O), 1589, 1502, 1470, 1444, 1407, 1339, 1232, 1196, 1044
2b[21]	$C_{18}H_{14}O_2S$ (294.37)	88	-	-	-	317 $[M+Na]^+$	[a] 3300-2400 (broad, COOH), 1704 (C=O), 1587, 1501, 1471, 1421, 1406, 1339, 1277, 1238, 1197, 1134, 1059
2c	$C_{18}H_{14}O_3$ (278.30)	51	77.51 (77.68)	4.97 (5.07)	-	301 $[M+Na]^+$	[a] 3300-2700 (broad, COOH), 1703 (C=O), 1662, 1590, 1490, 1455, 1390, 1370, 1243, 1221, 1183, 1107, 1041
2d	$C_{18}H_{18}O_3$ (282.33)	71	76.80 (76.57)	6.15 (6.43)	-	305 $[M+Na]^+$	[b] 2931, 2858; 1711 (C=O); 1605, 1577, 1489, 1455, 1409, 1333, 1240, 1183, 1106, 1024
2e	$C_{18}H_{14}O_3$ (278.30)	89	77.48 (77.68)	4.84 (5.07)	-	301 $[M+Na]^+$	[a] 3600-2500 (broad, COOH); 1699 (C=O); 1631, 1602, 1586, 1492, 1466, 1417, 1384, 1247, 1221, 1178, 1120
2f	$C_{18}H_{18}O_3$ (282.33)	89	76.45 (76.57)	6.78 (6.43)	-	305 $[M+Na]^+$	[a] 3400-2400 (broad, COOH); 1713 (C=O); 1612, 1587, 1491, 1458, 1410, 1344, 1244, 1183, 1146, 1113, 1055
3a[20]	$C_{17}H_{12}O_2S$ (280.34)	86	-	-	-	303 $[M+Na]^+$	[a] 3300-2300 (broad, COOH), 1674 (C=O), 1585, 1556, 1502, 1462, 1414, 1314, 1296, 1268, 1258, 1150, 1039
3b[21]	$C_{17}H_{12}O_2S$ (280.34)	98	-	-	-	303 $[M+Na]^+$	[a] 3300-2400 (broad, COOH), 1676 (C=O), 1562, 1464, 1435, 1417, 1319, 1294, 1273, 1260, 1154, 1059
3c[29,30]	$C_{17}H_{12}O_3$ (264.28)	49	-	-	-	265 $[M+H]^+$	[a] 3250-2300 (broad, COOH), 1693 (C=O), 1603, 1583, 1454, 1423, 1325, 1293
3d	$C_{17}H_{16}O_3$ (268.31)	77	75.88 (76.10)	6.30 (6.01)	-	291 $[M+Na]^+$	[a] 3250-2400 (broad, COOH), 1684 (C=O), 1601, 1573, 1484, 1449, 1414, 1307, 1271, 1239, 1165, 1089, 1023
4a[20]	$C_{17}H_{14}OS$ (266.36)	87	-	-	-	289 $[M+Na]^+$	[a] 3400-3100 (broad, O-H), 1588, 1564, 1504, 1440, 1379, 1358, 1332, 1253, 1192, 1065, 1033
4b[21]	$C_{17}H_{14}OS$ (266.36)	95	-	-	-	289 $[M+Na]^+$	[a] 3350-3100 (broad, O-H), 1587, 1441, 1337, 1263, 1192, 1045, 1031
4c	$C_{17}H_{14}O_2$ (250.29)	55	81.31 (81.58)	5.90 (5.64)	-	273 $[M+Na]^+$	[b] 3500-3100 (broad, O-H), 3054, 2924; 1594, 1574, 1506, 1487, 1455, 1392, 1261, 1234, 1184, 1156, 1108, 1079
4d	$C_{17}H_{18}O_2$ (254.32)	57	80.48 (80.29)	7.10 (7.13)	-	277 $[M+Na]^+$	[b] 3500-3100 (broad, O-H), 1604, 1577, 1486, 1454, 1332, 1238, 1184, 1108, 1039, 1025
5a	$C_{17}H_{13}BrS$ (329.26)	99	61.84 (62.01)	4.08 (3.98)	S: 10.12 (9.74)	328, 330 M^+	[b] 3054, 1588, 1564, 1503, 1465, 1443, 1381, 1256, 1218, 1141, 1058, 1038
5b	$C_{17}H_{13}BrS$ (329.26)	96	62.42 (62.01)	4.14 (3.98)	S: 9.84 (9.74)	328, 330 M^+	[b] 3054, 1624, 1588, 1500, 1469, 1443, 1341, 1265, 1220, 1133, 1058, 1038
5c[31]	$C_{17}H_{13}BrO$ (313.19)	81	65.01 (65.20)	4.49 (4.18)	-	312, 314 M^+	[b] 3055, 1595, 1574, 1506, 1487, 1455, 1392, 1261, 1237, 1189, 1157, 1139, 1091, 1045, 1015
5d	$C_{17}H_{17}BrO$ (317.22)	92	64.54 (64.37)	5.59 (5.40)	-	316, 318 M^+	[b] 2931, 1603, 1576, 1488, 1455, 1332, 1240, 1186, 1090, 1024
6a[20]	$C_{18}H_{13}NS$ (275.37)	72	-	-	-	275 M^+	[b] 3056; 2249 (C≡N), 1589, 1564, 1503, 1469, 1442, 1409, 1381, 1335, 1256, 1202, 1057, 1042
6b[21]	$C_{18}H_{13}NS$ (275.37)	86	-	-	-	275 M^+	[b] 3054; 2250 (C≡N), 1624, 1588, 1500, 1470, 1442, 1409, 1341, 1268, 1194, 1132, 1057
6c	$C_{18}H_{13}NO$ (259.30)	66	83.11 (83.38)	5.41 (5.05)	N: 5.66 (5.40)	259 M^+	[b] 3060; 2962, 2919; 2251 (C≡N), 1592, 1574, 1505, 1487, 1454, 1390, 1260, 1234, 1100, 1078, 1042, 1015
6d	$C_{18}H_{17}NO$ (263.33)	83	82.20 (82.10)	6.79 (6.51)	N: 5.79 (5.32)	286 $[M+Na]^+$	[b] 2932, 2858; 2251 (C≡N), 1604, 1577, 1489, 1455, 1413, 1332, 1240, 1178, 1100, 1024

Table 2. NMR data of intermediates **2-6** in δ/ppm, [a] in $CDCl_3$, [b] in DMSO-d_6

2a[20]	[b] ^{1}H: 3.90 (s, 2H, CH_2), 6.97 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H, arom.), 7.20 (dt, *J* = 7.6 Hz, 1.5 Hz, 1H, arom.), 7.31 (dt, *J* = 7.4 Hz, 1.3 Hz, 1H, arom.), 7.44-7.69 (m, 5H, arom.), 8.01-8.10 (m, 2H, arom.), 8.22-8.26 (m, 1H, arom.), 12.5-13.0 (b, 1H, COOH)
2b[21]	[a] ^{1}H: 3.91 (s, 2H, CH_2), 7.27-7.38 (m, 4H, arom.), 7.43-7.51 (m, 3H, arom), 7.66-7.82 (m, 4H, arom.)
2c	[b] ^{1}H: 3.68 (s, 2H, CH_2), 6.72 (d, *J* = 7.9 Hz, 1H, arom.), 6.88 (d, *J* = 7.5 Hz, 1H, arom.), 7.09-7.14 (m, 1H, arom.), 7.20-7.26 (m, 1H, arom.), 7.40-7.61 (m, 4H, arom.), 7.72 (d, *J* = 8.3 Hz, 1H, arom.), 7.98 (d, *J* = 7.8 Hz, 1H, arom.), 8.11 (d, *J* = 8.1 Hz, 1H, arom.), 12.32 (bs, 1H, COOH)
2d	[b] ^{1}H: 1.70-1.72 (m, 4H, 2×CH_2 tetralin), 2.59 (bs, 2H, tetralin), 2.77 (bs, 2H, tetralin), 3.60 (s, 2H, CH_2COOH), 6.57 (d, *J* = 7.5 Hz, 1H, arom.), 6.63 (dd, *J* = 8.1 Hz, 0.9 Hz, 1H, arom.), 6.89 (d, *J* = 7.3 Hz, 1H, arom.), 7.03-7.10 (m, 2H, arom.), 7.19-7.25 (m, 1H, arom.), 7.34 (dd, *J* = 7.4 Hz, 1.5 Hz, 1H, arom.), 12.19 (bs, 1H, COOH)
2e	[b] ^{1}H: 3.63 (s, 2H, CH_2), 6.94 (dd, *J* = 8.0 Hz, 1.1 Hz, 1H, arom.), 7.14 (dt, *J* = 7.4 Hz, 1.1 Hz, 1H, arom.), 7.23-7.33 (m, 3H, arom.), 7.40-7.51 (m, 3H, arom.), 7.78 (d, *J* = 7.9 Hz, 1H, arom.), 7.91 (dd, *J* = 8.6 Hz, 1H, arom.), 7.95 (d, *J* = 8.7 Hz, 1H, arom.), 12.2-12.5 (bs, 1H, COOH)
2f	[b] ^{1}H: 1.70-1.73 (bm, 4H, 2×CH_2 tetralin), 2.66-2.69 (bm, 4H, 2×CH_2 tetralin), 3.60 (s, 2H, CH_2COOH), 6.64-6.70 (m, 2H, arom.), 6.79 (dd, *J* = 8.1 Hz, 1.0 Hz, 1H, arom.), 7.04 (d, *J* = 8.3 Hz, 1H, arom.), 7.05-7.11 (m, 1H, arom.), 7.21-7.27 (m, 1H, arom.), 7.33-7.36 (m, 1H, arom.), 12.33 (bs, 1H, COOH) ^{13}C: 22.6, 22.9, 28.2, 29.0 (tetralin CH_2); 35.5 (CH_2COOH); 116.0, 118.1, 118.4, 123.2, 128.8, 130.2, 131.9 (CH); 126.4, 131.6, 138.3, 154.5, 155.4 (C); 172.4 (C=O)
3a[20]	[a] ^{1}H: 4.0-4.5 (b, 1H, COOH), 6.47-6.50 (m, 1H, arom.), 7.09-7.12 (m, 2H, arom.), 7.47-7.58 (m, 3H, arom.), 7.90-8.02 (m, 3H, arom.), 8.13-8.17 (m, 1H, arom.), 8.29-8.32 (m, 1H, arom.)
3b[21]	[b] ^{1}H: 6.79 (dd, *J* = 8.0 Hz, 0.7 Hz, 1H, arom.), 7.24 (dt, 1H, arom.), 7.36 (dt, *J* = 7.6 Hz, 1.6 Hz, 1H, arom.), 7.54 (dd, *J* = 8.5 Hz, 1.8 Hz, 1H, arom.), 7.58-7.66 (m, 2H, arom.), 7.96 (dd, *J* = 7.7 Hz, 1.5 Hz, 1H, arom.), 7.99-8.06 (m, 3H, arom.), 8.23 (bs, 1H, arom.), 13.0-13.5 (b, 1H, COOH)
3c[29,30]	[b] ^{1}H: 6.77-8.20 (m, 11H, arom.), 12.7-13.3 (b, 1H, COOH)
3d	[b] ^{1}H: 1.72 (bs, 4H, 2×CH_2 tetralin), 2.61 (bs, 2H, tetralin), 2.75 (bs, 2H, tetralin), 6.52 (d, *J* = 7.9 Hz, 1H, arom.), 6.80 (dd, *J* = 8.3 Hz, 0.8 Hz, 1H, arom.), 6.86 (d, *J* = 7.3 Hz, 1H, arom.), 7.06 (t, *J* = 7.8 Hz, 1H, arom.), 7.18 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H, arom.), 7.46-7.51 (m, 1H, arom.), 7.79 (dd, *J* = 7.7 Hz, 1.7 Hz, 1H, arom.), 12.83 (bs, 1H, COOH)
4a[20]	[a] ^{1}H: 1.79 (bs, 1H, OH), 4.87 (s, 2H, CH_2), 7.07 (dd, *J* = 7.8 Hz, 1.1 Hz, 1H, arom.), 7.15 (dt, *J* = 7.4 Hz, 1.3 Hz, 1H, arom.), 7.29 (dt, *J* = 7.4 Hz, 1.2 Hz, 1H, arom.), 7.36-7.39 (m, 2H, arom.), 7.50-7.55 (m, 3H, arom.), 7.78-7.82 (m, 1H, arom.), 7.86-7.90 (m, 1H, arom.), 8.29-8.33 (m, 1H, arom.)
4b[21]	[a] ^{1}H: 1.92 (bs, 1H, OH), 4.86 (s, 2H, CH_2), 7.28-7.59 (m, 8H, arom.), 7.70-7.84 (m, 3H, arom)
4c	[b] ^{1}H: 4.62 (d, *J* = 5.5 Hz, 2H, CH_2), 5.22 (t, *J* = 5.5 Hz, 1H, OH), 6.78-6.87 (m, 2H, arom.), 7.18-7.28 (m, 2H, arom.), 7.40-7.45 (m, 1H, arom.), 7.53-7.63 (m, 3H, arom.), 7.68 (d, *J* = 8.3 Hz, 1H, arom.), 7.96-8.03 (m, 1H, arom.), 8.13-8.18 (m, 1H, arom.) ^{13}C: 57.7 (CH_2); 112.0, 118.1, 121.4, 123.0, 124.0, 126.2, 126.3, 127.0, 127.9, 128.4, 128.5 (CH); 125,6, 132,8, 134.6, 152.5, 153.4 (C)
4d	[b] ^{1}H: 1.71 (bs, 4H, 2×CH_2 tetralin), 2.59 (bs, 2H, tetralin), 2.75 (bs, 2H, tetralin), 4.56 (d, *J* = 5.2 Hz, 2H, CH_2OH), 5.16 (t, *J* = 5.2 Hz, 1H, OH), 6.53 (d, *J* = 7.9 Hz, 1H, arom.), 6.63 (dd, *J* = 7.9 Hz, 1.0 Hz, 1H, arom.), 6.86 (d, *J* = 7,6 Hz, 1H, arom.), 7.02-7.13 (m, 2H, arom.), 7.16-7.22 (m, 1H, arom.), 7.51-7.54 (m, 1H, arom.)
5a	[a] ^{1}H: 4.81 (s, 2H, CH_2), 6.91 (dd, *J* = 7.9 Hz, 1.2 Hz, 1H, arom.), 7.07 (dt, *J* = 7.6 Hz, 1.5 Hz, 1H, arom.), 7.18 (dt, *J* = 7.5 Hz, 1.3 Hz, 1H, arom.), 7.40-7.48 (m, 2H, arom.), 7.51-7.61 (m, 3H, arom.), 7.85-7.92 (m, 2H, arom.), 8.32-8.37 (m, 1H, arom.)
5b	[a] ^{1}H: 4.80 (s, 2H, CH_2), 7.24-7.37 (m, 3H, arom.), 7.41 (dd, *J* = 8.6 Hz, 1.8 Hz, 1H, arom.), 7.49-7.56 (m, 3H, arom), 7.76-7.87 (m, 4H, arom.)
5c[31]	[a] ^{1}H: 4.69 (s, 2H, CH_2), 6.74 (d, *J* = 8.1 Hz, 1H, arom.), 6.95 (d, *J* = 7.5 Hz, 1H, arom.), 7.05-7.10 (m, 1H, arom.), 7.16-7.23 (m, 1H, arom.); 7.35-7.41 (m, 1H, arom.), 7.47-7.55 (m, 3H, arom.), 7.64 (d, *J* = 8.1 Hz, 1H, arom.), 7.86-7.89 (m, 1H, arom.), 8.21-8,27 (m, 1H, arom.)
5d	[b] ^{1}H: 1.71 (bs, 4H, 2×CH_2 tetralin), 2.61 (bs, 2H, tetralin), 2.76 (bs, 2H, tetralin), 4.74 (s, 2H, CH_2Br), 6.58 (dd, *J* = 8.2 Hz, 0.8 Hz, 1H, arom.), 6.68 (d, *J* = 7.9 Hz, 1H, arom.), 6.93 (d, *J* = 7.5 Hz, 1H, arom.), 7.05 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H, arom.), 7.12 (t, *J* = 7.8 Hz, 1H, arom.), 7.23-7.29 (m, 1H, arom.), 7.53 (dd, *J* = 7.5 Hz, 1.6 Hz, 1H, arom.)
6a[20]	[a] ^{1}H: 3.90 (s, 2H, CH_2), 6.96-7.43 (m, 5H, arom.), 7.49-7.58 (m, 3H, arom.), 7.78-7.90 (m, 2H, arom.), 8.25-8.32 (m, 1H, arom.)
6c	[a] ^{1}H: 3.87 (s, 2H, CH_2), 6.79-6.89 (m, 2H, arom.), 7.12-7.18 (m, 1H, arom.), 7.23-7.28 (m, 1H, arom.), 7.35-7.40 (m, 1H, arom.), 7.47-7.57 (m, 3H, arom.), 7.65 (d, *J* = 8.3 Hz, 1H, arom.), 7.86-7.90 (m, 1H, arom.), 8.15-8.18 (m, 1H, arom.)
6d	[b] ^{1}H: 1.71 (bs, 4H, 2×CH_2 tetralin), 2.59 (bs, 2H, tetralin), 2.77 (bs, 2H, tetralin), 4.00 (s, 2H, CH_2CN), 6.61 (dd, *J* = 8.2 Hz, 0.8 Hz, 1H, arom.), 6.68 (d, *J* = 7.4 Hz, 1H, arom.), 6.95 (d, *J* = 7.4 Hz, 1H, arom.), 7.07-7.15 (m, 2H, arom.), 7.24-7.30 (m, 1H, arom.), 7.48 (dd, *J* = 7.5 Hz, 1.3 Hz, 1H, arom.)

Cyclization of compounds **2b**,**e**,**f**, derived from 2-naphthalenols, can proceed either *via* electrophilic attack of acyl group on the *α*-position to obtain ketones **9** or *via* attack on the *β*-position to give isomeric ketones **1**, Scheme 6.



Scheme 6. Alternatives for intramolecular acylation of acids **2** derived from 2-naphthalenyl precursors

In the present case, isolated main products of cyclodehydration of acids **2b**,**e**,**f** are linearly condensed ketones with 2,3-disubstituted naphthalene moiety as represented by structure **1**, which is proved by ^{1}H NMR spectra possessing singlets for C-6 and C-11 protons in aromatic region of the compounds **1b**,**e**,**f**. Previously described synthesis of **1b** also brings evidence for formation of the linearly condensed isomer.[21] Moreover, confirmation of linear structure was obtained by single X-ray crystallographic analysis of the selected representative **12f** that was derived from ketone **1f** (see below). ORTEP diagram, molecular packing and unit cell of **12f** are depicted in Figure 2 with crystal data shown in Table 3. Crystallographic analysis also revealed angular arrangement of benzene *versus* tetrahydronaphathalene moiety in the so-called butterfly shape[32,33] due to non-planar conformation of the central oxepine ring.

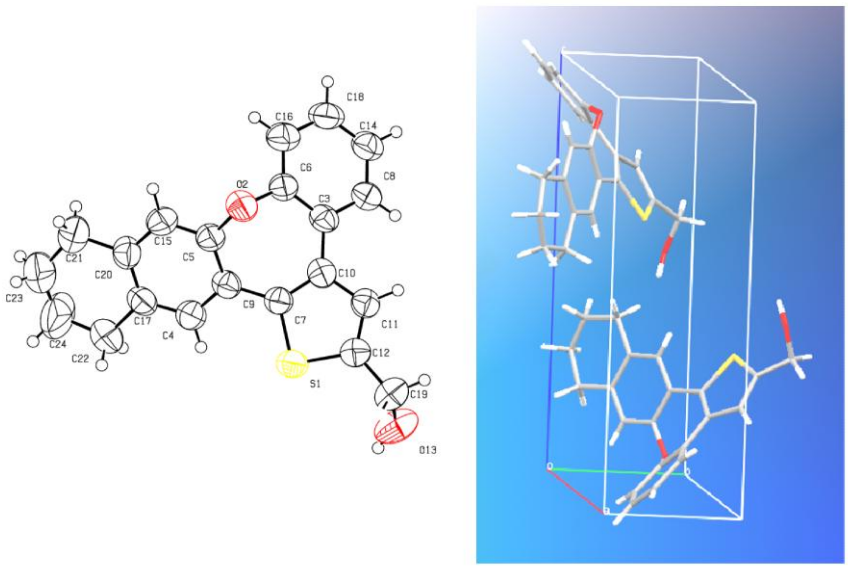


Figure 2. Molecular and crystal structure of compound **12f**

Table 3. Crystal data for compound **12f**

Molecular formula	$C_{21}H_{18}O_2S$	
Molecular weight	334.41	
Crystal system	Monoclinic	
Space group	$P\,2_1$	
Unit cell dimensions	a = 11.188(1) Å	α = 90.00 °
	b = 5.022(1) Å	β = 99.657(1) °
	c = 14.967(1) Å	γ = 90.00 °
Unit cell volume	829.02(2) $Å^3$	
No. of molecules in the unit cell	2	
Calculated density	1.34 g/cm^3	

In view of the greater reactivity of the naphthalene α-position in electrophilic substitutions, including Friedel-Crafts acylations, as compared with that of the β-position, we had to consider formation of the angular structure **9** that, however, is not compatible with the above given results (for analogies see refs 34-38). The preference for cyclization at 3-position can be explained either by spatial orientation of the carbonyl group *vis-à-vis* the naphthalene nuclei that sterically hinders formation of 1,2-disubstituted moiety,[21,35] or more likely, by the kinetically controlled formation of compounds **9** that under thermodynamically controlled conditions, e.g. in PPA at elevated temperatures, isomerise to more stable, less sterically hindered products **1**.[36,37]

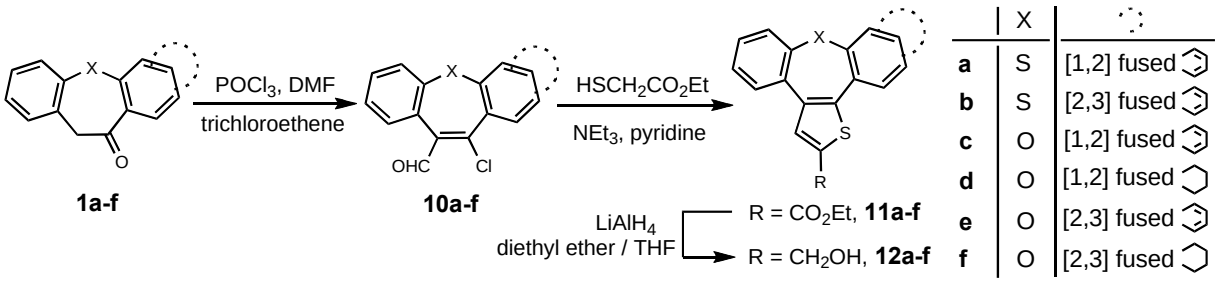
Compounds **1a**,**c**,**d**, derived from corresponding 1-(thio)naphthols and containing 1,2-disubstituted naphthalene moiety, possess in the aromatic region of ^{1}H NMR spectrum two characteristic doublets for C-5 and C-6 protons (see numbering in Scheme 5.), that are mutually coupled with J (*ortho*) = 8-9 Hz. In addition, notable feature in ^{1}H NMR spectra of **1a** and **1c** is the multiplet of the *peri*-naphthalene C-1 proton, separated from the signals of other aromatic protons and markedly shifted for approximately 1.0 ppm toward higher values of ppm with δ = 8.8-8.9 ppm. At position C-1 of analogous tetralin derivative **1d** a down-field shift of methylene protons for 0.25 ppm as compared to precursors is also noticeable. The rationale for this is probably associated with the vicinity of sulfur or oxygen atom respectively, that with nonbonding electron pairs deshield C-1 protons. This same phenomenon was observed also for subsequent compounds from **a**, **c** and **d** series (see below). ^{1}H NMR spectra of all ketones **1a-f** show significant deshielding of proton at position C-11 in linear and position C-6 in angular isomers due to the diamagnetic anisotropy of the nearby carbonyl group, as already reported for similar compounds.[36,37,39] Thus, signal of this proton is shifted down-field for 0.2-0.9 ppm depending on particular derivative, with linear compounds displaying the greatest signal shift.

To enable annulation of thiophene ring in the succeeding step, tetracyclic ketones **1a-f** were reacted with *in situ* formed Vilsmeier reagent to give β-chlorovinyl aldeydes **10a-f** (Scheme 7). A markedly lower

reactivity for thiepin derivatives comparing to oxepin analogs was noticed in chloroformylation reaction. Oxepin derivatives react quantitatively, with yields after work-up > 87%, while the reaction of thiepin analogs stops before completion, affording 42% of **10a** and 60% of **10b** after separation from unreacted ketones **1a** and **1b**, respectively. Dependency of the reactivity in Vilsmeier reaction on the heteroatom in the central seven-membered ring was already reported for similar ketones.[6]

Singlet of the aldehyde proton of compounds **10a-f** appears in the ^{1}H NMR spectra in the range of 10.5-10.8 ppm. Chloro atom exerts smaller deshielding effect on the closest aromatic proton comparing to carbonyl group in corresponding starting ketones. Nevertheless, the signal of the proton in the vicinity of chloro atom shows the highest δ value, except for compounds **10a** and **10c** where again C-1 proton suffers from the strongest deshielding effect of the nearby sulfur or oxygen atom, respectively (δ = 8.9 ppm for **10a** and δ = 8.65 ppm for **10c**).

To obtain compounds with fused thiophene ring, reaction of β-chlorovinyl aldeydes **10a-f** with ethyl 2-mercaptoacetate in the presence of triethylamine and pyridine was used. The thiophene ring was formed according to the well established process.[40-43] Cyclocondensation afforded series of novel, fused hetero-pentacyclic compounds: naphtho[1,2-*b*]thieno[2,3-*d*][1]benzothiepin **11a**, naphtho[2,3-*b*]thieno[2,3-*d*][1]benzothiepin **11b**, naphtho[1,2-*b*]thieno[2,3-*d*][1]benzoxepins **11c**,**d** and naphtho[2,3-*b*]thieno[2,3-*d*][1]benzoxepins **11e**,**f**, substituted with ethyloxycarbonyl at thiophene 2-position. Reaction proceeds with total conversion providing after purification crystalline products in very good yields (60-86%), Scheme 7.



Scheme 7. Final steps in the synthesis of naphtho[2,3-*b*]- and naphtho[1,2-*b*]-fused thieno[2,3-*d*][1]benzoxepins and thieno[2,3-*d*][1]benzothiepins

In the aromatic region of ^{1}H NMR spectra singlet of the thiophene proton is distinguished at δ approximately 8.0-8.2 ppm. For compounds **11a** and **11c** with [1,2]-fused naphthalene moiety deshielded *peri*-naphthalene proton in the vicinity of the heteroatom from the seven-membered ring repeatedly shows the signal with the greatest shift (δ = 9.2 ppm for **11a** and δ = 8.7 ppm for **11c**).

Guided by the designed structures of potentially biologically active target molecules,[44] ester group of **11a-f** was subjected to reduction. The reaction was performed with lithium aluminum hydride in ether and/or

THF to obtain crystalline alcohols **12a-f** in excellent yields after purification (73-98%).

Singlet of the thiophene proton is shifted toward lower values of ppm for approximately 0.7-0.8 ppm comparing to proton from preceding carboxyl-substituted thiophene ring, with δ about 7.3-7.4 ppm. Continually, doublet of deshielded *peri*-naphthalene proton next to thiepin or oxepin heteroatom in compounds **12a** and **12c** is considerably shifted down-field (δ = 8.9 ppm and δ = 8.7 ppm respectively).

The most salient features of the IR, ^{1}H NMR, ^{13}C NMR and MS spectra for compounds **1a-f**, **10a-f**, **11a-f** and **12a-f** are summarized in Experimental.

EXPERIMENTAL

Chemistry – general methods. Commercial reagents were used as received without additional purification. All used chemicals and solvents were p.a. purity. Melting points were determined using Büchi Melting Point B-545 apparatus and are uncorrected. IR spectra were recorded on Nicolet Magna IR 760 FT IR-spectrophotometer as a KBr pastille or as a film. NMR spectra were recorded at room temperature on Bruker Avance DPX 300 spectrometer at 300 MHz. Deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (DMSO-d_6) were used as solvent and tetramethylsilane (TMS) as internal standard. Mass spectra were acquired using ES (*Electrospray*) ionization at Platform LCZ (Micromass, UK) and LCQ Deca (Finnigan, US) instruments, and using chemical ionization (CI) at GC-MS system Varian Chrompack Saturn 2000. Purity of the compounds was estimated by HPLC-MS system Waters 2690 + Micromass Quattro Micro, by HPLC-UV system Waters 2690 + Waters 996 Photodiode Array Detector or by the above mentioned GC-MS system. Microanalyses were performed using Perkin-Elmer 2400 C H N S analyzer. Thin layer chromatography (TLC) was performed on aluminum plates Merck Silica gel 60 F_{254} with UV light detection at 254 nm and/or 365 nm. Proportions of solvents used for TLC are by volume. Column chromatography was performed on silica gel 60 (Merck, 0.063-0.200 nm). X-Ray diffraction data were collected on a Bruker Nonius FR591 diffractometer using CuK(α) radiation.

Spectroscopic and analytical data for compounds **2a-f**, **3a-d**, **4a-d**, **5a-d** and **6a-d** are given in Tables 1 and 2.

General procedure for preparation of 2-(naphthalenylthio)benzoic acids 3a,b. To an aqueous solution of KOH (11.70 g, 0.21 mol in 110 mL) heated to 50 °C, naphthalenethiol (62.4 mmol) was added. The reaction mixture was stirred at this temperature for additional 10 min, then 2-iodobenzoic acid (15.48 g, 62.4 mmol) and Cu powder (1.0 g, 15.7 mmol) were added. The mixture was refluxed under stirring for 8 h. Cu was removed by filtering off while the mixture was still hot. Filtrate was cooled to rt and acidified with conc. HCl to pH approximately 2. The colorless precipitate of the product (**3a**,**b**) was filtered off, washed a few times with water and dried.

General procedure for preparation of 2-(naphthalenyloxy)benzoic acids 3c,d. A mixture of naphthol (30.2 mmol), 2-iodobenzoic acid (7.5 g, 30.2 mmol), K_2CO_3 (6.27 g, 45.4 mmol) and Cu powder (0.15 g, 2.36 mmol) in nitrobenzene (10 mL) or xylene (10 mL) was heated with stirring at 140 °C for about 1 h. After the completion of the reaction water (100 mL) and EtOAc (50 mL) were added and the organic layer was separated. The aqueous layer was boiled with decolorizing charcoal for 5 min and then acidified with conc. HCl to pH approximately 2. The product precipitate (**3c**,**d**) was filtered off or extracted with EtOAc. Analytical sample was purified by recrystallization from the appropriate solvent or by column chromatography.

General procedure for preparation of [2-(naphthalenylthio)phenyl]methanols 4a,b and [2-(naphthalenyloxy)phenyl]methanols 4c,d. To a suspension of $LiAlH_4$ (4.40 g, 0.116 mol) in Et_2O (100 mL) acid **3a-d** was added in small portions with vigorous stirring (60.6 mmol). After 4 h of stirring at rt the excess of $LiAlH_4$ was decomposed by adding ether and water. The inorganic precipitate was filtered off and washed few times with Et_2O. The filtrate was dried (Na_2SO_4) and evaporated under reduced pressure to give a crude product (**4a-d**) which was purified by recrystallization from the appropriate solvent or by column chromatography.

General procedure for preparation of {[2-(bromomethyl)phenyl]thio}naphthalenes 5a,b. A mixture of alcohol **4a**,**b** (36.9 mmol) and 47% HBr (30 mL) was heated with stirring at reflux temperature for 2 h. After the completion of the reaction the mixture was cooled, cautiously poured into water (50 mL) and extracted with Et_2O (2×50 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$, dried (Na_2SO_4) and solvent evaporated under reduced pressure to give a crude product (**5a**,**b**) that was sufficiently pure for the next step reaction. Analytical sample was purified by column chromatography.

General procedure for preparation of {[2-(bromomethyl)phenyl]oxy}naphthalenes 5c,d. To a dichloromethane solution of alcohol **4c**,**d** (8.0 mmol in 30 mL) cooled to 0 °C, PBr_3 (290 μL, 3.05 mmol) was added dropwise and the mixture was stirred at this temperature for about 30 min (TLC control, hexane/EtOAc 2:1). Then the mixture was poured into cool water (100 mL), the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2×30 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$, dried (Na_2SO_4) and solvent evaporated under reduced pressure. The crude products (**5c**,**d**) were used in the next step without purification, but analytical sample was purified by column chromatography.

General procedure for preparation of [2-(naphthalenylthio)phenyl]acetonitriles 6a,b and [2-(naphthalenyloxy)phenyl]acetonitriles 6c,d. A mixture of bromide **5a-d** (36.4 mmol) and NaCN

(2.24 g, 45.7 mmol) in 96% EtOH (50 mL) was refluxed for approximately 4 h. After the completion of the reaction EtOH was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (100 mL) and water (60 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×50 ml). The combined organic extracts were washed with water (70 mL), dried (Na_2SO_4) and solvent evaporated under reduced pressure. The crude product (**6a-d**) was purified by column chromatography.

1-[2-(2-Naphthalenyloxy)phenyl]ethanone[45] **(7).** A mixture of 2-naphthalenol (5.0 g, 34.7 mmol), 2-chloracetophenone (4.0 g, 25.9 mmol), K_2CO_3 (5.36 g, 38.8 mmol) and CuCl (0.10 g) in isoamyl alcohol (3 mL) was refluxed overnight. The reaction mixture was then cooled and filtered and the precipitate was washed few times with EtOAc. Filtrate was washed with 10% aq. NaOH and water, dried (Na_2SO_4) and solvent evaporated under reduced pressure. The residue was distilled under high vacuum to give a pure product **7** in the form of a yellow liquid, 5.30 g (78%), bp 205 °C (10 mm Hg). IR (film) ν/cm^{-1}: 3058, 1681 (C=O), 1633, 1599, 1575, 1511, 1478, 1463, 1447, 1359, 1286, 1248, 1222, 1161, 1122. ^{1}H NMR ($CDCl_3$) δ/ppm: 2.68 (s, 3H, CH_3), 6.97 (dd, J = 8.3 Hz, 0.9 Hz, 1H, arom.), 7.10-7.33 (m, 3H, arom.), 7.40-7.50 (m, 3H, arom.), 7.69-7.72 (m, 1H, arom.), 7.82-7.91 (m, 3H, arom.). MS (CI) *m/z*: 263 (MH^+, 100%). Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.63; H, 5.55.

4-{2-[2-(2-Naphthalenyloxy)phenyl]ethanethioyl}morpholine (8). A mixture of compound **7** (5.25 g, 20.0 mmol), morpholine (2.41 g, 27.7 mmol) and sulfur (1.0 g, 31.2 mmol) was refluxed for about 2.5 h during which the reaction solution became dark red. The reaction mixture was purified by column chromatography (eluent hexane/EtOAc 1:1) to obtain the pure product **8** as yellow viscous substance, 4.24 g (58%). IR (film) ν/cm^{-1}: 3055, 2966, 2921, 2856; 1652, 1632, 1597, 1582, 1509, 1487, 1453, 1275, 1249, 1226, 1160, 1112, 1030. ^{1}H NMR ($CDCl_3$) δ/ppm: 3.43-3.46 (m, 2H, CH_2), 3.67-3.73 (m, 4H, 2×CH_2), 4.32-4.35 (m, 4H, 2×CH_2), 6.96 (dd, J = 8.0 Hz, 1.1 Hz, 1H, arom.), 7.14-7.28 (m, 3H, arom.), 7.38-7.53 (m, 3H, arom.), 7.59-7.67 (m, 2H, arom.), 7.75-7.89 (m, 2H, arom.). ^{13}C NMR ($CDCl_3$) δ/ppm: 43.6 (CH_2), 50.1, 50.7, 66.2, 66.4 (CH_2, morph.), 112.8, 119.0, 119.6, 124.6, 124.8, 126.8, 127.0, 127.8, 128.7, 129.7, 130.2 (CH), 127.6, 130.1, 134.2, 153.2, 154.9 (C), 200.3 (C=S). MS (ES^+) *m/z*: 386 ($[M+Na]^+$, 100%); 364 (MH^+, 20%). Anal. Calcd for $C_{22}H_{21}NO_2S$: C, 72.70; H, 5.82; N, 3.85; S, 8.82. Found: C, 72.35; H, 5.49; N, 4.00; S, 8.52.

General procedure for preparation of 2-substituted phenylacetic acids 2a-d. A mixture of nitrile **6a-d** (25.8 mmol) and KOH (3.76 g, 67.0 mmol) in EtOH (40 mL) and water (10 mL) was stirred under reflux for approximately 15 h. Then EtOH was evaporated under reduced pressure. The residue was diluted with water (80 mL) and the aqueous solution was washed with CH_2Cl_2 (40 mL). The aqueous layer was acidified

with conc. HCl to pH approximately 2 and thus separated product was filtered off or extracted with EtOAc (3×70 mL). The crude product (**2a-d**) was used in the next step without purification. Analytical sample was purified by recrystallization or column chromatography.

[2-(2-Naphthalenyloxy)phenyl]acetic acid (2e). A mixture of compound **8** (4.15 g, 11.4 mmol), acetic acid (6.1 mL) and 50% H_2SO_4 (1.2 mL) was stirred under reflux for about 8 h. Then the reaction mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined dichloromethane extracts were washed with 10% aq. NaOH. Alkaline aqueous phase was acidified with conc. HCl to pH approximately 2. The separated product was extracted with CH_2Cl_2 (3×50 mL), the combined organic extracts dried (Na_2SO_4) and boiled with decolorizing charcoal for 5 min. Solvent was removed under reduced pressure to obtain **2e** as colorless crystals.

[2-(5,6,7,8-Tetrahydro-2-naphthalenyloxy)phenyl]acetic acid (2f). A mixture of 2-chlorophenylacetic acid (11.51 g, 67.5 mmol) and K_2CO_3 (17.40 g, 0.126 mol) was heated with stirring to 80 °C, then 5,6,7,8-tetrahydro-2-naphthalenol (10.0 g, 67.5 mmol) and CuCl (700 mg) were added. Temperature was elevated to 160 °C and during warming-up the mixture temporarily solidified and stirring was disabled. Afterwards the mixture was heated with stirring at 160 °C for about 2.5 h with TLC monitoring (CH_2Cl_2/MeOH 95:5). The mixture was cooled; water (100 mL) and EtOAc (100 mL) were added. The layers were agitated. The organic layer was discarded and the aqueous phase was washed once more with EtOAc (30 mL), boiled with decolorizing charcoal for 5 min and acidified with conc. HCl to pH approximately 2. The precipitate was filtered off, washed with water and dried to obtain **2f** as pale brown crystals. Analytical sample was prepared by recrystallization from EtOH.

General procedure for preparation of tetracyclic ketones 1a-f. To a reaction flask containing PPA (50 g) heated to 90 °C, acid **2a-f** (25 mmol) was portion-wise added and mixed in. The mixture was vigorously stirred at 110 °C for about 2 h, whereby it became dark. Reaction course was monitored by TLC (hexane/EtOAc 3:1). The mixture was poured into ice-water (500 mL) and then extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with 10% aq. NaOH and water, boiled with decolorizing charcoal for 10 min, dried (Na_2SO_4) and solvent evaporated under reduced pressure to obtain products **1a-f**. Analytical samples were prepared by column chromatography purification or by vacuum distillation.

*Benzo[*b*]naphtho[2,1-*f*]thiepin-7(8*H*)-one*[20] ***(1a)***. This compound was obtained starting from **2a**, light yellow solid, 88%. IR (film) ν/cm^{-1}: 3056, 1666 (C=O), 1594, 1471, 1444, 1312, 1270. ^{1}H NMR ($CDCl_3$) δ/ppm: 4.51 (s, 2H, CH_2), 7.21 (dt, J = 7.5 Hz, 1.5 Hz, 1H, arom.), 7.41 (dt, J = 7.5 Hz, 1.3 Hz, 1H,

arom.), 7.49-7.52 (m, 1H, arom.), 7.60-7.74 (m, 4H, arom.), 7.82-7.85 (m, 1H, arom.), 8.22 (d, *J* = 8.8 Hz, 1H, arom. 6-H), 8.86-8.90 (m, 1H, arom. 1-H). MS (CI) *m/z*: 277 (MH^+, 100%).

*Benzo[*b*]naphtho[2,3-*f*]thiepin-12(13*H*)-one*[21] ***(1b)***. This compound was obtained starting from **2b**, light yellow solid, 97%. IR (KBr) *ν*/cm^{-1}: 3045, 1677 (C=O), 1620, 1574, 1468, 1428, 1316, 1250, 1217, 1142, 1134, 1075. ^{1}H NMR ($CDCl_3$) *δ*/ppm: 4.55 (s, 2H, CH_2), 7.21 (dt, *J* = 7.5 Hz, 1,4 Hz, 1H, arom.), 7.36 (dt, *J* = 7.5 Hz, 1.3 Hz, 1H, arom.), 7.44-7.50 (m, 2H, arom.), 7.53-7.59 (m, 1H, arom.), 7.70 (dd, *J* = 7.5 Hz, 1.0 Hz, 1H, arom.), 7.78 (d, *J* = 8.3 Hz, 1H, arom.), 7.91 (d, *J* = 8.1 Hz, 1H, arom.), 8.11 (s, 1H, arom. 6-H), 8.78 (s, 1H, arom. 11-H). MS (CI) *m/z*: 277 (MH^+, 100%).

*Benzo[*b*]naphtho[2,1-*f*]oxepin-7(8*H*)-one ***(1c)***.* This compound was obtained starting from **2c**, purified by column chromatography (eluent hexane/EtOAc 2:1), yellow viscous oil, 84%. IR (film) *ν*/cm^{-1}: 3061, 1674 (C=O), 1625, 1598, 1567, 1487, 1457, 1427, 1398, 1371, 1345, 1277, 1232, 1181, 1147, 1113, 1078, 1025. ^{1}H NMR ($CDCl_3$) *δ*/ppm: 4.20 (s, 2H, CH_2), 7.19-7.41 (m, 4H, arom.), 7.57 (d, *J* = 8.7 Hz, 1H, arom. 5-H), 7.62-7.68 (m, 2H, arom.), 7.80-7.84 (m, 1H, arom.), 8.04 (d, *J* = 8.7 Hz, 1H, arom. 6-H), 8.74-8.78 (m, 1H, arom. 1-H). ^{13}C NMR ($CDCl_3$) *δ*/ppm: 48.5 (CH_2); 120.2, 123.4, 124.1, 125.0, 126.5, 126.9, 127.7, 128.3, 129.3, 129.8 (CH); 121.5, 127.2, 131.9, 137.2, 157.2, 158.0 (C); 190.6 (C=O). MS (CI) *m/z*: 261 (MH^+, 100%). Anal. Calcd for $C_{18}H_{12}O_2$: C, 83.06; H, 4.65. Found: C, 83.45; H, 4.70.

*1,2,3,4-Tetrahydrobenzo[*b*]naphtho[2,1-*f*]oxepin-7(8*H*)-one ***(1d)***.* This compound was obtained starting from **2d**, purified by column chromatography (eluent hexane/EtOAc 3:1), pale yellow solid, 90%. IR (KBr) *ν*/cm^{-1}: 2934, 1678 (C=O), 1601, 1563, 1488, 1456, 1414, 1332, 1319, 1283, 1260, 1231, 1181, 1112, 1069. ^{1}H NMR (DMSO-d_6) *δ*/ppm: 1.70-1.80 (m, 2H, tetralin), 1.80-1.89 (m, 2H, tetralinski), 2.76-2.81 (m, 2H, tetralin), 3.02-3.06 (m, 2H, tetralin), 4.08 (s, 2H, $C\underline{H_2}C$=O), 6.99 (d, *J* = 8.1 Hz, 1H, arom. 5-H), 7.22-7.34 (m, 2H, arom.), 7.37-7.44 (m, 2H, arom.), 7.66 (d, *J* = 8.1 Hz, 1H, arom. 6-H). MS (CI) *m/z*: 265 (MH^+, 100%). Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.55; H, 5.85.

*Benzo[*b*]naphtho[2,3-*f*]oxepin-12(13*H*)-one ***(1e)***.* This compound was obtained starting from **2e**, distilled under high vacuum, yellow solid, 69%, bp 195 ° C (10 mm Hg). IR (film) *ν*/cm^{-1}: 3058, 1682 (C=O), 1628, 1586, 1487, 1444, 1338, 1237, 1144, 1127. ^{1}H NMR (DMSO-d_6) *δ*/ppm: 4.26 (s, 2H, CH_2), 7.26-7.30 (m, 1H, arom.), 7.36-7.56 (m, 4H, arom.), 7.63-7.67 (m, 1H, arom.), 7.99 (d, 1H, arom.), 8.00 (s, 1H, arom. 6-H), 8.12 (d, *J* = 8.2 Hz, 1H, arom.), 8.64 (s, 1H, arom. 11-H). MS (CI) *m/z*: 261 (MH^+, 100%). Anal. Calcd for $C_{18}H_{12}O_2$: C, 83.06; H, 4.65. Found: C, 83.01; H, 4.44.

*7,8,9,10-Tetrahydrobenzo[*b*]naphtho[2,3-*f*]oxepin-12(13*H*)-one ***(1f)***.* This compound was obtained starting from **2f**, distilled under high vacuum, light yellow solid, 44%, bp 180 °C (10 mm Hg). IR (KBr) *ν*/cm^{-1}: 2931, 1680 (C=O), 1612, 1586, 1480, 1456, 1416, 1316, 1275, 1231, 1177, 1129. ^{1}H NMR (DMSO-d_6) *δ*/ppm: 1.70-1.73 (m, 4H, 2×CH_2 tetralin), 2.68-2.74 (bm, 2H, tetralin), 2.76-2.82 (bm, 2H, tetralin), 4.08 (s, 2H, $C\underline{H_2}CO$), 7.18 (s, 1H, arom. 6-H), 7.21-7.33 (m, 3H, arom.), 7.40-7.43 (m, 1H,

arom.), 7.61 (s, 1H, arom. 11-H). MS (CI) *m/z*: 265 (MH^+, 100%). Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.50; H, 5.99.

General procedure for preparation of *β*-chlorovinylaldehydes 10a-f. To *N*,*N*-dimethylformamide (6.30 mL, 81 mmol) in trichloroethene (5 mL) previously cooled to –5 °C, $POCl_3$ (5.0 mL, 54.0 mmol) was added dropwise with continuous stirring while maintaining the reaction temperature below 18 °C. The mixture was stirred at rt for 30 min, whereupon the solution of ketone **1a-f** (18.0 mmol) in trichloroethene (10.0 mL) was added stepwise. The resulting mixture was refluxed for 8 h when by TLC checking (CH_2Cl_2) the reaction progress wasn't further noticeable. The reaction mixture was cooled and 30% aq. NaOAc (20 mL) was added very slowly dropwise. When exothermic reaction was finished the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were boiled with decolorizing charcoal for 5 min, dried (Na_2SO_4) and solvent removed under reduced pressure. The crude product was purified by column chromatography. Analytical samples were obtained by recrystallization from EtOAc/hexane.

*7-Chlorobenzo[*b*]naphtho[2,1-*f*]thiepin-8-carbaldehyde (**10a**).* This compound was obtained starting from **1a**, separated from unreacted **1a** by column chromatography (eluent CH_2Cl_2), pale yellow solid, 42%. ^{1}H NMR ($CDCl_3$) *δ*/ppm: 7.23-7.84 (m, 8H, arom.), 8.21-8.23 (m, 1H, arom.), 8.87-8.91 (m, 1H, arom. 1-H), 10.79 (s, 1H, CHO). MS (CI) *m/z*: 323, 325 (MH^+, 100%, 37%). Anal. Calcd for $C_{19}H_{11}ClOS$: C, 70.69; H, 3.43; S, 9.93. Found: C, 70.32; H, 3.40; S, 10.17.

*12-Chlorobenzo[*b*]naphtho[2,3-*f*]thiepin-13-carbaldehyde (**10b**).* This compound was obtained starting from **1b**, separated from unreacted **1b** by column chromatography (eluent CH_2Cl_2), pale yellow solid, 60%. ^{1}H NMR ($CDCl_3$) *δ*/ppm: 7.27-7.37 (m, 3H, arom.), 7.50-7.57 (m, 2H, arom.), 7.61-7.64 (m, 1H, arom.), 7.77-7.80 (m, 1H, arom.), 7.85-7.88 (m, 1H, arom.), 8.07 (s, 1H, arom. 6-H), 8.32 (s, 1H, arom. 11-H), 10.73 (s, 1H, CHO). MS (CI) *m/z*: 323, 325 (MH^+, 100%, 37%). Anal. Calcd for $C_{19}H_{11}ClOS$: C, 70.69; H, 3.43; S, 9.93. Found: C, 71.02; H, 3.55; S, 10.20.

*7-Chlorobenzo[*b*]naphtho[2,1-*f*]oxepin-8-carbaldehyde (**10c**).* This compound was obtained starting from **1c**, light yellow solid, 97%. IR (KBr) *ν*/cm^{-1}: 3062, 2926; 2761, 1682 (C=O), 1626, 1595, 1583, 1557, 1487, 1444, 1386, 1371, 1343, 1309, 1260, 1201, 1152, 1124, 1088, 1064. ^{1}H NMR ($CDCl_3$) *δ*/ppm: 7.18-7.23 (m, 1H, arom.), 7.33-7.41 (m, 2H, arom.), 7.55-7.58 (m, 1H, arom.), 7.60-7.72 (m, 3H, arom.), 7.79-7.87 (m, 2H, arom.), 8.64-8.67 (m, 1H, arom. 1-H), 10.73 (s, 1H, CHO). MS (CI) *m/z*: 307, 309 (MH^+, 100%, 39%). Anal. Calcd for $C_{19}H_{11}ClO_2$: C, 74.40; H, 3.61. Found: C, 74.61; H, 3.26.

*7-Chloro-1,2,3,4-tetrahydrobenzo[*b*]naphtho[2,1-*f*]oxepin-8-carbaldehyde (**10d**).* This compound was obtained starting from **1d**, yellowish solid, 87%. IR (KBr) *ν*/cm^{-1}: 2934; 1681 (C=O), 1601, 1565, 1486, 1441, 1416, 1318, 1202, 1125. ^{1}H NMR (DMSO-d_6) *δ*/ppm: 1.65-1.87 (bm, 4H, tetralin), 2.74-2.79 (m,

2H, tetralin), 3.00-3.05 (bm, 2H, tetralin), 7.11 (d, *J* = 8.2 Hz, 1H, arom. 5-H), 7.22-7.28 (m, 1H, arom.), 7.40-7.46 (m, 3H, arom.), 7.56 (d, *J* = 8.2 Hz, 1H, arom. 6-H), 10.51 (s, 1H, CHO). MS (CI) *m/z*: 311, 313 (MH^+, 100%, 37%). Anal. Calcd for $C_{19}H_{15}ClO_2$: C, 73.43; H, 4.86. Found: C, 73.74; H, 5.09.

*12-Chlorobenzo[*b*]naphtho[2,3-*f*]oxepin-13-carbaldehyde (**10e**).* This compound was obtained starting from **1e**, yellowish solid, 90%. IR (KBr) *ν*/cm^{-1}: 3057, 2927; 2754, 1681 (C=O), 1598, 1487, 1443, 1310, 1239, 1209. ^1H NMR ($CDCl_3$) *δ*/ppm: 7.19-7.58 (m, 6H, arom.), 7.68 (s, 1H, arom. 6-H), 7.81-7.94 (m, 2H, arom.), 8.38 (s, 1H, arom. 11-H), 10.73 (s, 1H, CHO). MS (CI) *m/z*: 307, 309 (MH^+, 100%, 39%). Anal. Calcd for $C_{19}H_{11}ClO_2$: C, 74.40; H, 3.61. Found: C, 74.74; H, 3.88.

*12-Chloro-7,8,9,10-tetrahydrobenzo[*b*]naphtho[2,3-*f*]oxepin-13-carbaldehyde (**10f**).* This compound was obtained starting from **1f**, yellowish solid, 96%. IR (KBr) *ν*/cm^{-1}: 2933, 2858, 1683 (C=O), 1608, 1552, 1483, 1443, 1411, 1308, 1286, 1248, 1205, 1124, 1062. ^1H NMR (DMSO-d_6) *δ*/ppm: 1.67-1.71 (m, 4H, 2×CH_2 tetralin), 2.71-2.79 (bm, 4H, 2×CH_2 tetralin), 7.13 (s, 1H, arom. 6-H), 7.21-7.26 (m, 1H, arom.), 7.33-7.37 (m, 1H, arom.), 7.41-7.47 (m, 2H, arom.), 7.51 (s, 1H, arom. 11-H), 10.51 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6) *δ*/ppm: 21.9, 22.2, 28.0, 28.7 (tetralin CH_2); 120.66, 120.73, 124.7, 129.6, 130.75, 130.80 (CH); 124.8, 126.2, 132.6, 134.5, 144.2, 145.8, 157.0, 159.0 (C); 190.5 (CHO). MS (CI) *m/z*: 311, 313 (MH^+, 100%, 35%). Anal. Calcd for $C_{19}H_{15}ClO_2$: C, 73.43; H, 4.86. Found: C, 73.41; H, 5.02.

General procedure for preparation of pentacyclic esters 11a-f. To the solution of chloroaldehyde **10a-f** (6.20 mmol) in pyridine (15 mL) ethyl 2-mercaptoacetate (0.76 g, 4.6 mmol) and Et_3N (2 mL) were added. The reaction mixture was stirred at 70 °C for 1 h and then at reflux temperature for additional 2 h. Solvent was removed under reduced pressure till dryness and the residue was partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate (2×25 mL). The combined organic extracts were washed with dil. HCl (5%) and water, boiled with decolorizing charcoal for 5 min, dried (Na_2SO_4) and solvent evaporated. Thus obtained crude product **11a-f** was purified by recrystallization or column chromatography.

*Ethyl naphtho[1,2-*b*]thieno[2,3-*d*][1]benzothiepin-8-carboxylate (**11a**).* This compound was obtained starting from **10a**, purified by column chromatography (eluent hexane/EtOAc 3:1), yellowish solid, 75%. ^1H NMR ($CDCl_3$) *δ*/ppm: 1.33 (t, *J* = 7.1 Hz, 3H, CH_3), 4.20 (q, *J* = 7.1 Hz, 2H, CH_2), 7.09-8.06 (m, 9H, arom.), 8.36-8.40 (m, 1H, arom.); 9.18-9.22 (m, 1H, arom. 1-H). MS (CI) *m/z*: 389 (MH^+, 100%). Anal. Calcd for $C_{23}H_{16}O_2S_2$: C, 71.11; H, 4.15; S, 16.51. Found: C, 71.60; H, 4.49; S, 16.58.

*Ethyl naphtho[2,3-*b*]thieno[2,3-*d*][1]benzothiepin-2-carboxylate (**11b**).* This compound was obtained starting from **10b**, purified by column chromatography (eluent hexane/EtOAc 3:1), light yellow solid, 80%. ^1H NMR ($CDCl_3$) *δ*/ppm: 1.43 (t, *J* = 7.1 Hz, 3H, CH_3), 4.43 (q, *J* = 7.1 Hz, 2H, CH_2), 7.30-7.41 (m, 2H, arom.), 7.49-7.56 (m, 3H, arom.), 7.71 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H, arom.), 7.78-7.85 (m, 2H, arom.),

8.01 (s, 1H, thioph.), 8.04 (s, 1H, arom. 9-H), 8.17 (s, 1H, arom. 14-H). MS (CI) *m/z*: 389 (MH^+, 100%). Anal. Calcd for $C_{23}H_{16}O_2S_2$: C, 71.11; H, 4.15; S, 16.51. Found: C, 71.45; H, 4.01; S, 16.40.

*Ethyl naphtho[1,2-*b*]thieno[2,3-*d*][1]benzoxepin-8-carboxylate (**11c**).* This compound was obtained starting from **10c**, purified by column chromatography (eluent hexane/EtOAc 2:1), yellowish crystals, 86%. IR (KBr) *v*/cm^{-1}: 3056, 2980; 1714 (C=O), 1598, 1546, 1494, 1477, 1456, 1436, 1393, 1366, 1293, 1277, 1244, 1198, 1152, 1128, 1082, 1017. ^{1}H NMR ($CDCl_3$) *δ*/ppm: 1.43 (t, *J* = 7.1 Hz, 3H, CH_3), 4.42 (q, *J* = 7.1 Hz, 2H, CH_2), 7.21-7.26 (m, 1H, arom.), 7.35-7.41 (m, 1H, arom.), 7.48-7.59 (m, 4H, arom.), 7.63-7.73 (m, 2H, arom.), 7.85 (d, *J* = 8.0 Hz, 1H, arom.), 8.09 (s, 1H, thioph.), 8.65-8.69 (m, 1H, arom. 1-H). MS (ES^+) *m/z*: 395 ($[M+Na]^+$, 100%). Anal. Calcd for $C_{23}H_{16}O_3S$: C, 74.17; H, 4.33; S, 8.61. Found: C, 74.54; H, 4.04; S, 8.52.

*Ethyl 1,2,3,4-tetrahydronaphtho[1,2-*b*]thieno[2,3-*d*][1]benzoxepin-8-carboxylate (**11d**).* This compound was obtained starting from **10d**, purified by column chromatography (eluent hexane/EtOAc 2:1), yellowish crystals, 83%. IR (KBr) *v*/cm^{-1}: 2934, 1705 (C=O), 1604, 1543, 1493, 1459, 1432, 1381, 1324, 1277, 1249, 1197, 1129, 1082, 1071. ^{1}H NMR (DMSO-d_6) *δ*/ppm: 1.34 (t, *J* = 7.1 Hz, 3H, CH_3), 1.68-1.88 (bm, 4H, tetralin), 2.72-2.76 (m, 2H, tetralin), 3.02-3.07 (m, 2H, tetralin), 4.35 (q, *J* = 7.1 Hz, 2H, ester CH_2), 7.02 (d, *J* = 8.0 Hz, 1H, arom. 5-H), 7.27-7.32 (m, 1H, arom.), 7.31 (d, *J* = 8.0 Hz, 1H, arom. 6-H), 7.42-7.44 (m, 2H, arom.), 7.72 (d, *J* = 7.7 Hz, 1H, arom.), 8.14 (s, 1H, thioph.). MS (CI) *m/z*: 377 (MH^+, 100%). Anal. Calcd for $C_{23}H_{20}O_3S$: C, 73.38; H, 5.35; S, 8.52. Found: C, 73.70; H, 5.49; S, 8.90.

*Ethyl naphtho[2,3-*b*]thieno[2,3-*d*][1]benzoxepin-2-carboxylate (**11e**).* This compound was obtained starting from **10e**, purified by column chromatography (eluent hexane/EtOAc 2:1), then crystallized from hexane, colorless crystals, 60%. IR (KBr) *v*/cm^{-1}: 1714 (C=O), 1547, 1494, 1478, 1443, 1383, 1262, 1206, 1132, 1085, 1023. ^{1}H NMR (DMSO-d_6) *δ*/ppm: 1.37 (t, *J* = 7.1 Hz, 3H, CH_3), 4.38 (q, *J* = 7.1 Hz, 2H, CH_2), 7.30-7.35 (m, 1H, arom.), 7.44-7.60 (m, 4H, arom.), 7.75-7.79 (m, 1H, arom.), 7.93-7.96 (m, 1H, arom.), 7.99 (s, 1H, arom. 9-H), 8.02-8.05 (m, 1H, arom.), 8.22 (s, 1H, thioph.), 8.27 (s, 1H, arom. 14-H). MS (ES^+) *m/z*: 395 ($[M+Na]^+$, 100%). Anal. Calcd for $C_{23}H_{16}O_3S$: C, 74.17; H, 4.33; S, 8.61. Found: C, 74.41; H, 3.98; S, 8.80.

*Ethyl 10,11,12,13-tetrahydronaphtho[2,3-*b*]thieno[2,3-*d*][1]benzoxepin-2-carboxylate (**11f**).* This compound was obtained starting from **10f**, crystallized from EtOAc, pale yellow crystals, 80%. IR (KBr) *v*/cm^{-1}: 2925, 1705 (C=O), 1613, 1543, 1492, 1468, 1437, 1384, 1245, 1197, 1174, 1127, 1079. ^{1}H NMR (DMSO-d_6) *δ*/ppm: 1.34 (t, *J* = 7.1 Hz, 3H, CH_3), 1.70 (bs, 4H, 2×CH_2 tetralin), 2.69-2.75 (bm, 4H, 2×CH_2 tetralin), 4.35 (q, *J* = 7.1 Hz, 2H, ester CH_2), 7.14 (s, 1H, arom. 9-H), 7.24 (s, 1H, arom. 14-H), 7.25-7.31 (m, 1H, arom.), 7.35-7.46 (m, 2H, arom.), 7.68 (d, *J* = 7.5 Hz, 1H, arom.), 8.12 (d, *J* = 0.7 Hz, 1H, thioph.). ^{13}C NMR (DMSO-d_6) *δ*/ppm: 14.3 (CH_3); 22.3, 22.5, 28.1, 28.7 (tetralin CH_2); 61.4 (ester

CH_2); 121.70, 121.74, 125.9, 128.6, 128,8, 130.2, 133.6 (CH); 123.4, 127.5, 131.4, 134.8, 136.1, 141.0, 143.1, 154.9, 156.7 (C); 161.2 (C=O). MS (CI) *m/z*: 377 (MH^+, 100%). Anal. Calcd for $C_{23}H_{20}O_3S$: C, 73.38; H, 5.35; S, 8.52. Found: C, 73.67; H, 5.24; S, 8.44.

General procedure for preparation of pentacyclic alcohols 12a-f. To the suspension of $LiAlH_4$ (0.17 g, 4.5 mmol) in Et_2O (50 mL) and/or THF (30 mL) ester **11a-f** (4.50 mmol) was added in small portions. The mixture was stirred at room temperature for 2 h, when TLC (hexane/EtOAc 3:1) showed total conversion. The excess of $LiAlH_4$ was decomposed by dropwise addition of water/Et_2O 1:1. The inorganic precipitate was filtered off and washed few times with ether, and filtrate was evaporated under reduced pressure. Thus obtained crude product **12a-f** was purified by recrystallization or column chromatography.

*Naphtho[1,2-*b*]thieno[2,3-*d*][1]benzothiepin-8-ylmethanol (**12a**).* This compound was obtained starting from **11a**, purified by column chromatography (eluent hexane/EtOAc 1:1), yellowish crystals, 92%. ^{1}H NMR (DMSO-d_6) δ/ppm: 4.79 (d, J = 5.7 Hz, 2H, CH_2), 5.75 (t, J = 5.7 Hz, 1H, OH), 7.37-7.49 (m, 3H, arom.), 7.60-7.80 (m, 5H, arom.), 7.68 (d, J = 8.5 Hz, 1H, arom. 5-H), 8.00 (d, J = 8.5 Hz, 1H, arom. 6-H), 8.94 (d, J = 8.0 Hz, 1H, arom. 1-H). MS (ES^+) *m/z*: 329 ($[M\text{-}OH]^+$, 100%). Anal. Calcd for $C_{21}H_{14}OS_2$: C, 72.80; H, 4.07; S, 18.51. Found: C, 72.35; H, 4.42; S, 18.62.

*Naphtho[2,3-*b*]thieno[2,3-*d*][1]benzothiepin-2-ylmethanol (**12b**).* This compound was obtained starting from **11b**, purified by column chromatography (eluent hexane/EtOAc 2:1), pale yellow crystals, 96%. ^{1}H NMR ($CDCl_3$) δ/ppm: 1.70 (bs, 1H, OH), 4,95 (s, 1H, CH_2), 7.26 (s, 1H, thioph.), 7.27-7.38 (m, 2H, arom.), 7.45-7.51 (m, 3H, arom.), 7.68-7.71 (m, 1H, arom.), 7.78-7.83 (m, 2H, arom.), 7.98 (s, 1H, arom. 9-H), 8.16 (s, 1H, arom. 14-H). ^{13}C NMR ($CDCl_3$) δ/ppm: 60.2 (CH_2); 126.6, 126.9, 127.2, 127.8, 128.0, 128.3, 128.7, 128.8, 129.0, 131.9, 133.1 (CH); 133.0, 133.4, 134.4, 135.00, 135.07, 138.9, 139.3, 140.7, 143.0 (C). MS (ES^+) *m/z*: 329 ($[M\text{-}OH]^+$, 100%). Anal. Calcd for $C_{21}H_{14}OS_2$: C, 72.80; H, 4.07; S, 18.51. Found: C, 73.15; H, 4.41; S, 18.71.

*Naphtho[1,2-*b*]thieno[2,3-*d*][1]benzoxepin-8-ylmethanol (**12c**).* This compound was obtained starting from **11c**, purified by column chromatography (eluent hexane/EtOAc 1.5:1), colorless crystals, 81%. IR (KBr) ν/cm^{-1}: 3600-3100 (broad, O-H), 3052, 2922, 2852; 1598, 1565, 1495, 1462, 1438, 1362, 1242, 1202, 1150, 1121, 1045, 1015. ^{1}H NMR ($CDCl_3$) δ/ppm: 1.69 (bs, 1H, OH), 4.94 (s, 2H, CH_2), 7.18-7.23 (m, 1H, arom.), 7.33 (s, 1H, thioph.), 7.33-7.38 (m, 1H, arom.), 7.48-7.56 (m, 4H, arom.), 7.61-7.67 (m, 2H, arom.), 7.83 (d, J = 7.9 Hz, 1H, arom.), 8.67 (d, J = 8.2 Hz, 1H, arom. 1-H). MS (ES^+) *m/z*: 313 ($[M\text{-}OH]^+$, 100%). Anal. Calcd for $C_{21}H_{14}O_2S$: C, 76.34; H, 4.27; S, 9.70. Found: C, 76.55; H, 4.49; S, 9.52.

*1,2,3,4-Tetrahydronaphtho[1,2-*b*]thieno[2,3-*d*][1]benzoxepin-8-ylmethanol (**12d**).* This compound was

obtained starting from **11d**, crystallized from hexane/EtOAc 1:1, then filtrate purified by column chromatography (eluent hexane/EtOAc 2:1), colorless crystals, overall 98%. IR (KBr) ν/cm^{-1}: 3500-3100 (broad, O-H), 2932; 1493, 1459, 1435, 1417, 1372, 1323, 1250, 1219, 1205, 1155, 1126, 1011. ^{1}H NMR (DMSO-d_6) δ/ppm: 1.69-1.84 (dm, 4H, tetralin), 2.71-2.75 (m, 2H, tetralin), 3.02-3.07 (m, 2H, tetralin), 4.70 (d, J = 5.7 Hz, 2H, C$\underline{H_2}$OH), 5.64 (t, J = 5.7 Hz, 1H, OH), 6.96 (d, J = 7.9 Hz, 1H, arom. 5-H), 7.16 (d, J = 7.9 Hz, 1H, arom. 6-H), 7.23-7.28 (m, 1H, arom.), 7.32 (s, 1H, thioph.), 7.34-7.41 (m, 2H, arom.), 7.54-7.57 (m, 1H, arom.). MS (CI) *m/z*: 334 (M^+, 100%). Anal. Calcd for $C_{21}H_{18}O_2S$: C, 75.42; H, 5.43; S, 9.59. Found: C, 75.75; H, 5.49; S, 9.77.

*Naphtho[2,3-*b*]thieno[2,3-*d*][1]benzoxepin-2-ylmethanol (**12e**).* This compound was obtained starting from **11e**, purified by crystallization from hexane/EtOAc 1:1, colorless crystals, 73%. IR (KBr) ν/cm^{-1}: 3600-3100 (broad, O-H), 3049, 2922, 2852; 1498, 1487, 1443, 1375, 1338, 1327, 1257, 1235, 1207, 1156, 1129, 1115, 1024. ^{1}H NMR (DMSO-d_6) δ/ppm: 4.76 (d, J = 5.7 Hz, 2H, CH_2), 5.74 (t, J = 5.7 Hz, 1H, OH), 7.27-7.33 (m, 1H, arom.), 7.41 (s, 1H, thioph.), 7.40-7.55 (m, 4H, arom.), 7.60-7.63 (m, 1H, arom.), 7.90-7.93 (m, 1H, arom.), 7.93 (s, 1H, arom. 9-H), 7.98-8.02 (m, 1H, arom.), 8.05 (s, 1H, arom. 14-H). MS (ES^+) *m/z*: 313 ($[M\text{-}OH]^+$, 100%). Anal. Calcd for $C_{21}H_{14}O_2S$: C, 76.34; H, 4.27; S, 9.70. Found: C, 76.71; H, 3.98; S, 9.44.

*10,11,12,13-Tetrahydronaphtho[2,3-*b*]thieno[2,3-*d*][1]benzoxepin-2-ylmethanol (**12f**).* This compound was obtained starting from **11f**, crystallized from EtOAc, light yellow crystals, 90%. IR (KBr) ν/cm^{-1}: 3400-3100 (broad, O-H), 2930, 1493, 1438, 1396, 1354, 1255, 1209, 1171, 1113. ^{1}H NMR (DMSO-d_6) δ/ppm: 1.69 (bs, 4H, 2×CH_2 tetralin), 2.68-2.73 (bm, 4H, 2×CH_2 tetralin), 4.71 (d, J = 5.7 Hz, 2H, Ar-CH_2), 5.65 (t, J = 5.7 Hz, 1H, OH), 7.08 (s, 1H, arom. 9-H), 7.10 (s, 1H, arom. 14-H), 7.22-7.28 (m, 1H, arom.), 7.33 (s, 1H, thioph.), 7.33-7.40 (m, 2H, arom.), 7.52-7.56 (m, 1H, arom.). ^{13}C NMR (DMSO-d_6) δ/ppm: 22.2, 22.5, 28.0, 28.4 (tetralin CH_2); 58.4 (CH_2OH); 121.3, 121.5, 124.43, 125.5, 127.87, 127.93, 129.3 (CH); 124.40, 128.4, 134.1, 134.7, 135.2, 138.9, 146.0, 154.1, 156.3 (C). MS (CI) *m/z*: 334 (M^+, 100%). Anal. Calcd for $C_{21}H_{18}O_2S$: C, 75.42; H, 5.43; S, 9.59. Found: C, 75.70; H, 5.10; S, 9.28.

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