An efficient and chemoselective synthesis of benzo[*e*][1,4]thiazepin-2-(1*H*,3*H*,5*H*)-ones *via* a microwave-assisted multi-component reaction in water†

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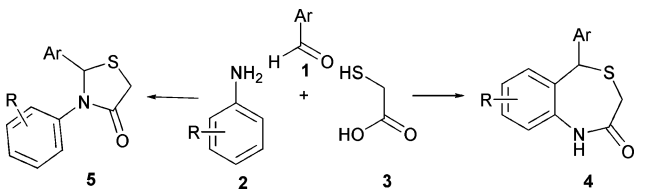
A new and efficient strategy for the synthesis of benzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-ones *via* a microwave-assisted multi-component reaction in aqueous media is described.

Introduction

Because of their interesting biological properties, functionalized benzothiazepinones and their fused analogues represent an important class of heterocycles that have been tested and applied as potential drugs.[1] Especially, benzo[*e*][1,4]thiazepin-2-ones were used as a potential therapeutic medicine for type II diabetes.[2] Therefore, these molecules have attracted considerable synthetic effort. Presently, benzo[*e*][1,4]thiazepin-2-ones are generally synthesized by *S*-alkylation of 2-aminobenzhydrols with methyl thioglycolate followed by cyclization. This can be achieved (1) through a laborious multistep procedure;[3] (2) through a two-step procedure with a long reaction time to complete the *S*-alkylation;[4] (3) through an efficient *S*-alkylation procedure by using corrosive strong organic acid such as CF_3COOH.[2] However, the key starting material 2-aminobenzhydrol is not a commercially available reagent and needs to be prepared itself *via* complicated procedures by (1) reduction of the corresponding 2-aminobenzophenones using $NaBH_4$[3] or $LiAlH_4$;[2] (2) selective ortho-lithiation of pivaloylanilide by *n*-butyllithium followed by condensation with aromatic aldehydes.[5] Furthermore, all the above mentioned reactions suffer from time-consuming and costly procedures, including the purification of intermediates and the protection and deprotection of functional groups, and the use of low temperature. Therefore, the design of new, concise, and efficient synthetic routes for this important class of compounds using easily accessible raw materials is highly desired.[6]

At the same time, because of growing environmental concerns, organic chemists are required to develop environmentally benign synthetic methodologies.[7] Naturally abundant water appears to be a better option as a reaction medium because of its non-toxic, non-corrosive and nonflammable nature.[8a] In this respect, one of the most promising approaches is to perform organic reactions in aqueous media using microwave (MW) irradiation.[8b] Water is a good absorber for microwave energy and has been successfully employed as a solvent for various MW promoted organic syntheses.[8c–h]

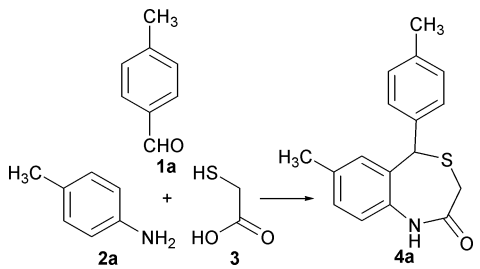
As part of our ongoing research program[9] on "Heterocyclic Privileged Medicinal Scaffolds"[10] based on MCRs, we explored the use of water as a reaction medium in conjunction with microwave irradiation as a useful, environmentally benign treatment for the synthesis of benzothiazepinones. Here we report a highly efficient and chemoselective synthetic route to the benzothiazepinones **4** and thiazolidinones **5** *via* a microwave-assisted, three-component reaction between an aromatic aldehyde, aniline and mercaptoacetic acid (Scheme 1).



Scheme 1

Result and discussion

In order to find suitable conditions for efficient microwave-assisted formation of the benzothiazepinones, the influences of different solvents were investigated using the reaction of *p*-methylbenzaldehyde **1a** with *p*-toluidine **2a** and mercaptoacetic acid **3** as a model reaction at 90 °C (Scheme 2). When the reaction was carried out in aprotic solvents such as benzene, dichloromethane, DMF and THF it afforded the thiazolidinones **5** with excellent yields. Interestingly, the use of protic solvents



Scheme 2

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Table 1 Solvent effect on the synthesis of compounds **4a** at 90 °C

Entry	Solvent	Time (min)	Yield (%)
1	benzene	13	trace
2	dichloromethane	13	trace
3	DMF	13	trace
4	THF	13	trace
5	glycol	13	10
6	ethanol	13	17
7	HOAc	13	55
8	H_2O	13	65

Table 2 Temperature optimization of the synthesis of compounds **4a** in water

Entry	Temp. (°C)	Time (min)	Yield (%)
1	90	13	65
2	95	13	68
3	100	10	70
4	105	9	80
5	110	9	94
6	115	9	93
7	120	9	92

such as glycol, ethanol, glacial acetic acid (HOAc) and water gave low to moderate yields of the product **4a**. The best protic solvent found was water. In this solvent, 7-methyl-5-*p*-tolylbenzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-one was obtained in a better yield than with other protic solvents (Table 1, entry **8**). Furthermore, the above-mentioned reaction was performed at temperatures ranging from 90 °C to 120 °C in water. As seen from Table 2, when the temperature was increased from 90 °C to 110 °C, the yield of **4a** improved from 65% to 94%. However, no significant increase in the yield was observed as the reaction temperature was raised further from 110 °C to 120 °C. Therefore, the temperature of 110 °C was chosen for all further microwave-assisted reactions.

In further investigation, the scope of the methodology was studied; a wide range of substituted aromatic aldehydes as well as heteroaromatic aldehydes were found to take part in reactions with mercaptoacetic acid and different substituted aromatic amines under the optimum reaction conditions. The results are summarized in Table 3.

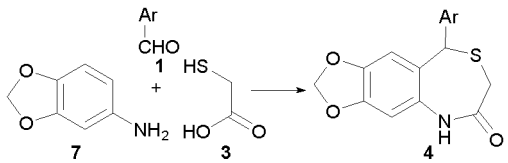
It is worthy of note that there is a delicate electronic effect on the chemoselectivity in these reactions. In search of the reaction scope in regard to the aldehydes, various aromatic amines with different substituents, ranging from electron-donating groups such as *p*-methoxy to electron-withdrawing groups such as *p*-chloro, were allowed to react with different aromatic aldehydes (Table 3, entries 1–14), and the results indicate that aromatic aldehydes bearing electron-donating functional groups such as methyl or methoxy as well as heteroaromatic aldehydes are suitable for the formation of **4**. Surprisingly, the aldehydes with electron-withdrawing substituents generated no product **4**. Instead, thiazolidinones **5** were afforded with excellent yields. (Table 3, entries 26–30). It should be pointed out that although there are many reports on the synthesis of the thiazolidinones,[11] to the best of our knowledge, the synthesis of the biologically active derivatives **5** in aqueous media has seldom

Table 3 Synthesis of benzothiazepinone derivatives **4** or thiazolidinones **5** under microwave irradiation in water at 110 °C

Entry	Product	Aldehydes	Amines	Time (min)	Yield (%)[a]	Mp (°C)
1	**4a**	4-Methylbenzaldehyde	*p*-Toluidine	9	94	>300
2	**4b**	4-Methoxybenzaldehyde	*p*-Toluidine	8	92	269–270
3	**4c**	4-(Dimethylamino)benzaldehyde	*p*-Toluidine	8	90	>300
4	**4d**	3,4-Methylenedioxybenzaldehyde	*p*-Toluidine	9	90	249–251
5	**4e**	3,4-Dimethoxybenzaldehyde	*p*-Toluidine	10	91	206–207
6	**4f**	2-Thiophenecarboxaldehyde	*p*-Toluidine	9	92	214–216
7	**4g**	4-Methoxybenzaldehyde	4-Methoxybenzenamine	8	90	268–269
8	**4h**	4-(Dimethylamino)benzaldehyde	4-Methoxybenzenamine	8	94	>300
9	**4i**	Benzaldehyde	Aniline	10	90	281–283
10	**4j**	4-Methylbenzaldehyde	Aniline	9	91	257
11	**4k**	2-Thiophenecarboxaldehyde	Aniline	9	93	171–172
12	**4l**	3,4-Methylenedioxybenzaldehyde	*m*-Toluidine	11	92	256–258
13	**4m**	2-Thiophenecarboxaldehyde	*m*-Toluidine	9	90	222
14	**4n**	4-Methylbenzaldehyde	4-Chlorobenzenamine	9	95	>300
15	**4o**	4-Methylbenzaldehyde	3,4-(Methylenedioxy)aniline	9	93	260–263
16	**4p**	4-Methoxybenzaldehyde	3,4-(Methylenedioxy)aniline	9	93	>300
17	**4q**	4-(Dimethylamino)benzaldehyde	3,4-(Methylenedioxy)aniline	8	96	254–258
18	**4r**	3,4-Methylenedioxybenzaldehyde	3,4-(Methylenedioxy)aniline	9	96	247–248
19	**4s**	3,4,5-Trimethoxybenzaldehyde	3,4-(Methylenedioxy)aniline	8	93	261–263
20	**4t**	2-Thiophenecarboxaldehyde	3,4-(Methylenedioxy)aniline	9	93	217–218
21	**4u**	2-Methoxybenzaldehyde	3,4-(Methylenedioxy)aniline	8	90	238–240
22	**4v**	4-Bromobenzaldehyde	3,4-(Methylenedioxy)aniline	9	91	245–246
23	**4w**	4-Chlorobenzaldehyde	3,4-(Methylenedioxy)aniline	10	92	238
24	**4x**	2-Chlorobenzaldehyde	3,4-(Methylenedioxy)aniline	9	92	245–249
25	**4y**	2,4-Dichlorobenzaldehyde	3,4-(Methylenedioxy)aniline	9	94	235–236
26	**5a**	4-Bromobenzaldehyde	*p*-Toluidine	8	92	159–162
27	**5b**	4-Fluorobenzaldehyde	*p*-Toluidine	7	89	171–174
28	**5c**	4-Chlorobenzaldehyde	*p*-Toluidine	9	90	180
29	**5d**	4-Chlorobenzaldehyde	Aniline	10	91	170–171
30	**5e**	4-Chlorobenzaldehyde	4-Methoxybenzenamine	10	92	169–170

[a] Isolated yields.

been studied. To further explore the scope of the reactions leading to **4**, we chose 3,4-(methylenedioxy)aniline as the amine to react with aromatic aldehydes and mercaptoacetic acid (Scheme 3). The results indicate that in this case, aromatic aldehydes bearing either electron-withdrawing or electron-donating functional groups such as chloro, fluoro, bromo, methyl or methoxy uniformly give the target products **4** (Table 3, entries 15–25) without the formation of **5**. It seems that the electronic effect on the chemoselectivity is quite sophisticated and more comprehensive and in-depth study is required to achieve a complete knowledge of the electronic effect.



Scheme 3

All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR spectra and HRMS data. The structure of **4a** was also established by X-ray crystallographic analysis (Fig. 1).[12]† The compounds **4i**, **4n**, **5a**, **5b**, **5c**, **5d** were reported in the literature.[2,4,11]

To explain the mechanism of this one-pot multi-component tandem reaction, we propose a plausible reaction mechanism illustrated in Scheme 4. The nature of the groups in the aromatic aldehydes is important in deciding the reaction path. The aromatic aldehydes with electron-donating groups (*p*-OMe, $\sigma_p = -0.27$ or *p*-Me, $\sigma_p = -0.17$) take part in the reaction by pathway A *via* initial condensation with the aromatic amine **2** to afford the intermediates **8**, which then undergo a [4 + 3] annulation with mercaptoacetic acid to give the seven-member ring lactams **4** good yield. The aldehydes with electron-withdrawing groups (EWG) such as *p*-chloro ($\sigma_p = +0.23$) are prone to afford the thiazolidinones through pathway B, where the five-member ring lactams **5** are produced by the [3 + 2] cycloaddition of the Schiff's base **9** with mercaptoacetic acid. In extreme cases, when the electron-donating substituent on the aromatic amine is sufficiently strong (as in the case of 3,4-(methylenedioxy)aniline), the deactivating effect of the EWG on aromatic aldehydes can be overcome, and all the aldehydes with either electron-withdrawing or electron-donating groups are found to be compatible with the corresponding [4 + 3] annulation pathway to give the target compounds **4**.

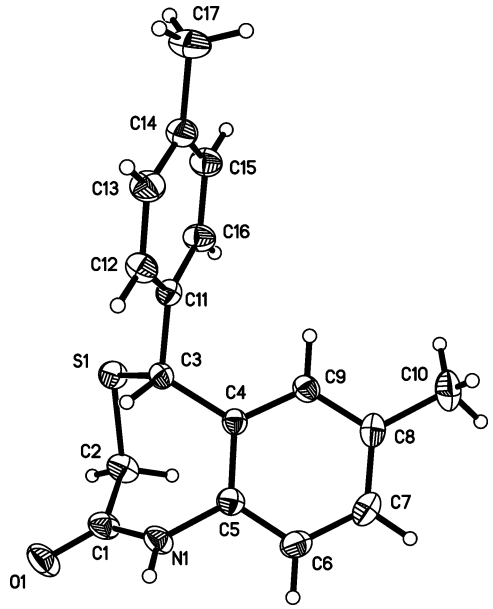


Fig. 1 ORTEP diagram of **4a**.

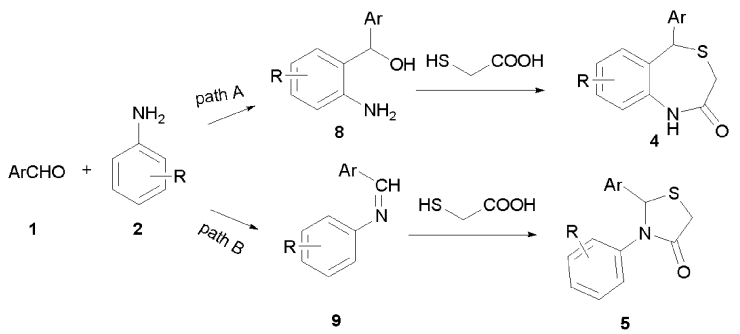
Conclusion

In conclusion, an efficient MW-assisted multi-component tandem reaction to give benzothiazepinones has been developed. The reaction is easy to perform using inexpensive starting materials and generates products in high yields with a chemoselectivity depending on the electronic effect of the substituents on the aromatic aldehyde and the amine. The one pot operational simplicity and the environmentally friendly nature make this new heterocycle synthetic strategy highly attractive and promising for the access of compounds of potential biological interest.

Experimental

General

Microwave irradiation was carried out with a microwave oven (Emrys™ Creator from Personal Chemistry, Uppsala, Sweden). Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^{1}H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shifts (δ) given in ppm relative to



Scheme 4

TMS as internal standard. High-resolution mass spectra (HRMS) were obtained on a Varian IonSpec QFT-MS spectrometer with the technique of electrospray ionization. X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer.

General procedure for the synthesis of compounds 4 with microwave irradiation. All the reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. In a 10 mL Emrys™ reaction vial, aldehyde **1** (1 mmol), aromatic amine **2** (1 mmol), mercaptoacetic acid **3** (1 mmol) and water (1.0 mL) were mixed and then capped. The mixture was irradiated at 110 °C (initial power 100 W and maximum power 200 W). Upon completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature. The solid product was filtered, washed with EtOH (95%). The solid was purified by recrystallization from EtOH/acetone (V/V = 1:1).

General procedure for the synthesis of 5. In a 10 mL Emrys™ reaction vial, aldehyde **1** (1 mmol), aromatic amine **2** (1 mmol), mercaptoacetic acid **3** (1 mmol) and water (1.0 mL) were mixed and then capped. The mixture was irradiated at 110 °C (initial power 100 W and maximum power 200 W). Upon completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature. The solid product was filtered, washed with EtOH (95%). The solid was purified by recrystallization from EtOH.

7-Methyl-5-*p*-tolylbenzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-one (4a). IR (KBr, ν, cm^{-1}): 3213, 3181, 3109, 2981, 2926, 1682, 1366, 818, 755, 762 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.51 (s, 1H, NH), 7.37 (d, J = 8.0 Hz, 2H, ArH), 7.22 (d, J = 8.0 Hz, 2H, ArH), 7.10 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H, ArH), 6.93 (d, J = 8.0 Hz, 1H, ArH), 6.74 (s, 1H, ArH), 5.55 (s, 1H, CH), 3.10 (d, J_1 = 12.0 Hz, 1H,CH$_2$); 2.87 (d J = 13.2 Hz, 1H, CH$_2$); 2.18 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): 168.6, 137.2, 135.6, 134.8, 134.5, 133.7, 129.2, 139.1, 128.7, 128.2, 124.0, 46.5, 31.1, 20.7; HRMS (ESI) m/z: calc. for [M + Na]$^+$ $C_{17}H_{17}NOS$: 306.0923; found: 306.0926.

5-(4-Methoxyphenyl)-7-methylbenzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-one (4b). IR (KBr, ν, cm^{-1}): 3178, 3076, 3033, 2957, 2884, 1680, 1482, 1250, 1301, 790, 668 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.51 (s, 1H, NH), 7.42 (d, J = 8.4 Hz, 2H, ArH), 7.11 (d, J = 8.0 Hz, 2H, ArH), 6.98 (d, J = 8.8 Hz, 2H, ArH), 6.94 (d, J = 8.0 Hz, 2H, ArH), 5.56 (s, 1H, CH), 3.79(s, 3H, OCH$_3$), 3.12 (d, J = 12.4 Hz, 1H, CH$_2$); 2.86 (dd, J_1 = 12.0 Hz, J_2 = 1.20 Hz, 1H, CH$_2$); 2.19 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): 168.6, 135.6, 134.8, 133.9, 130.4, 129.2, 128.7, 138.1, 123.9, 114.0, 55.1, 46.1, 31.2, 20.7; HRMS (ESI) m/z: calc. for [M + Na]$^+$ $C_{17}H_{17}NO_2S$: 322.0872; found: 322.0875.

5-(4-(Dimethylamino)phenyl)-7-methylbenzo[*e*][1,4]thiazepin-2-(1*H*,3*H*,5*H*)-one (4c). IR (KBr, ν, cm^{-1}): 3176, 3066, 2952, 2875, 1681, 1575, 1365, 827, 785, 705 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.53 (s, 1H, NH), 7.30 (d, J = 8.0 Hz, 2H, ArH), 7.10-7.08 (m, 1H, ArH), 7.10-7.08 (m, 1H, ArH), 6.96-6.92 (m, 1H, ArH), 6.76-6.74 (m, 3H, ArH), 5.48 (s, 1H, CH), 3.12 (dd, J_1 = 12.0 Hz, J_2 = 1.20 Hz, 1H, CH$_2$); 2.92 (s, 6H, N(CH$_3$)$_2$), 2.81 (dd, J_1 = 12.8 Hz, J_2 = 0.8 Hz, 1H, CH$_2$); 2.18 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): 168.6, 150.0, 135.5, 134.7, 134.2, 130.0, 128.0, 123.8, 112.7, 112.3, 46.2, 31.4, 20.8; HRMS (ESI) m/z: calc. for [M + Na]$^+$ $C_{18}H_{20}N_2OS$: 335.1189; found: 335.1185.

5-(Benzo[*d*][1,3]dioxol-6-yl)-7-methylbenzo[*e*][1,4]thiazepin-2-(1*H*,3*H*,5*H*)-one (4d). IR (KBr, ν, cm^{-1}): 3181, 3051, 2952, 2891, 680, 1619, 1503, 1414, 935, 812, 752 cm^{-1}; ^{1}H NMR (400 MHz, MSO-d_6) (δ, ppm): 9.51 (s, 1H, NH), 7.10 (dd, J_1 = 7.9 Hz, J_2 = 1.60 Hz, 1H, ArH), 7.04 (d, J = 1.2 Hz, 1H, ArH), 7.03-6.98(m, 1H, ArH), 6.94 (d, J = 8.0 Hz, 2H, ArH), 6.79 (s, 1H, ArH), 6.05 (dd, J = 6.4 Hz, 2H, ArH), 5.52 (s, 1H, CH), 3.09 (d, J = 8.4 Hz, 1H, CH$_2$); 2.86 (dd, J_1 = 12.0 Hz, J_2 = 1.20 Hz, 1H, CH$_2$); 2.21 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz, DMSO-d_6, 25 oC): δ = 168.7, 146.7, 145.5, 137.3, 134.6, 131.2, 129.2, 129.1, 128.9, 127.3, 127.2, 107.8, 107.4, 107.1, 105.1, 101.7, 101.4, 63.7, 46.5, 32.6, 31.0, 20.7; HRMS (ESI) m/z: calc. for [M + Na]$^+$ $C_{17}H_{15}NO_3S$: 336.0665; found: 336.0672.

5-(3,4-Dimethoxyphenyl)-7-methylbenzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-one (4e). IR (KBr, ν, cm^{-1}): 3170, 3094, 2954, 2876, 1682, 1479, 1374, 1036, 932, 829, 771 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.53 (s, 1H, NH), 7.12-6.99 (m, 4H, ArH), 6.93 (d, J = 8.0 Hz, 1H, ArH), 6.78 (s, 1H, ArH), 5.55 (s, 1H, CH), 3.78 (s, 3H, OCH$_3$), 3.74 (s, 3H, OCH$_3$), 3.12 (d, J = 12.0 Hz, 1H, CH$_2$); 2.86 (dd, J_1 = 12.0 Hz, J_2 = 0.8 Hz, 1H, CH$_2$); 2.19 (s, 3H, CH$_3$);^{13}C NMR (100 MHz, DMSO-d_6): 168.6, 148.5, 148.3, 135.6, 134.8, 133.8, 128.7, 128.1, 123.9, 121.4, 112.9, 111.6, 55.5, 46.4, 30.7, 20.8; HRMS (ESI) m/z: calc. for [M + Na]$^+$ $C_{18}H_{19}NO_3S$: 352.0978; found: 352.0974.

7-Methyl-5-(thiophen-2-yl)benzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-one (4f). IR (KBr, ν, cm^{-1}): 3189, 3067, 2974, 2872, 1682, 1586, 1295, 1150, 909, 740, 695, 650 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.53 (s, 1H, NH), 7.55-7.54 (m, 1H, ArH), 7.16-7.13 (m, 2H, ArH), 7.07-7.06 (m, 1H, ArH), 6.95-6.92 (m, 2H, ArH), 5.82 (s, 1H, CH), 3.08 (d, J_1 = 12.4 Hz, J_2 = 1.20 Hz, 1H, CH$_2$); 2.94 (d, J = 12.0 Hz, 1H, CH$_2$); 2.23 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): 168.4, 142.0, 135.7, 134.7, 133.7, 129.2, 128.1, 127.3, 127.1, 126.2, 124.1, 42.1, 31.3, 20.7; HRMS (ESI) m/z: calc. for [M + Na]$^+$ $C_{14}H_{13}NOS_2$: 298.0331; found: 298.0331.

7-Methoxy-5-(4-methoxyphenyl)benzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-one (4g). IR (KBr, ν, cm^{-1}): 3257, 3199, 3085, 1681, 1600, 1332, 1079, 901, 835, 755, 691 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) (δ, ppm): 9.43 (s, 1H, NH), 7.42 (d, J = 8.8 Hz, 2H, ArH), 7.01-6.97 (m, 3H, ArH), 6.88 (dd, J_1 = 8.8 Hz, J_2 = 3.2 Hz, 1H, ArH), 6.42 (s, 1H, ArH), 5.54 (s, 1H, CH), 3.78 (s, 3H, OCH$_3$), 3.64 (s, 3H, OCH$_3$), 3.13 (d, J = 12.4 Hz, 1H, CH$_2$), 2.86 (d, J = 12.4 Hz, 1H, CH$_2$); ^{13}C NMR (100 MHz, DMSO-d_6): 168.6, 158.9, 157.4, 135.6, 130.3, 130.1, 129.1, 125.4, 114.0, 113.9, 112.5, 55.2, 55.1, 46.1, 31.2; HRMS (ESI) m/z: calc. for [M + Na]$^+$ $C_{17}H_{17}NO_3S$: 338.0821; found: 338.0829.

5-(4-(Dimethylamino)phenyl)-7-methoxybenzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-one (4h). IR (KBr, ν, cm^{-1}): 3199, 3065, 1683, 1582, 1482, 1145, 759, 701, 650 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6,) (δ, ppm): 9.42 (s, 1H, NH), 7.30 (d, J = 8.8 Hz, 2H, ArH), 6.99 (d, J = 7.6 Hz, 1H, ArH), 6.87 (d, J = 8.8 Hz, 1H, ArH), 6.75 (d, J = 8.8 Hz, 1H, ArH), 6.43 (s, 1H, ArH), 5.47 (s, 1H, CH), 3.64 (s, 3H, OCH$_3$), 3.14 (d, J = 12.0 Hz, 1H, CH$_2$); 2.92 (s, 6H, N(CH$_3$)$_2$), 2.80 (d, J = 12.0 Hz, 1H, CH$_2$);^{13}C NMR (100 MHz,

DMSO-d_6): 168.8, 157.4, 150.1, 136.0, 130.0, 129.9, 125.2, 124.0, 114.0, 112.2, 122.2, 55.2, 46.2, 31.3; HRMS (ESI) m/z: calc. for $[M + Na]^+$ $C_{18}H_{20}N_2O_2S$: 329. 1318; found: 329.1324.

5-*p*-Tolylbenzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-one (4j). IR (KBr, ν, cm^{-1}): 3190, 3067, 3029, 1682, 1589, 1513, 1383, 1276, 904, 864, 825, 730 cm^{-1}; ^1H NMR (400 MHz, DMSO- d_6) (δ, ppm): 9.63 (s, 1H, NH), 7.38 (d, $J = 8.0$ Hz, 2H, ArH), 7.32-7.29 (m, 1H, ArH), 7.22 (d, $J = 8.0$ Hz, 2H, ArH), 7.16 (t, $J = 7.6$ Hz, 1H, ArH), 7.04 (d, $J = 8.0$ Hz, 1H, ArH), 6.91 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.20$ Hz, 1H, ArH), 5.60 (s, 1H, CH), 3.13 (d, $J = 12.0$ Hz, 1H, CH_2); 2.90 (dd, $J_1 = 11.6$ Hz, $J_2 = 1.20$ Hz, 1H, CH_2), 2.32 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 168.5, 137.4, 137.3, 134.5, 133.9, 129.2, 129.1, 128.2, 128.0, 126.4, 125.5, 124.0, 46.4, 31.1, 20.7; HRMS (ESI) m/z: calc. for $[M + Na]^+$ $C_{16}H_{15}NOS$: 292.0767; found: 292.0772.

5-(Thiophen-2-yl)benzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-one (4k). IR (KBr, ν, cm^{-1}): 3191, 3068, 1683, 1591, 1194, 852, 810, 746 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.65 (s, 1H, NH), 7.55 (dd, $J = 5.2$ Hz, 1H, ArH), 7.34 (t, $J = 7.6$ Hz, 1H, ArH), 7.22 (t, $J = 7.6$ Hz, 1H, ArH), 7.14-7.04 (m, 4H, ArH), 5.88 (s, 1H, CH), 3.10 (d, $J = 12.0$ Hz, 1H, CH_2); 2.90 (d, $J = 12.0$ Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 168.4, 141.8, 137.3, 133.9, 128.7, 127.8, 127.3, 127.2, 126.5, 126.3, 124.1, 42.1, 31.3; HRMS (ESI) m/z: calc. for $[M + Na]^+$ $C_{13}H_{11}NOS_2$: 284.0174; found: 284.0179.

5-(Benzo[*d*][1,3]dioxol-6-yl)-8-methylbenzo[*e*][1,4]thiazepin-2-(1*H*,3*H*,5*H*)-one (4l). IR (KBr, ν, cm^{-1}): 3188, 3066, 1682, 1491, 1096, 970, 824, 759 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.59 (s, 1H, NH), 7.07-6.97 (m, 3H, ArH), 6.93 (d, $J = 8.0$ Hz, 1H, ArH), 6.85 (d, $J = 8.0$ Hz, 1H, ArH), 6.05-6.04 (m, 2H, ArH), 5.52 (s, 1H, CH), 3.11 (d, $J = 12.0$ Hz, 1H, CH_2), 2.87 (d, $J = 12.4$ Hz, 1H, CH_2), 2.26 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 168.7, 147.4, 146.8, 137.8, 137.2, 131.4, 131.0, 127.9, 127.0, 124.3, 122.5, 109.4, 108.1, 101.2, 46.3, 31.1, 20.4; HRMS (ESI) m/z: calc. for $[M + Na]^+$ $C_{17}H_{15}NO_3S$: 336.0665; found: 336.0669.

8-Methyl-5-(thiophen-2-yl)benzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-one (4m). IR (KBr, ν, cm^{-1}): 3189, 3079, 1681, 1589, 1267, 1141, 817, 784 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.60 (s, 1H, NH), 7.53 (dd, $J_1 = 5.2$ Hz, $J_2 = 0.80$ Hz, 1H, ArH), 7.11 (s 1H, ArH), 7.07-7.03 (m, 2H, ArH), 6.98 (d, $J = 8.0$ Hz, 1H, ArH), 6.85 (s, 1H, ArH), 5.82 (s, 1H, CH), 3.09 (d, $J = 12.4$ Hz, 1H, CH_2), 2.95 (d, $J = 12.4$ Hz, 1H, CH_2), 2.28 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 168.3, 142.0, 135.7, 134.7, 133.7, 129.2, 138.1, 127.2, 127.1, 126.3, 124.1, 42.1, 31.3, 20.7; HRMS (ESI) m/z: calc. for $[M + Na]^+$ $C_{14}H_{13}NOS_2$: 298.0331; found: 298.0337.

9-Methyl-10-*p*-tolyl-5,9-dihydro-1,3-dioxa-8-thia-5-aza-cyclohepta[*f*]inden-6-one (4o). IR (KBr, ν, cm^{-1}): 3180, 3035, 2935, 1683, 1487, 1217, 1009, 896, 823, 762, 616 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.42 (s, 1H, NH), 7.36 (d, $J =$ 7.6 Hz, 2H, ArH), 7.22 (d, $J = 8.0$ Hz, 2H, ArH), 6.63 (s, 1H, ArH), 6.34 (s, 1H, ArH), 6.01-5.97 (m, 2H, OCH_2O), 5.53 (s, 1H, CH), 3.15 (s, 3H, OCH_3), 3.15 (d, $J = 12.0$ Hz, 1H, CH_2); 2.88 (dd, $J_1 = 11.6$ Hz, $J_2 = 1.20$ Hz, 1H, CH_2), 2.32 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 168.7, 146.7, 145.5, 137.3, 134.6, 131.2, 129.2, 129.1, 128.9, 127.3, 127.2, 107.1, 105.1, 101.7, 46.6, 31.0, 20.7; HRMS (ESI) m/z: calc. for $[M + Na]^+$ $C_{17}H_{15}NO_3S$: 336.0665; found: 336.0672.

10-(4-Methoxy-phenyl)-9-methyl-5,9-dihydro-1,3-dioxa-8-thia-5-aza-cyclohepta[*f*]inden-6-one (4p). IR (KBr, ν, cm^{-1}): 3189, 3066, 1686, 1599, 1369, 1141, 908, 791, 757, 707, 651 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.41 (s, 1H, NH), 7.40 (d, $J = 8.4$ Hz, 2H, ArH), 6.97 (d, $J = 8.4$ Hz, 2H, ArH), 6.64 (s, 1H, ArH), 6.33 (s, 1H, ArH), 6.01-5.99 (m, 2H, OCH_2O), 5.53 (s, 1H, CH), 3.78 (s, 3H, OCH_3), 3.16 (d, $J = 12.4$ Hz, 1H, CH_2), 2.85 (dd, $J_1 = 12.0$ Hz, $J_2 = 1.20$ Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 168.8, 158.9, 146.6, 145.5, 131.1, 130.3, 129.2, 127.4, 114.0, 107.0, 105.0, 101.7, 55.1, 46.1, 31.1; HRMS (ESI) m/z: calc. for $[M + Na]^+$ $C_{17}H_{15}NO_4S$: 352.0614; found: 352.0618.

9-(4-Dimethylamino-phenyl)-5,9-dihydro-1,3-dioxa-8-thia-5-aza-cyclohepta[*f*]inden-6-one (4q). IR (KBr, ν, cm^{-1}): 3188, 3050, 2973, 2929, 1686, 1470, 1345, 805, 747, 711 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.42 (s, 1H, NH), 7.28 (d, $J = 8.4$ Hz, 2H, ArH), 6.75 (d, $J = 8.8$ Hz, 2H, ArH), 6.63 (s, 1H, ArH), 6.33 (s, 1H, ArH), 5.98 (d, $J = 8.4$ 2H, OCH_2O), 5.46 (s, 1H, CH), 3.16 (d, $J = 12.0$ Hz, 1H, CH_2); 2.92 (s, 6H, $N(CH_3)_2$), 2.79 (dd, $J_1 = 12.0$ Hz, $J_2 = 1.20$ Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d6): 168.7, 147.5, 146.9, 146.7, 145.5, 131.3, 131.1, 127.2, 122.4, 109.4, 108.2, 107.1, 105.0, 101.7, 101.3, 46.5, 31.1; HRMS (ESI) m/z: calc. for $[M + Na]^+$ $C_{18}H_{18}N_2O_3S$: 343.1111; found: 343.1108.

10-Benzo[1,3]dioxol-5-yl-9-methyl-5,9-dihydro-1,3-dioxa-8-thia-5-aza-cyclohepta[*f*]inden-6-one (4r). IR (KBr, ν, cm^{-1}): 3188, 3050, 2973, 2929, 1686, 1470, 1345, 805, 747, 711 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.40 (s, 1H, NH), 7.02-6.93 (m, 3H, ArH), 6.63 (s, 1H, ArH), 6.41 (s, 1H, ArH), 6.05 (d, $J = 4.4$ Hz, 2H, ArH), 6.01 (d, $J = 8.4$ Hz, 2H, OCH_2O), 5.50 (s, 1H, CH), 3.79 (s, 3H, OCH_3), 3.13 (d, $J = 12.0$ Hz, 1H, CH_2); 2.87 (dd, $J_1 =$ 12.0 Hz, $J_2 = 1.20$ Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d6): 168.7, 147.5, 146.9, 146.7, 145.5, 131.3, 131.1, 127.2, 122.4, 109.4, 108.2, 107.1, 105.0, 101.7, 101.3, 46.5, 31.1; HRMS (ESI) m/z: calc. for $[M + Na]^+$ $C_{17}H_{13}NO_5S$: 366.0407; found: 366.0408.

9-(3,4,5-Trimethoxy-phenyl)-5,9-dihydro-1,3-dioxa-8-thia-5-aza-cyclohepta[*f*]inden-6-one (4s). IR (KBr, ν, cm^{-1}): 3182, 3073, 2979, 2921, 1683, 1495, 1422, 1368, 1139, 825, 752, 621 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.43 (s, 1H, NH), 6.80 (s, 1H, ArH), 6.64 (s, 1H), 6.48 (s, 1H, ArH), 6.01 (d, $J = 7.6$ Hz, 2H, OCH_2O), 5.52 (s, 1H, CH), 3.77(s, 6H, $N(CH_3)_2$), 3.68 (s, 3H, OCH_3), 3.16 (d, $J = 12.0$ Hz, 1H, CH_2); 2.87 (dd, $J_1 = 12.4$ Hz, $J_2 = 1.20$ Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 168.8, 152.8, 146.7, 145.5, 136.9, 133.1, 131.1, 127.0, 11.27, 107.2, 106.4, 105.0, 101.7, 60.0, 55.9, 47.1, 31.0; HRMS (ESI) m/z: calc. for $[M + Na]^+$ $C_{19}H_{19}NO_6S$: 412.0825; found: 412.0819.

9-Thiophen-2-yl-5,9-dihydro-1,3-dioxa-8-thia-5-aza-cyclohepta-[*f*]inden-6-one (4t). IR (KBr, ν, cm^{-1}): 3189, 3075, 2980, 2926, 2832, 1683, 1609, 1496, 1423, 1255, 1177, 1039, 832, 769, cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.41 (s, 1H, NH), 7.55 (d, $J = 5.2$ Hz, 1H, ArH), 7.15 (m, 1H, ArH), 7.07(d, $J = 5.2$ Hz, 1H, ArH), 6.63 (s, 1H, ArH), 6.55(s, 1H, ArH), 6.02 (d, $J = 8.4$ Hz,2H, OCH_2O), 5.79 (s, 1H, CH), 3.12 (d, $J = 12.4$ Hz, 1H, CH_2); 2.94 (d, $J = 12.4$ Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 168.5, 147.0, 145.6, 141.9, 131.2, 127.3, 127.2, 127.1, 126.2, 107.0,

105.2, 101.8, 42.1, 31.2; HRMS (ESI) m/z: calc. for [M + Na]$^+$ $C_{14}H_{11}NO_3S_2$: 328.0073; found: 328.0068.

9-(2-Methoxy-phenyl)-5,9-dihydro-1,3-dioxa-8-thia-5-aza-cyclohepta[*f*]inden-6-one (4u). IR (KBr, ν, cm-1): 3167, 3029, 1682, 1589, 1513, 1383, 1276, 904, 864, 825, 730 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.52 (s, 1H, NH), 7.62 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H, ArH), 7.39 (t, J = 8.4 Hz, 1H, ArH), 7.11-7.06 (m, 2H, ArH), 6.65 (s, 1H, ArH), 6.19 (s, 1H, ArH), 5.98 (d, J = 8.0 Hz, 2H, OCH_2O), 5.94 (s, 1H, CH), 3.71 (s, 3H, OCH_3), 3.19 (d, J = 12.4 Hz, 1H, CH_2); 2.84 (dd, J_1 = 12.0 Hz, J_2 = 1.20 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 168.8, 156.2, 146.7, 145.5, 131.3, 130.0, 129.5, 126.6, 124.8, 120.4, 111.5, 106.2, 105.0, 101.7, 55.7, 31.1; HRMS (ESI) m/z: calc. for [M + Na]$^+$ $C_{17}H_{15}NO_4S$: 352.0614; found: 352.0608.

9-(4-Bromo-phenyl)-5,9-dihydro-1,3-dioxa-8-thia-5-aza-cyclohepta[*f*]inden-6-one (4v). IR (KBr, ν, cm^{-1}): 3184, 3086, 1684, 1608, 1482, 1329, 1093, 1007, 837, 819, 769, 717 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.32 (s, 1H, NH), 7.59 (d, J = 7.6 Hz, 2H, ArH), 7.41 (d, J = 8.4 Hz, 2H, ArH), 6.62 (s, 1H, ArH), 6.50 (s, 1H, ArH), 6.02 (d, J = 7.6 Hz, 2H, ArH), 5.53 (s, 1H, CH), 3.08 (d, J = 12.0 Hz, 1H, CH_2), 2.96 (d, J = 12.4 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 168.7, 146.9, 145.5, 137.9, 131.4, 131.3, 130.9, 126.9, 120.8, 107.6, 105.3, 101.8, 46.4, 30.7; HRMS (ESI) m/z: calc. for [M + Na]$^+$ $C_{16}H_{12}BrNO_3S$: 399.9613; found: 399.9621.

9-(4-Chloro-phenyl)-5,9-dihydro-1,3-dioxa-8-thia-5-aza-cyclohepta[*f*]inden-6-one (4w). IR (KBr, ν, cm-1): 3189, 3006, 1683, 1586, 1127, 817 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.33 (s, 1H, NH), 7.48 (q, J = 12.0 Hz, 4H, ArH), 6.62 (s, 1H, ArH), 6.49 (s, 1H, ArH), 6.02 (d, J = 5.8 Hz, 2H, OCH_2O), 5.55 (s, 1H, CH), 3.08 (d, J = 12.4 Hz, 1H, CH_2), 2.96 (d, J = 12.4 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 168.7, 146.9, 145.5, 137.4, 132.2, 131.3, 130.6, 128.5, 127.0, 107.6, 105.3, 101.8, 46.3, 30.7; HRMS (ESI) m/z: calc. for [M + Na]$^+$ $C_{16}H_{12}ClNO_3S$: 356.0119; found: 356.0125.

9-(2-Chloro-phenyl)-5,9-dihydro-1,3-dioxa-8-thia-5-aza-cyclohepta[*f*]inden-6-one (4x). IR (KBr, ν, cm-1): 3167, 3008, 1683, 1480, 1255, 828, 784 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.63 (s, 1H, NH), 7.79 (d, J = 7.6 Hz, 1H, ArH), 7.53 (q, J = 13.6 Hz, 2H, ArH), 7.47-7.43 (m, 1H, ArH), 6.69 (s, 1H, ArH), 6.07 (s, 1H, ArH), 6.01 (d, J = 5.6 Hz, 2H, OCH_2O), 5.91 (s, 1H, CH), 3.20 (d, J = 12.0 Hz, 1H, CH_2), 2.94 (d, J = 12.0 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 168.6, 147.0, 145.7, 134.7, 132.9, 131.5, 130.8, 130.1, 130.0, 127.6, 125.5, 106.1, 105.1, 101.8, 43.4, 31.0; HRMS (ESI) m/z: calc. for [M + Na]$^+$ $C_{16}H_{12}ClNO_3S$: 334.0299; found: 334.0294.

9-(2,4-Dichloro-phenyl)-5,9-dihydro-1,3-dioxa-8-thia-5-aza-cyclohepta[*f*]inden-6-one (4y). IR (KBr, ν, cm-1): 3178, 3078, 1682, 1586, 1292, 1151, 1038, 905, 809, 739, 695, 650 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 9.60 (s, 1H, NH), 7.78 (d, J = 8.4 Hz, 1H, ArH), 7.71 (s, 1H, ArH), 7.59 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, ArH), 6.68 (s, 1H, ArH), 6.16 (s, 1H, ArH), 6.03 (m, 2H, OCH_2O), 5.84 (s, 1H, CH), 3.18 (d, J = 12.0 Hz, 1H, CH_2), 2.96 (d, J = 12.0 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 168.6, 147.1, 145.8, 134.0, 133.8, 133.5, 132.1, 129.5, 127.8, 125.0, 106.4, 105.1, 101.8, 43.2, 30.9; HRMS (ESI) m/z: calc. for [M + Na]$^+$ $C_{16}H_{11}Cl_2NO_3S$: 389.9729; found: 389.9736.

2-(4-Chlorophenyl)-3-(4-methoxyphenyl)thiazolidin-4-one (5e). IR (KBr, ν, cm^{-1}): 3078, 1689, 1586, 1292, 1151, 1038, 905, 809, 739, 695, 650 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.41 (d, J = 8.4 Hz, 2H, ArH), 7.34 (d, J = 8.4 Hz, 2H, ArH), 7.17 (d, J = 8.8 Hz, 2H, ArH), 6.84 (d, J = 8.4 Hz, 2H, ArH), 6.41 (s, 1H, CH), 4.03 (dd, J_1 = 14.6 Hz, J_2 = 2.4 Hz, 1H, CH_2), 3.86 (d, J = 14.6 Hz, 1H, CH_2), 3.68 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6):170.2, 157.5, 139.3, 132.9, 130.1, 129.1, 128.6, 127.2, 1134.0, 62.9, 55.1, 32.5; HRMS (ESI) m/z: calc. for [M + Na]$^+$ $C_{16}H_{14}ClNO_2S$: 342.0326; found: 342.0333.

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12 tThe single-crystal growth was carried out in a mixed solvent of acetone and ethanol at room temperature. X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer (graphite monochromator, MoKa radiation k = 0.71073 Å). Crystal data for **4a**: Empirical formula C17 H17 N O S colorless, crystal dimensions 0.35 × 0.12 × 0.10 mm, orthorhombic pccn, space group Pccn, a = 14.4220(12), b = 25.714(3) (12), c = 7.9543 (10)Å, a = 90, b = 90, c = 90°,V = 2949.8(5) A^3, Mr = 283.38, Z = 8, Dc = 1.267 Mg m − 3, k = 0.71073 Å, l (Mo-Ka) = 0.214 mm-1, F(000)= 1200, S = 1.012, R1 = 0.0578, wR2 = 0.1029.