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A FACILE SYNTHESIS AND CHEMICAL PROPERTIES OF 3,4-DIHYDRO-2*H*-1,5,2-BENZO[*f*]DITHIAZEPIN-3-ONES WITH POTENTIAL ANTICANCER ACTIVITY

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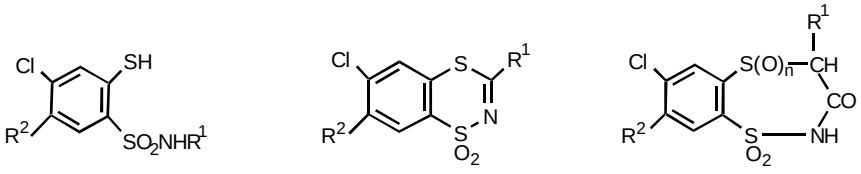
Abstract –The syntheses of 3,4-dihydro-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxides (**8-11**, **14**, **17-20**) and corresponding 1,1,5,5-tetraoxides (**12**, **13**) are described. Reactivity of these compounds in their alcoholysis, alkaline hydrolysis and alkylation is also reported. Evaluation performed at the US National Cancer Institute (Bethesda) revealed the *in vitro* antitumor activity of 7-chloro-3,4-dihydro-8-methyl-4-phenyl-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxide (**11**).

Arylsulfonamides represent a class of drugs with a well-established safety profile.[1] Currently there is intense interest in the discovery and development of novel arylsulfonamides for the treatment of cancer[2] and HIV infections.[3] As part of a broad investigation of structures containing 2-mercaptoarylsulfonamide moiety, a series of anticancer compounds[4] and potent inhibitors of HIV-1 integrase was discovered in our laboratories (MBSAs, Figure 1).[5] We also found that cyclic sulfonamides of type (**A**) possess interesting biological properties, particularly as anticancer agents.[6] This prompted us to investigate further the chemistry and biological activity of the related heterocyclic system (**B**) which may be considered "bridged" version of MBSAs (Figure 1).



MBSAs
2-mercaptobenzenesulfonamides

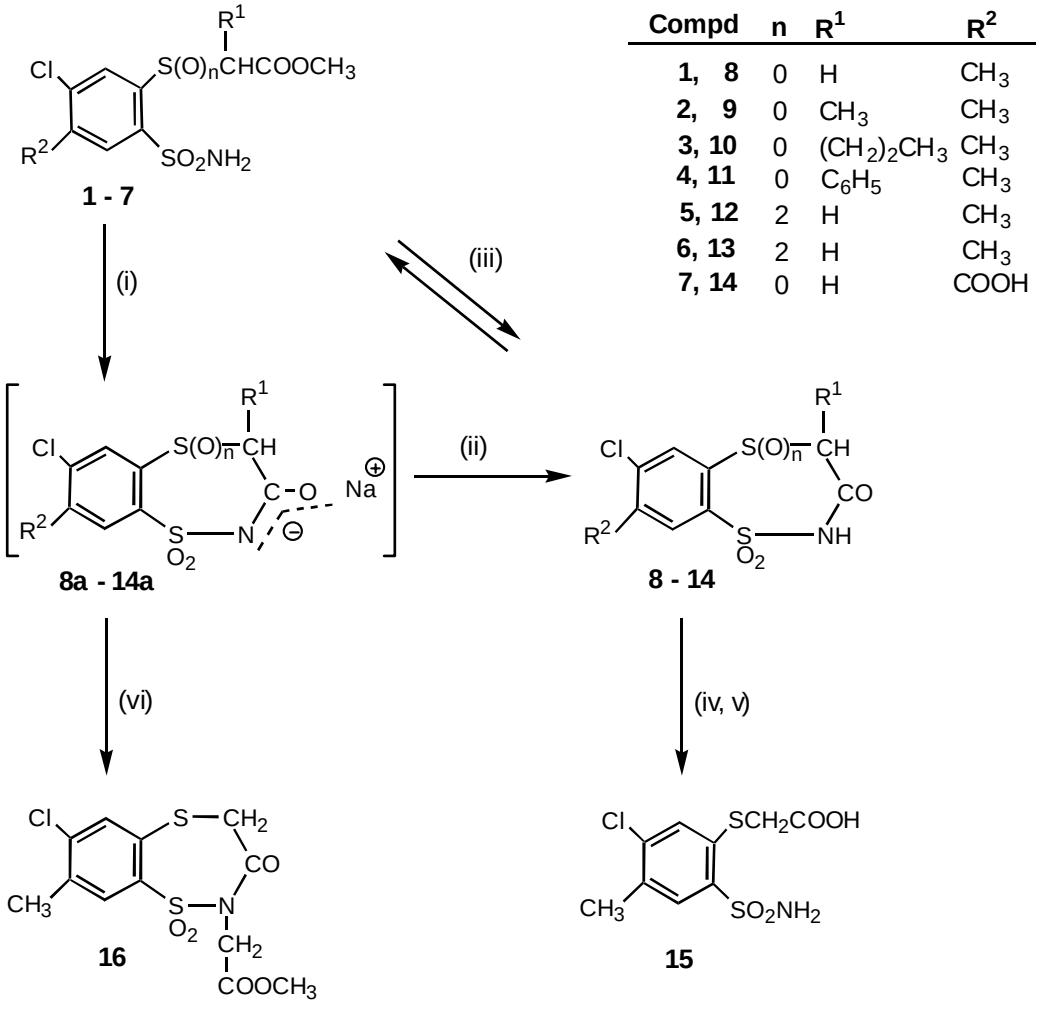
A

B

Figure 1

As outlined in Scheme 1, the 3,4-dihydro-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxides (**8-14**) were obtained in 42-74% yield starting from suitable 2-sulfamoylphenyl(thio or sulfonyl)alkanoates (**1-7**),[7-9] based on the cyclocondensation carried out in methanol in the presence of sodium methoxide. It should be mentioned, that the compound (**8**) has been previously isolated from the reaction of **1** with biguanide in 17% yield.[7]

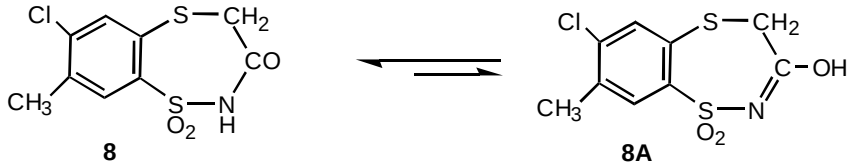
Compounds (**8-14**) containing a lactam group proved to be susceptible to base-catalysed hydrolysis. Thus, heating of **8** in 1% aqueous NaOH at 90 °C for 3 h, followed by treatment with 5% hydrochloric acid, furnished the carboxylic acid derivative (**15**). Moreover, the compounds (**8-14**) were found to undergo methanolysis upon prolonged heating in boiling methanol. The reaction is reversible and, depending on the nature of substituents R^1 and R^2, reaches a state of equilibrium within 10-20 h. For example, the alcoholysis of **8** reaches the ring-chain equilibrium after 10 h, and the proportion of product (**1**) to the starting material was about 53%.



Compd	n	R^1	R^2
1, 8	0	H	CH_3
2, 9	0	CH_3	CH_3
3, 10	0	$(CH_2)_2CH_3$	CH_3
4, 11	0	C_6H_5	CH_3
5, 12	2	H	CH_3
6, 13	2	H	CH_3
7, 14	0	H	COOH

Scheme 1. (i) CH_3ONa / CH_3OH / reflux; (ii) HCl / H_2O; (iii) CH_3OH / reflux; (iv) 1% NaOH / H_2O / 90 °C; (v) 5% HCl; (vi) $ClCH_2COOCH_3$ / toluene / DMF / reflux.

Although the IR spectra run in KBr of the secondary lactams (**8-14**) exhibited characteristic C=O vibrations in the range of 1690-1730 cm^{-1} and no keto-enol tautomerism was observed in solution (S-$C\underline{H}_2$ signals in ^1H NMR spectra), the probable lactam-lactim tautomerism shown in Scheme 2 was studied by means of *ab initio* MO calculations.[10] Comparison of the calculated energies of the lactam (**8**) and lactim (**8A**) confirmed that in vapor phase **8** is more stable by 8.36 kcal/mol, and therefore, the equilibrium lies well to the side of the lactam form.



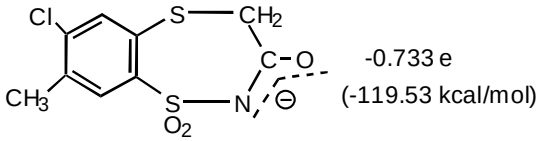
8 **8A**

E = −1878.9507225 hartree E = −1878.9373878 hartree

ΔE = −0.0133347 hartree = −8.36 kcal/mol

Scheme 2

Deprotonation of the lactam (**8**) with sodium methoxide in methanol and successive alkylation of the resulting ambident nucleophile (**8a**) with methyl chloroacetate in the toluene-DMF medium gave the tertiary lactam (**16**) (Scheme 1). The reaction was regioselective since no *O*-alkylation side reaction was observed. In order to confirm the preferential susceptibility of the nitrogen atom to the electrophilic attack, the distribution of electron density in **8a** was computed at *ab initio* level by direct Hartree-Fock method.[10] The formal charges and values of the electrostatic potential on the electron density isosurface corresponding to the van der Waals surface are shown in Figure 2. For the two nucleophilic sites in **8a** the following charges were calculated: −1.121 e (the nitrogen atom) and −0.733 e (the oxygen atom), while the values of electrostatic potential were −138.93 kcal/mol and −119.53 kcal/mol respectively. In this viewpoint, the electrophile can easily approach the former site, giving rise to the formation of the product (**16**).

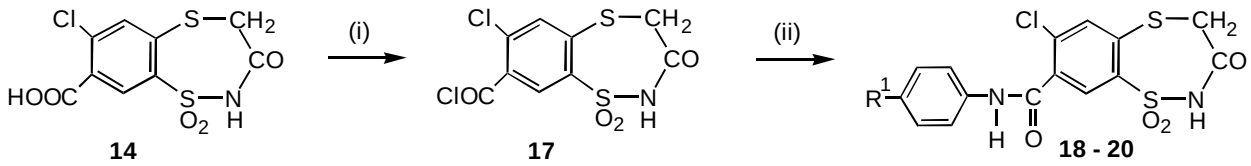


8a

Figure 2

As depicted in Scheme 3, the obtained acid (**14**) was converted into the acid chloride (**17**), which in turn underwent aminolysis to the corresponding amides (**18-20**). The structures of the compounds (**8-14**) and

(**16-20**) were confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectra as well as elemental analyses (see experimental section).



Compd	R^1
18	H
19	Cl
20	CH_3

Scheme 3. (i) $SOCl_2$ / THF / reflux; (ii) 4-$R^1C_6H_4NH_2$ / THF / rt.

The compounds obtained were tested at the US National Cancer Institute (Bethesda) for their *in vitro* anticancer activity. The antitumor activity was evaluated using a total of 60 human cell lines derived from nine different cancer types (lung, colon, melanoma, prostate, breast, renal, ovarian, CNS, and leukemia). The compounds were tested in a broad concentration range (10^{-4} M – 10^{-8} M). The response parameters GI_{50}, TGI, and LC_{50} are interpolated values representing the concentration at which the Percentage Growth is +50, 0, and –50 respectively and were calculated from dose-response curves.[11] It was found that compound (**11**) was the only cyclic analogue of MBSAs which showed a moderate activity in some tumor cell lines. The data presented in Table 1 display the highest activity of **11** against the melanoma cell lines SK-MEL-2 with the mean graph midpoints values of $\log_{10}$ GI_{50}, $\log_{10}$ TGI, and $\log_{10}$ LC_{50} equal to –4.76, –4.48, –4.20, respectively.

Table 1. *In vitro* anticancer data for compound (**11**)

Panel Cell Line	**GI_{50}** μM	**TGI** μM	**LC_{50}** μM
Leukemia			
HL-60 (TB)	29.3	58.9	*
MOLT-4	26.0	60.7	*
SR	27.6	73.8	*
Non-Small Cell Lung Cancer			
NCI-H23	24.4	56.2	*
NCI-H522	25.9	59.7	*
Colon Cancer			
HCC-2998	30.3	70.8	*
HCT-116	20.5	45.6	*
HCT-15	25.0	64.0	*
CNS Cancer			
SF-539	26.7	73.3	*
CNS Cancer			
U251	23.0	60.5	*
Melanoma Cancer			
SK-MEL-2	17.3	32.9	62.8
SK-MEL-5	21.6	48.8	*
Ovarian Cancer			
OVCAR-3	21.6	53.4	*
Renal Cancer			
A498	26.9	75.5	*
UO-31	28.1	75.1	*
Prostate Cancer			
PC-3	26.4	70.8	*
Breast Cancer			
HS 578T	27.5	59.4	*

The response parameters **GI_{50}**, **TGI**, and **LC_{50}** are interpolated values of the concentrations at which the Percentage Growth is +50, 0, and –50, respectively. *The values of **LC_{50}** > 100 μM.

In conclusion, we have presented facile syntheses of 3,4-dihydro-2*H*-1,5,2-benzo[*f*]dithiazepin-3-ones, which, as exemplified by **8**, exist predominantly in the lactam form. The *in vitro* evaluation showed anticancer activity of the compound (**11**).

EXPERIMENTAL

Melting points were determined on a Bűchi 535 apparatus and are uncorrected. IR (KBr pellets) spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer, ν values in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (200 MHz). Chemical shifts were reported in ppm (δ) downfield from Me_4Si. The starting methyl 5-chloro-4-R^2-2-sulfamoylphenyl(thio or sulfonyl)alkanoates (**1-7**) were obtained by the methods described previously.[7-9]

General procedure for the preparation of 4-R^1-7-chloro-3,4-dihydro-8-methyl-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-di(or 1,1,5,5-tetra)oxides (8-13). A mixture of the appropriate ester (**1-6**) (16 mmol) and sodium methoxide (0.86 g, 16 mmol) in anhydrous methanol (60 mL) was refluxed for 20 h. Then, solvent was partly removed under reduced pressure. The precipitate thus obtained was collected by filtration, washed with methanol (6 mL) and dried. The sodium salt (**8a-13a**) was dissolved in water (300-700 mL), filtered off with charcoal added and the pH of filtrate was adjusted to 3 with 1% hydrochloric acid. After stirring at rt for 2 h, the crude product (**8-13**) was separated by suction, washed with water (15 mL), dried and purified by recrystallization from suitable solvent.

7-Chloro-3,4-dihydro-8-methyl-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxide (**8**): mp 223-225 °C (acetic acid) (lit.,[7] mp 223-225 °C); yield 74%. IR: 3125, 3025 (NH), 1700 (CO), 1350, 1170 (SO_2). ^1H NMR (DMSO-d_6): 2.35 (s, 3H, 8-CH_3); 4.31 (s, 2H, SCH_2); 7.69 (s, 1H, 6-H); 7.92 (s, 1H, 9-H). ^{13}C NMR (DMSO-d_6): 18.88 (8-CH_3); 32.82 (SCH_2); 128.69, 129.24, 132.58, 133.78, 134.23, 138.27 (6 C arom.); 166.48 (CO). *Anal*. Calcd for $C_9H_8NO_3ClS_2$: C, 38.92; H, 2.90; N, 5.04. Found: C, 38.69; H, 2.61; N, 5.10.

7-Chloro-3,4-dihydro-4,8-dimethyl-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxide (**9**): mp 281-282 °C (methanol); yield 70%. IR: 3120, 3035 (NH), 1690 (CO), 1345, 1165 (SO_2). ^1H NMR (DMSO-d_6): 1.40 (d, J = 6.8 Hz, 3H, CHC<u>H</u>$_3$); 2.36 (s, 3H, 8-CH_3); 5.23 (q, J = 6.8 Hz, 1H, SC<u>H</u>CH_3); 7.68 (s, 1H, 6-H); 7.95 (s, 1H, 9-H). ^{13}C NMR (DMSO-d_6): 13.97 (CH_3); 18.87 (8-CH_3); 38.05 (SCH); 128.19, 129.03, 132.63, 133.86, 133.96, 138.29 (6 C arom.); 168.73 (CO). *Anal*. Calcd for $C_{10}H_{10}NO_3ClS_2$: C, 41.16; H, 3.45; N, 4.80. Found: C, 40.97; H, 3.16; N, 4.96.

7-Chloro-3,4-dihydro-8-methyl-4-propyl-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxide (**10**): mp 158-160 °C (methanol); yield 42%. IR: 3135, 3065 (NH), 1695 (CO), 1350, 1165 (SO_2). ^1H NMR (DMSO-d_6): 0.91 (t, J = 7.0 Hz, 3H, CH_2C<u>H</u>$_3$); 1.32-2.11 (m, 4H, CH_2CH_2); 2.36 (s, 3H, CH_3); 5.10 (t, J = 6.7 Hz,

1H, SC<u>H</u>CH_2); 7.69 (s, 1H, 6-H); 7.96 (s, 1H, 9-H). *Anal*. Calcd for $C_{12}H_{14}NO_3ClS_2$: C, 45.06; H, 4.41; N, 4.38. Found: C, 45.35; H, 4.36; N, 4.26.

7-Chloro-3,4-dihydro-8-methyl-4-phenyl-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxide (**11**): mp 187-190 ^oC (methanol); yield 67%. IR: 3130, 3050 (NH), 1695 (CO), 1360, 1170 (SO_2). ^1H NMR (DMSO-d_6): 2.39 (s, 3H, CH_3); 6.31 (s, 1H, SCH); 7.38-7.51 (m, 5H, ArH); 7.73 (s, 1H, 6-H); 8.01 (s, 1H, 9-H). *Anal*. Calcd for $C_{15}H_{12}NO_3ClS_2$: C, 50.92; H, 3.42; N, 3.98. Found: C, 50.54; H, 3.13; N, 3.77.

7-Chloro-3,4-dihydro-8-methyl-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1,5,5-tetraoxide (**12**): mp 195-197 ^oC (toluene); yield 45%. IR: 3260 (NH), 1730 (CO), 1350, 1315, 1175, 1140 (SO_2). ^1H NMR (DMSO-d_6): 2.50 (s, 3H, CH_3); 5.26 (s, 2H, SO_2CH_2); 8.07 (s, 1H, 6-H); 8.09 (s, 1H, 9-H). *Anal*. Calcd for $C_9H_8NO_5ClS_2$: C, 34.93; H, 2.60; N, 4.52. Found: C, 34.64; H, 2.31; N, 4.49.

7-Chloro-3,4-dihydro-4,8-dimethyl-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1,5,5-tetraoxide (**13**): mp 237-240 ^oC (toluene); yield 60%. IR: 3135, 3065 (NH), 1710 (CO), 1350, 1315, 1170, 1140 (SO_2). ^1H NMR (DMSO-d_6): 1.55 (d, J = 6.8 Hz, 3H, $SO_2CHC\underline{H}_3$); 2.50 (s, 3H, CH_3); 5.91 (q, J = 6.8 Hz, 1H, $SO_2C\underline{H}CH_3$); 8.09 (s, 1H, 6-H); 8.13 (s, 1H, 9-H). *Anal*. Calcd for $C_{10}H_{10}NO_5ClS_2$: C, 37.10; H, 3.11; N, 4.33. Found: C, 36.84; H, 2.92; N, 4.59.

7-Chloro-1,1,3-trioxo-3,4-dihydro-2*H*-1,5,2-benzo[*f*]dithiazepin-8-carboxylic acid (14). A solution of ester (**6**) (5.44 g, 16 mmol) and solution of sodium methoxide (1.73 g, 32 mmol) in anhydrous methanol (70 mL) was refluxed for 20 h. Then the solvent was distilled off with rotary evaporator. The dry residue was dissolved in water (150 mL), filtered off with charcoal added and the pH of the filtrate was adjusted to 2 with 1% hydrochloric acid. After stirring for 2 h, the precipitate was collected by filtration, washed with water (15 mL), dried and purified by recrystallization from methanol to give **14** (3.6 g, 73%), mp 295-297 ^oC. IR: 3200-2490 (3120, 3090, 3020, 3010, 2850, 2785, 2640 NH, CH_2, OH), 1710 (CO lactam), 1695 (CO acid), 1360, 1170 (SO_2). ^1H NMR (DMSO-d_6): 4.40 (s, 2H, SCH_2); 7.87 (s, 1H, 6-H); 8.34 (s, 1H, 9-H). *Anal*. Calcd for $C_9H_6NO_5ClS_2$: C, 35.13; H, 1.97; N, 4.55. Found: C, 34.97; H, 1.69; N, 4.40.

7-Chloro-3,4-dihydro-8-methyl-*N*-(methoxycarbonyl)methyl-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxide (15). A mixture of **8** (2 g, 7 mmol) and sodium methoxide (0.38 g, 7 mmol) in anhydrous methanol (30 mL) was refluxed for 2 h, then allowed to cool. The precipitate was filtered off, washed with methanol and dried to give 1.7 g (81%) of the sodium salt (**8a**).

To a stirred suspension of **8a** (1.7 g, 5.7 mmol) in dry toluene (65 mL) and dry DMF (40 mL), methyl chloroacetate (0.68 g, 6.3 mmol) was added. The suspension was refluxed for 20 h, then solvent was distilled off under reduced pressure. The dry residue was treated with water (200 mL) and the resulting mixture was neutralized to pH 7.5 with 5% aqueous Na_2CO_3 and stirred at rt for 30 min. The product that precipitated was collected by filtration, washed with water, dried and purified by recrystallization from

methanol to give **15** (1.1 g, 55%), mp 96-99 °C. IR: 2965, 2920, 2850 (CH_2, CH_3), 1755 (CO), 1710 (CO lactam), 1360, 1170 (SO_2). ^{1}H NMR (Acetone-d_6): 2.42 (s, 3H, 8-CH_3); 3.60 (s, 3H, OCH_3); 4.59 (s, 4H, SCH_2 and NCH_2); 7.58 (s, 1H, 6-H); 7.91 (s, 1H, 9-H). ^{13}C NMR (Acetone-d_6): 19.79 (8-CH_3); 34.87 (SCH_2); 47.61 (OCH_3); 53.07 (NCH_2); 129.55, 129.87, 131.42, 134.91, 135.04, 140.25 (6 C arom.); 167.01 (CO); 168.81 (CO lactam). *Anal*. Calcd for $C_{12}H_{12}NO_5ClS_2$: C, 41.20; H, 3.46; N, 4.00. Found: C, 41.06; H, 3.24; N, 3.92.

Hydrolysis of 1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxide (8). A suspension of **8** (0.5 g, 2 mmol) in 1% aqueous NaOH (30 mL) was stirred at 90 °C for 3 h. The resulting solution was acidified with 5% hydrochloric acid to pH 2. The precipitate was filtered off, washed with water and dried to give (5-chloro-4-methyl-2-sulfamoylphenylthio)acetic acid (**16**) (0.4 g, 75%) (lit.,[9] mp 179-181 °C).

Alcoholysis of 1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxide (8). A suspension of **8** (0.5 g, 2 mmol) in anhydrous methanol (15 mL) was refluxed for 10 h. Then, the solvent was distilled off under reduced pressure and the dry residue was treated with water (60 mL). The mixture thus obtained was neutralized to pH 7.5 with 5% aqueous Na_2CO_3 and filtered off (filtrate **A**'' was stored for further workup) to give methyl (5-chloro-4-methyl-2-sulfamoylphenylthio)acetate (**1**) (0.3 g, 53%) (lit.,[9] mp 138-139 °C).

After separation of **1**, the filtrate **A**'' was acidified with 1% hydrochloric acid to pH 3 to afford the starting material (**8**).

7-Chloro-1,1,3-trioxo-3,4-dihydro-2*H*-1,5,2-benzo[*f*]dithiazepin-8-carbonyl chloride (17). A solution of the acid derivative (**14**) (30.77 g, 100 mmol) and thionyl chloride (11 mL, 150 mmol) in THF (300 mL) was refluxed for 4 h. The solvent and excess of thionyl chloride were evaporated under vacum and coevaporated with toluene (3 x 50 mL) and benzene (3 x 50 mL). The dry residue was treated with benzene (150 mL) to give **17** which was collected by filtration and dried. Yield: 25.5 g, (78%), mp 170-173 °C. IR: 3140-3000 (3135, 3080, 3010 NH), 1780 (CO), 1720 (CO lactam), 1350, 1170 (SO_2). ^{1}H NMR (Acetone-d_6): 4.53 (s, 2H, SCH_2); 7.87 (s, 1H, 6-H); 8.78 (s, 1H, 9-H). *Anal*. Calcd for $C_9H_5NO_4Cl_2S_2$: C, 33.14; H, 1.54; N, 4.29. Found: C, 33.27; H, 1.31; N, 4.39.

General procedure for the preparation of 7-chloro-3,4-dihydro-8-(4-R^1-phenylcarbamoyl)-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxides (18-20). To a solution of the chloride (**17**) (3.26 g, 10 mmol) in THF (20 mL) a solution of the appropriate amine (20 mmol) in THF (20 mL) was added dropwise with stirring while the temperature was maintained below 15 °C with external cooling. Stirring was continued at rt for 24 h, and then, the solvent was distilled off and a dry residue was suspended in 0.05% aqueous HCl (200 mL). The resulting mixture was stirred for 2 h and the crude product was filtered off and purified by crystallization from acetic acid.

According to the above procedure the following compounds were obtained:

7-Chloro-3,4-dihydro-8-(phenylcarbamoyl)-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxide (**18**): mp 279-281 ^{o}C; yield 80%. IR: 3275, 3255 (NH), 1710 (CO lactam), 1650 (CO), 1345, 1170 (SO_2). ^{1}H NMR (DMSO-d_6): 4.40 (s, 2H, SCH_2); 7.09-7.92 (m, 5H, ArH); 7.98 (s, 1H, 6-H); 8.06 (s, 1H, 9-H); 10.65 (s, 1H, CONH). *Anal*. Calcd for $C_{15}H_{11}N_2O_4ClS_2$: C, 47.06; H, 2.90; N, 7.32. Found: C, 46.83; H, 2.64; N, 7.07.

7-Chloro-3,4-dihydro-8-(4-chlorophenylcarbamoyl)-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxide (**19**): mp 296-298 ^{o}C; yield 69%. IR: 3280, 3250 (NH), 1710 (CO lactam), 1650 (CO), 1345, 1170 (SO_2). ^{1}H NMR (DMSO-d_6): 4.40 (s, 2H, SCH_2); 7.41-7.73 (m, 4H, ArH); 7.93 (s, 1H, 6-H); 8.09 (s, 1H, 9-H); 10.78 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): 33.31 (SCH_2); 121.61, 127.90, 128.09, 129.06, 129.97, 133.45, 134.39, 135.11, 137.72, 137.99 (12 C arom.); 163.0 (CO); 166.43 (CO lactam). *Anal*. Calcd for $C_{15}H_{10}N_2O_4Cl_2S_2$: C, 43.17; H, 2.41; N, 6.71. Found: C, 42.91; H, 2.31; N, 6.66.

7-Chloro-3,4-dihydro-8-(4-methylphenylcarbamoyl)-2*H*-1,5,2-benzo[*f*]dithiazepin-3-one 1,1-dioxide (**20**) mp 291-293 ^{o}C; yield 60%. IR: 3280, 3240 (NH), 1710 (CO lactam), 1650 (CO), 1340, 1170 (SO_2). ^{1}H NMR (DMSO-d_6): 2.28 (s, 3H, 4-CH_3); 4.40 (s, 2H, SCH_2); 7.15-7.58 (m, 4H, ArH); 7.91 (s, 1H, 6-H); 8.04 (s, 1H, 9-H); 10.78 (s, 1H, CONH). *Anal*. Calcd for $C_{16}H_{13}N_2O_4ClS_2$: C, 48.42; H, 3.30; N, 7.06. Found: C, 48.14; H, 3.16; N, 6.84.

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