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Synthesis of new indeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-diones as potential antitumor agents

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ABSTRACT

Novel racemic indeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-diones **3–29** were obtained regioselectivily from the reaction of 5,6-diamino-3,4-dihydropyrimidin-4-ones **1** and 2-arylideneindandiones **2** as reagents. These compounds have been evaluated at the US National Cancer Institute (NCI) for their ability to inhibit approximately 60 different human tumor cell lines, where **5** and **6** presented remarkable activity against 57 and 48 cancer cell lines, respectively, with the most important GI_{50} values ranging from 0.49 to 1.46 μM, in vitro assay.

1. Introduction

The 1,4-diazepine system is considered today a relevant pharmacophore in a wide range of biological activities, with special examples in the well-known benzodiazepines extensively studied synthetically and pharmacologically.[1,2] Recently, the syntheses of analogues possessing heterocycles or even more complex fused systems such as a pyrimidine ring attracted attention since they showed to be promising pharmacophores,[3–5] and some of them found to be specially active against different cancer types, as described in one of our previous papers.[6]

On the other hand, previous works have shown that fusing an indeno moiety to the main core could enhance the pharmacologic potential of a target molecule, there have been found derivatives with 1,3-indandione moiety as potential drugs in a wide range of bioactivities including antioxidants,[7] anticoagulants,[8] antibacterials,[9–12] and CDK (Cyclin-Dependent Kinases) inhibitors.[13,14] Considering this information, the fusion of pyrimidodiazepine core and indeno moiety becomes an interesting synthetic strategy to search pharmacologically target molecules.

In this work, targeting the preparation of such indeno fused bioactive heterocycles, we report the regioselective synthesis and cytotoxic activities of 6-aryl-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-diones **3–29**.

The compounds were evaluated for their antitumoral activity against approximately 60 different human tumor cell lines, representing leukemia, melanoma, and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney.

2. Results and discussion

2.1. Chemistry

Heating of 5,6-diamino-2-methylthiopyrimidin-4(3*H*)-one (**1a**) or 5,6-diamino-2-methoxypyrimidin-4(3*H*)-one (**1b**) or the corresponding 3-methyl derivatives of both (**1c**,**d**) with equimolar quantities of 2-arylideneindandiones **2a–h** in ethanol in the presence of catalytic amounts of acetic acid afforded the desired structures **3–29** in good yields (see Scheme 1).

The synthesis of all compounds proceeded regioselectively, and most of the derivatives were obtained as amorphous solids with the exception of compounds **4**, **22**, and **27b**, isolated as crystals suitable for X-ray diffraction analysis, which, combined with NMR studies and elemental analysis provided the full characterization of such compounds.

In the X-ray crystal structures of compounds **4** and **22** (structures (A) and (B) in Figure 1, respectively), 1,4-diazepine ring exhibits a boat-like conformation with the aryl ring out of the

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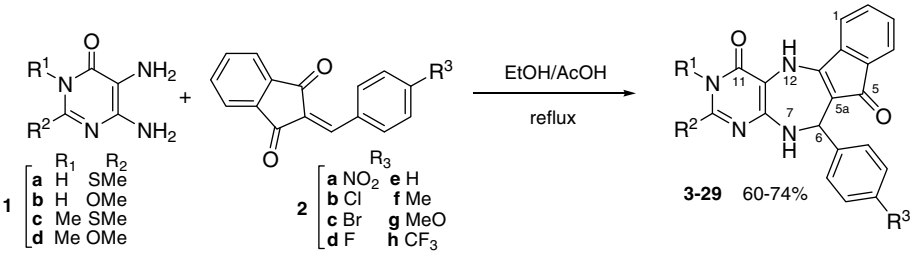


Compound	R^1	R^2	R^3	Compound	R^1	R^2	R^3
3	H	SCH_3	Cl	**17**	CH_3	SCH_3	Cl
4	H	SCH_3	Br	**18**	CH_3	SCH_3	Br
5	H	SCH_3	F	**19**	CH_3	SCH_3	F
6	H	SCH_3	H	**20**	CH_3	SCH_3	H
7	H	SCH_3	CH_3	**21**	CH_3	SCH_3	CH_3
8	H	SCH_3	OCH_3	**22**	CH_3	SCH_3	OCH_3
9	H	SCH_3	CF_3	**23**	CH_3	SCH_3	CF_3
10	H	OCH_3	NO_2	**24**	CH_3	OCH_3	NO_2
11	H	OCH_3	Cl	**25**	CH_3	OCH_3	Cl
12	H	OCH_3	Br	**26**	CH_3	OCH_3	Br
13	H	OCH_3	H	**27a,b**	CH_3	OCH_3	H
14	H	OCH_3	CH_3	**28**	CH_3	OCH_3	CH_3
15	H	OCH_3	OCH_3	**29**	CH_3	OCH_3	OCH_3
16	CH_3	SCH_3	NO_2				

Scheme 1. Synthesis of novel Indeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-diones **3–29**.

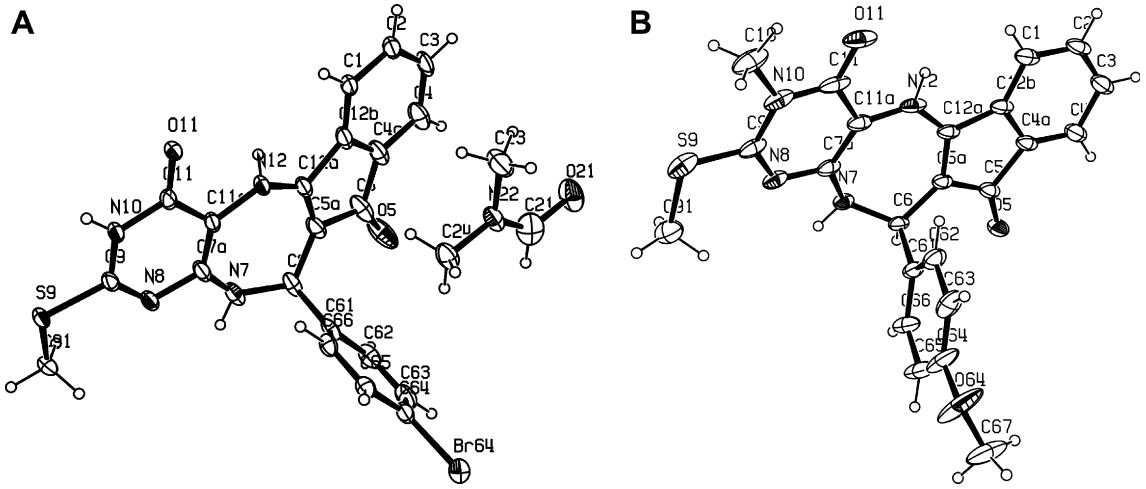


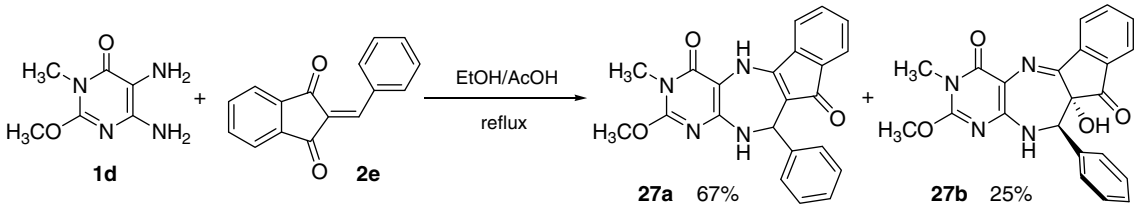
Figure 1. ORTEP drawing of compound **4**···DMF (A) and **22** (B).

plane. Such a conformation is slightly distorted by the fused indeno moiety, but according to the expected behavior of 1,4-diazepine ring as reported in some studies.[15,16]

In the particular case of compound **27a**, an additional unexpected product (denoted as **27b**) was isolated in a moderate yield compared to the main product (see Scheme 2), and was characterized as a 5a-hydroxy derivative formed probably from compound **27a** by protonation of the carbonyl oxygen belonging to the indeno moiety, followed by addition of a water molecule to C-5a. Then, tautomerization of carbonyl group and addition of a proton to C-12a with further oxidation generated the C=N group, yielded the structure **27b**.

The structure of derivative **27b** was unambiguously determined by X-ray diffraction analysis (see Fig. 2).

The X-ray crystal structure of derivative **27b** (Fig. 2) shows that the introduction of the hydroxyl group caused an inversion of the aryl group in the conformation described above for compounds **4** and **22**. In this particular case, the boat-like conformation remains but is more pronounced with the aryl ring entering the plane and the hydroxyl group out of the plane. This fact could be expected,



Scheme 2. Synthesis of compound **27** and the hydroxy derivative **27b**.

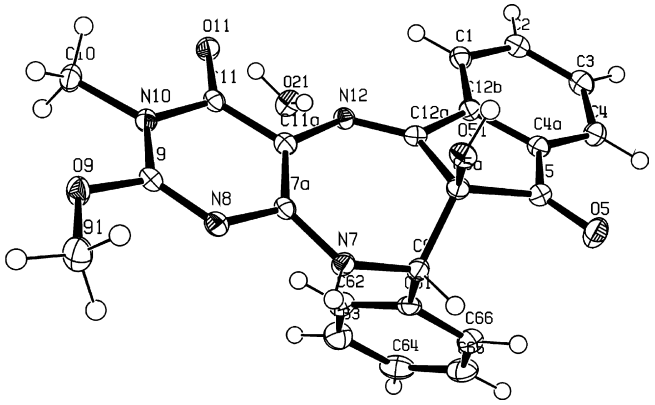


Figure 2. ORTEP drawing of compound **27b**···H_2O.

probably due to the difference in planarity of indeno moiety with and without the α,β-unsaturation for the studied structures, as well as its contribution to the conformation of the main diazepine core.

The high regioselectivity observed in all the reactions could be explained as a matter of the major nucleophilicity of the amino group on C-5 of *ortho*-diamines **1**, enhanced by the electronic effect of the pyrimidine ring and the groups attached to it.[17,18] Therefore, condensation between such amino group and one of the carbonyl groups of 2-arylideneindandiones **2** can be followed by a Michael's addition of the less nucleophilic amino group (amino group on C-6) to the C=C double bond.

The IR spectra for all products show typical bands between 3210 and 3381 cm^{-1} (NH groups) and 1524–1690 cm^{-1} (C=O, C=N and C=C groups). Nitro-derivatives (**10**, **16**, and **24**), show characteristic bands at 1338–1340 and 1521–1531 cm^{-1} due to NO_2 asymmetric and symmetric stretching vibrations, respectively.

The structure elucidations of compounds **3–29** were based on the spectral data (^{1}H NMR, ^{13}C NMR, and mass spectrometry) summarized in the experimental section. In the ^{1}H NMR spectra for all compounds, there are three characteristic protons of the 1,4-diazepine ring. Proton H-6 in the stereogenic center appears as a doublet at δ = 4.99–5.70 ppm with a coupling constant of ^3J = 4.5–4.9 Hz (except for the particularly high value of **27b** with ^3J = 6.6 Hz), due to the vicinal position of proton NH-7 observed as a doublet as well at δ = 7.13–8.98 ppm, while proton NH-12 does not lead to any coupling appearing as singlet at δ = 7.93–10.54 ppm. Pyrimidine proton NH-10 of derivatives **3–15** is displayed as a singlet at δ = 9.95–12.78 ppm. Compound **27b** presents the analogue signals of diazepine ring, except for N-12 which in this case belongs to C=N group and 5a-OH which appears as a singlet at δ = 6.49 ppm.

Analysis of ^{13}C, DEPT-135, and two-dimensional heteronuclear NMR spectra provided the final structural elucidation of compounds **3–29**. So, the signal for C-6 is in the range δ 52.9–55.6 ppm, whereas the signal of C-5a and C-12a is displayed at δ 104.4–107.2 ppm and δ = 152.4–153.0 ppm, respectively. Quaternary carbon C-4a presents a peak at δ 100.0–104.6 ppm while signals for C-9a are displayed between δ 142.7–149.3 ppm. This great difference in the chemical shifts of such carbons can be taken as a hint for a push–pull substituted C=C double bond in structures **3–29**.

Finally, ^{13}C NMR, DEPT-135, and two-dimensional heteronuclear NMR spectra provided the final structural elucidation of derivatives **3–29**. Mass spectra of all compounds exhibit well-defined molecular ions with some particular fragmentation patterns such as the loss of the fused indeno moiety ($M^{+\cdot}$-128, $M^{+\cdot}$-157), CO ($M^{+\cdot}$-28), aryl group, and Ar-C≡N. The latter fragmentation occurs by a cleavage on C–C bond in β position to diazepine NH (type-B homolytic process) followed by a C–N scission (type-A_5 heterolytic process), which generates a constant and stable radical.[19]

2.2. Anticancer activity

The two-stage screening process started with the evaluation of seven compounds (**5**, **6**, **8**, **20**, **22**, **27**, and **29**) selected by NCI, against the 60 cell lines at a single dose of 1.0 μM. The output from the single dose screen was reported as a mean graph available for analysis by the COMPARE program. The results of the primary assay showed that compounds **8**, **20**, **22**, **27**, and **29** were essentially inactive, while compounds **5** and **6** were active (Table 1).

Therefore, a secondary screening was performed, in order to determine their cytostatic activity, against the 60 cell lines panel representing leukemia, melanoma, and cancers of lung, colon, brain, ovary, breast, prostate, and kidney. The compounds were evaluated at five concentration levels (100, 10, 1.0, 0.1, and 0.01 μM). The test consisted of a 48 h continuous drug exposure protocol using sulforhodamide B (SRB) protein assay to estimate cell growth. Details of this evaluation method, and the complementary information related with the activity pattern over all cell lines, have been published.[20–22] Table 2 showed that compound **5** displayed the most remarkable activity against 57 human tumor cell lines, SNB-75 (CNS) and MDA-MB-435 (breast cancer) being the most sensitive strains (GI_{50}: 1.46 and 1.65 μM, respectively, and LC_{50} > 100 μM for both). In a similar way to previous derivative, compound **6** (active against 48 human tumor cell lines) was found especially effective against the cell line MDA-MB-435 of breast cancer panel exhibiting a considerably better GI_{50} of 0.49 μM (LC_{50} > 100 μM), as well as a GI_{50} of 1.41 μM (LC_{50} > 100 μM) for cell line NCI-H522 of non-small cell lung cancer panel. In summary, derivatives **5** and **6** show significant activities (Table 2), with GI_{50} ranges from 1.46–49.3 μM and 0.49–22.0 μM, respectively; against other cell lines from the different panels of cancer types and as discussed above, they share activity against cell line MDA-MB-435 of breast cancer panel. The cytotoxicities associated with compounds **5** and **6**, and measured as LC_{50} goes from 35.1 μM to >100 μM, for all cell lines, indicating a low toxicity of the title compounds for normal human cell lines as required for potential antitumor agents.

3. Conclusion

The synthesis and cytotoxic activity of novel 6-aryl-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-diones have been performed. Results showed that among the seven indenopyrimidodiazepines evaluated, derivatives **5** and **6** exhibited the highest activities against different cancer cell lines with remarkable values. These compounds could be lead compounds for synthesizing new series of analogues of 1,4-diazepines with potential antitumor activities.

4. Experimental

Melting points were determined in a Buchi Melting Point Apparatus and are uncorrected. The ^{1}H- and ^{13}C NMR spectra

Table 1
Results of primary anticancer assay for seven compounds selected by the NCI

Compound	Activity[a]
5	A
6	A
8	NA
20	NA
22	NA
27a	NA
29	NA

[a] Activity denoted as: A = active; NA = not active.

Table 2
In vitro testing results expressed as growth inhibition of cancer cell lines for compounds **5** and **6**[a]

Compound	Number of cell lines			Most sensitive cell lines (GI_{50} < 20 μM)			
	Investigated	Giving positive GI_{50} GI_{50}[b] (μM)		Panel	Cell line	GI_{50}[b] (μM)	LC_{50}[c] (μM)
		No	Range				
5	59	59	1.46–49.3	Leukemia	CCRF-CEM	8.16	>100
					HL-60 (TB)	6.54	>100
					K-562	4.05	>100
					MOLT-4	19.5	>100
					RPMI-8226	4.20	>100
					SR	6.31	>100
				Non-small cell	A549/ATCC	12.6	>100
					EKVX	18.2	>100
				Lung cancer	HOP-62	11.9	95.6
					HOP-92	9.52	>100
					NCI-H226	15.3	>100
					NCI-H23	13.5	>100
					NCI-H322M	13.9	>100
					NCI-H460	5.10	>100
					NCI-H522	3.17	>100
				Colon cancer	COLO 205	13.0	>100
					HCC-2998	12.2	76.1
					HCT-116	7.23	44.7
					HCT-15	4.57	>100
					HT29	3.36	35.1
					KM12	3.77	39.5
					SW-620	4.48	>100
				CNS cancer	SF-268	12.7	>100
					SF-295	3.67	>100
					SF-539	8.90	92.0
					SNB-19	15.9	>100
					SNB-75	1.46	>100
					U251	5.43	48.6
				Melanoma	LOX IMVI	8.78	95.2
					MALME-3M	19.6	>100
					M14	6.29	>100
					SK-MEL-28	9.03	>100
					SK-MEL-5	6.13	>100
					UACC-62	3.04	>100
				Ovarian cancer	IGROV1	11.3	>100
					OVCAR-3	3.38	61.8
					OVCAR-4	15.4	>100
					OVCAR-5	17.7	95.6
					OVCAR-8	13.1	95.2
					SK-OV-3	14.1	>100
				Renal cancer	786-0	12.4	60.4
					A498	4.88	57.7
					ACHN	11.6	>100
					CAKI-1	3.30	>100
					RXF 393	14.5	92.8
					TK-10	12.9	>100
					UO-31	16.3	>100
				Prostate cancer	PC-3	7.72	>100
					DU-145	16.2	>100
				Breast cancer	MCF7	5.18	>100
					NCI/ADR-RES	6.42	>100
					MDA-MB-231/ATCC	12.6	>100
					HS 578T	5.85	>100
					MDA-MB-435	1.65	>100
					T-47D	14.2	>100
					BT-549	8.50	>100
6	59	56	0.49–22.0	Leukemia	CCRF-CEM	5.92	>100
					HL-60 (TB)	2.51	>100
					K-562	1.27	>100
					MOLT-4	5.24	>100
					RPMI-8226	3.01	>100
					SR	1.51	>100
				Non-small cell	A549/ATCC	6.98	>100
					EKVX	12.8	>100
				Lung cancer	HOP-62	5.37	>100
					HOP-92	12.0	>100
					NCI-H226	4.20	>100
					NCI-H23	5.82	>100

(*continued on next page*)

Table 2 (*continued*)

Compound	Number of cell lines			Most sensitive cell lines (GI_{50} < 20 μM)			
	Investigated	Giving positive GI_{50} GI_{50}[b] (μM)		Panel	Cell line	GI_{50}[b] (μM)	LC_{50}[c] (μM)
		No	Range				
					NCI-H322M	13.5	>100
					NCI-H460	3.16	>100
					NCI-H522	1.41	>100
				Colon cancer	COLO 205	3.53	>100
					HCC 2998	6.75	>100
					HCT-116	4.21	>100
					HCT-15	2.80	>100
					HT 29	2.97	>100
					KM 12	2.27	>100
					SW 620	2.92	>100
				CNS cancer	SF-268	4.55	>100
					SF-295	1.91	>100
					SF-539	2.84	>100
					SNB-75	1.27	>100
					U251	3.52	>100
				Ovarian cancer	IGROV1	4.54	>100
					OVCAR-3	2.12	46.4
					OVCAR-4	5.62	>100
					OVCAR-8	19.1	>100
					SK-OV-3	7.65	>100
				Renal cancer	786-0	6.44	>100
					A498	2.00	>100
					ACHN	3.73	>100
					CAKI-1	2.18	>100
					SN12C	6.39	>100
					UO-31	5.23	>100
				Prostate cancer	PC	3.64	>100
					DU	13.4	>100
				Breast cancer	MCF7	2.40	>100
					NCI/ADR-RES	4.54	>100
					MDA-MB-231/ATCC	4.09	>100
					HS 578T	2.10	>100
					MDA-MB-435	0.49	>100
					BT-549	5.35	>100
					T-47D	4.61	>100

[a] Data obtained from NCI's in vitro disease-oriented human tumor cell lines screen.[20–22]
[b] GI_{50} was the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. Determined at five concentration levels (100, 10, 1.0, 0.1, and 0.01 μM).
[c] LC_{50} is a parameter of cytotoxicity and reflects the molar concentration needed to kill 50% of the cells.

were run on a Bruker Avance 400 spectrometer operating at 400 MHz and 100 MHz, respectively, using dimethyl sulfoxide-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra were obtained on a Hewlett Packard HP Engine-5989 spectrometer (equipped with a direct inlet probe) operating at 70 eV. The elemental analyses have been obtained using a LECO CHNS-900 elemental analyzer.

4.1. General Procedure for synthesis of 6-aryl-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-diones (3–29)

A mixture of 3.0 mmol of **1** (5,6-diamino-2-methylthiopyrimidin-4(3*H*)-one or 5,6-diamino-2-methoxypyrimidin-4(3*H*)-one or 5,6-diamino-3-methyl-2-methylthiopyrimidin-4(3*H*)-one or 5,6-diamino-3-methyl-2-methoxypyrimidin-4(3*H*)-one) and 3.0 mmol of 2-arylideneindandiones **2** was refluxed in 15 mL of absolute ethanol and 1 mL of acetic acid for 6–8 h (TLC control). After cooling, the reaction mixture was neutralized with a solution of 10% $NaHCO_3$ and cooled to 0 °C. The precipitate formed overnight was filtered off and recrystallized from dimethylformamide yielding compounds **4**, **22**, and **27b** as crystals and the remaining compounds as amorphous solids.

4.1.1. 9-methylthio-6-(4-chlorophenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (3)

The compound was obtained as a red powder in a yield of 74%; mp 285–286 °C; FTIR (KBr) *ν* 3360 (NH); 1619 (C=O); 1565 (C=N and C=C) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 2.45 (s, 3H, SCH_3), 5.38 (d, 2H, H-6, *J* = 4.5 Hz), 7.21 (d, 2H, H-*o*, *J* = 8.5 Hz), 7.56 (d, 2H, H-*m*, *J* = 8.5 Hz), 7.29 (d, 1H, H-4, *J* = 7.0 Hz), 7.33 (t, 1H, H-3, *J* = 7.2 Hz), 7.40 (t, 1H, H-2, *J* = 6.8 Hz), 7.62 (d, 1H, H-1, *J* = 7.3 Hz), 7.71 (d, 1H, H-7, *J* = 4.8 Hz), 7.93 (s, 1H, H-12) , 12.75 (s, 1H, H-10) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 13.1, 53.8, 102.0, 106.1, 118.1, 118.5, 120.6, 128.5, 128.8, 130.2, 131.5, 134.8, 137.8, 144.2, 148.9, 153.0, 154.3, 160.5, 188.5 ppm. MS (70 eV) *m*/*z* (%): 422 ($M^{\cdot+}$, 100), 394 (17), 311 (21), 265 (58). Anal. Calcd. For $C_{21}H_{15}ClN_4O_2S$: C, 59.64; H, 3.58; N, 13.15; S, 7.58. Found: C, 59.57; H, 3.62; N, 13.19; S, 7.41

4.1.2. 9-methylthio-6-(4-bromophenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (4)

The compound was obtained as red crystals in a yield of 70%; mp 272–273 °C; FTIR (KBr) *ν* 3338 (NH); 1624 (C=O); 1571 (C=N and C=C) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): *δ* 2.46 (s, 3H, SCH_3), 5.37 (d, 2H, H-6, *J* = 4.6 Hz), 7.15 (d, 2H, H-*o*, *J* = 8.4 Hz), 7.30 (d, 1H, H-4, *J* = 7.0 Hz), 7.33 (t, 1H, H-3, *J* = 7.3 Hz), 7.39 (d, 2H, H-*m*, *J* = 8.4 Hz), 7.40 (t, 1H, H-2, *J* = 6.8 Hz), 7.61 (d, 1H, H-1,

J = 7.3 Hz), 7.70 (d, 1H, H-7, J = 4.5 Hz), 7.93 (s, 1H, H-12), 12.78 (s, 1H, H-10) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.1, 53.9, 101.5, 106.1, 118.1, 120.2, 120.6, 128.9, 130.2, 131.5, 131.7, 134.8, 137.8, 144.7, 148.7, 153.0, 154.2, 159.2, 188.4 ppm. MS (70 eV) m/z (%): 468 (M^+, 100), 440 (12), 312 (19), 311 (72). Anal. Calcd. For $C_{21}H_{15}BrN_4O_2S$: C, 53.97; H, 3.24; N, 11.99; S, 6.86. Found: C, 54.01; H, 3.19; N, 12.03; S, 6.91.

Crystallographic data for **4** were collected at 120 K on a Bruker Nonius Kappa Roper CCD area diffractometer using Mo-Kα X-ray radiation (λ = 0.71073 Å) and deposited at Cambridge Crystallographic data Center (CCDC reference: 692350).

4.1.3. 9-Methylthio-6-(4-fluorophenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (5)

The compound was obtained as an orange powder in a yield of 68%; mp 245–246 °C; FTIR (KBr) ν 3353 (NH); 1618 (C=O); 1524 (C=N and C=C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.94 (s, 3H, SCH_3), 5.36 (d, 2H, H-6, J = 4.6 Hz), 7.09 (d, 2H, H-o, J = 8.9 Hz), 7.61 (d, 2H, H-m, J_F = 5.6 Hz, J_{o-m} = 8.9 Hz), 7.21 (d, 1H, H-4, J = 6.8 Hz), 7.35 (t, 1H, H-3, J = 7.4 Hz), 7.43 (t, 1H, H-2, J = 7.3 Hz), 7.74 (d, 1H, H-1, J = 4.8 Hz), 7.75 (d, 1H, H-7, J = 7.2 Hz), 8.79 (s, 1H, H-12), 12.72 (s, 1H, H-10) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.6, 52.9, 101.3, 105.7, 135.5, 115.3, 118.3, 120.0, 128.0, 131.0, 131.7, 134.2, 137.8, 144.1, 148.4, 152.6, 153.6, 159.6, 187.7 ppm. MS (70 eV) m/z (%): 406 (M^+, 100), 378 (11), 311 (16), 249 (92). Anal. Calcd. For $C_{21}H_{15}FN_4O_2S$: C, 62.06; H, 3.72; N, 13.79; S, 7.89. Found: C, 61.99; H, 3.79; N, 13.75; S, 7.78.

4.1.4. 9-Methylthio-6-phenyl-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (6)

The compound was obtained as a dark-red powder in a yield of 69%; mp 268–269 °C; FTIR (KBr) ν 3341 (NH); 1613 (C=O); 1582 (C=N and C=C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (s, 3H, SCH_3), 5.33 (d, 2H, H-6, J = 4.9 Hz), 7.12 (t, 1H, H-p, J = 7.9 Hz), 7.17 (d, 2H, H-o, J = 8.5 Hz), 7.25 (d, 2H, H-m, J = 7.6 Hz), 7.28 (d, 1H, H-4, J = 7.1 Hz), 7.32 (t, 1H, H-3, J = 6.8 Hz), 7.40 (t, 1H, H-2, J = 7.2 Hz), 7.69 (d, 1H, H-1, J = 7.3 Hz), 7.70 (d, 1H, H-7, J = 4.6 Hz), 8.74 (s, 1H, H-12), 12.74 (s, 1H, H-10) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.1, 54.4, 101.9, 106.8, 118.0, 120.6, 126.6, 127.0, 128.8, 130.1, 131.5, 134.9, 137.9, 145.4, 148.9, 152.9, 153.9, 160.0, 188.4 ppm. MS (70 eV) m/z (%): 388 (M^+, 100), 360 (8), 311 (13), 231 (68). Anal. Calcd. For $C_{21}H_{16}N_4O_2S$: C, 64.93; H, 4.15; N, 14.42; S, 8.25. Found: C, 64.88; H, 4.19; N, 14.50; S, 8.38.

4.1.5. 9-Methylthio-6-(4-methylphenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (7)

The compound was obtained as a dark-red powder in a yield of 62%; mp 267–268 °C; FTIR (KBr) ν 3340 (NH); 1639 (C=O); 1584 (C=N and C=C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, p-CH_3), 2.45 (s, 3H, SCH_3), 5.32 (d, 2H, H-6, J = 4.6 Hz), 7.04 (d, 2H, H-o, J = 8.4 Hz), 7.08 (d, 2H, H-m, J = 8.4 Hz), 7.29 (d, 1H, H-4, J = 7.0 Hz), 7.33 (t, 1H, H-3, J = 7.3 Hz), 7.41 (t, 1H, H-2, J = 6.8 Hz), 7.63 (d, 1H, H-7, J = 4.8 Hz), 7.73 (d, 1H, H-1, J = 7.3 Hz), 8.74 (s, 1H, H-12), 12.68 (s, 1H, H-10) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.5, 53.3, 101.2, 106.1, 118.2, 119.9, 126.1, 129.0, 129.6, 130.9, 134.3, 135.67, 137.2, 142.1, 148.5, 152.5, 153.2, 158.5, 187.7 ppm. MS (70 eV) m/z (%): 402 (M^+, 100), 374 (11), 311 (19), 245 (72). Anal. Calcd. For $C_{22}H_{18}N_4O_2S$: C, 65.65; H, 4.51; N, 13.92; S, 7.97. Found: C, 65.73; H, 4.44; N, 14.51; S, 7.89.

4.1.6. 9-Methylthio-6-(4-methoxyphenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (8)

The compound was obtained as a dark-red powder in a yield of 65%; mp 295–296 °C; FTIR (KBr) ν 3353 (NH); 1618 (C=O); 1524 (C=N and C=C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.48 (s, 3H, SCH_3), 3.47 (s, 3H, p-OCH_3), 5.37 (d, 2H, H-6, J = 4.8 Hz), 7.01 (d, 2H, H-o, J = 8.5 Hz), 7.08 (d, 2H, H-m, J = 8.5 Hz), 7.29 (d, 1H, H-4, J = 6.8 Hz), 7.32 (t, 1H, H-3, J = 7.0 Hz), 7.39 (t, 1H, H-2, J = 7.3 Hz), 7.60 (d, 1H, H-1, J = 7.2 Hz), 7.65 (d, 1H, H-7, J = 5.0 Hz), 8.65 (s, 1H, H-12), 12.70 (s, 1H, H-10) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.1, 54.2, 101.9, 106.9, 117.9, 120.5, 126.6, 129.4, 130.1, 131.5, 134.9, 136.3, 137.8, 142.3, 149.0, 152.9, 154.0, 159.2, 188.5 ppm. MS (70 eV) m/z (%): 418 (M^+, 100), 390 (9), 311 (16), 261 (83). Anal. Calcd. For $C_{22}H_{18}N_4O_3S$: C, 63.14; H, 4.34; N, 13.39; S, 7.66. Found: C, 63.10; H, 4.40; N, 13.31; S, 7.73.

4.1.7. 9-Methylthio-6-(4-trifluoromethylphenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (9)

The compound was obtained as a dark-red powder in a yield of 60%; mp 298–299 °C; FTIR (KBr) ν 3342 (NH); 1616 (C=O); 1581 (C=N and C=C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.44 (s, 3H, SCH_3), 5.39 (d, 2H, H-6, J = 4.6 Hz), 7.24 (d, 2H, H-m, J = 8.3 Hz), 7.27 (d, 1H, H-4, J = 6.8 Hz), 7.33 (t, 1H, H-3, J = 7.4 Hz), 7.38 (d, 2H, H-o, J = 8.3 Hz), 7.40 (t, 1H, H-2, J = 7.2 Hz), 7.62 (d, 1H, H-1, J = 7.2 Hz), 7.74 (d, 1H, H-7, J = 4.8 Hz), 8.85 (s, 1H, H-12), 12.65 (s, 1H, H-10) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.1, 54.0, 101.9, 105.6, 118.2, 120.6, 127.5, 128.1, 130.2, 131.5, 134.8, 137.9, 148.6, 150.0, 152.8, 154.2, 159.1, 188.3 ppm. MS (70 eV) m/z (%): 456 (M^+, 100), 428 (11), 311 (18), 299 (65). Anal. Calcd. For $C_{22}H_{15}F_3N_4O_2S$: C, 57.89; H, 3.31; N, 12.27; S, 7.03. Found: C, 57.95; H, 3.27; N, 12.22; S, 6.86.

4.1.8. 9-Methoxy-6-(4-nitrophenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (10)

The compound was obtained as a red powder in a yield of 71%; mp 269 °C; FTIR (KBr) ν 3357 (NH); 1614 (C=O); 1583 (C=N and C=C); 1521, 1340 (NO_2) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.89 (s, 3H, OCH_3), 5.18 (d, 1H, H-6, J = 4.6 Hz), 6.81 (d, 2H, H-o, J = 8.9 Hz), 7.23 (t, 1H, H-3, J = 7.7 Hz), 7.33 (d, 1H, H-4, J = 7.4 Hz), 7.40 (t, 1H, H-2, J = 7.9 Hz), 7.64 (d, 2H, H-m, J = 8.9 Hz), 8.03 (t, 1H, H-1, J = 7.9 Hz), 8.98 (d, 1H, H-7, J = 4.6 Hz), 10.54 (s, 1H, H-12), 11.67 (s, 1H, H-10) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.4, 55.3, 98.8, 102.2, 119.7, 119.9, 120.2, 120.4, 124.4, 129.2, 132.8, 134.7, 143.7, 143.8, 144.6, 149.7, 153.6, 156.5, 194.0 ppm. MS (70 eV) m/z (%): 417 (M^+, 89), 389 (17), 295 (13), 260 (100). Anal. Calcd. For $C_{21}H_{15}N_5O_5$: C, 60.43; H, 3.62; N, 16.78. Found: C, 60.39; H, 3.53; N, 16.72.

4.1.9. 9-Methoxy-6-(4-chlorophenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (11)

The compound was obtained as a yellow powder in a yield of 67%; mp 259 °C; FTIR (KBr) ν 3339 (NH); 1621 (C=O); 1587 (C=N and C=C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.57 (s, 3H, OCH_3), 5.32 (d, 1H, H-6, J = 4.6 Hz), 6.82 (d, 2H, H-o, J = 8.5 Hz), 7.13 (d, 2H, H-m, J = 8.5 Hz), 7.53 (t, 1H, H-3, J = 7.1 Hz,), 7.61 (d, 1H, H-4, J = 7.7 Hz), 7.70 (t, 1H, H-2, J = 7.0 Hz), 7.78 (d, 1H, H-7, J = 4.6 Hz), 8.03 (s, 1H, H-12), 8.32 (d, 1H, H-1, J = 7.9 Hz), 12.52 (s, 1H, H-10) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.4, 54.4, 102.7, 120.4, 120.7, 125.6, 125.9, 130.0, 130.1, 133.3, 138.0, 138.9, 144.2, 146.9, 147.2, 152.8, 156.4, 160.2, 192.3 ppm. MS (70 eV) m/z (%): 406 (M^+, 100), 378 (6), 295 (19), 250 (89). Anal. Calcd. For $C_{21}H_{15}ClN_4O_3$: C, 62.00; H, 3.72; N, 13.77. Found: C, 61.86; H, 3.68; N, 13.81.

4.1.10. 9-Methoxy-6-(4-bromophenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (12)

The compound was obtained as an orange powder in a yield of 63%; mp 264 °C; FTIR (KBr) ν 3341 (NH); 1615 (C=O); 1589 (C=N and C=C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.62 (s, 3H,

OCH_3), 5.29 (d, 1H, H-6, J = 4.6 Hz), 6.75 (d, 2H, H-*o*, J = 8.5 Hz), 7.27 (d, 2H, H-*m*, J = 8.5 Hz), 7.53 (t, 1H, H-3, J = 7.0 Hz), 7.60 (d, 1H, H-4, J = 7.7 Hz), 7.70 (t, 1H, H-2, J = 7.9 Hz), 7.85 (d, 1H, H-7, J = 4.6 Hz), 8.13 (s, 1H, H-12), 8.34 (d, 1H, H-1, J = 7.9 Hz), 12.47 (s, 1H, H-10) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.3, 54.8, 102.2, 120.7, 121.0, 125.1, 126.1, 130.5, 130.6, 133.3, 134.1, 138.3, 139.0, 146.4, 147.3, 153.2, 156.4, 160.8, 194.9 ppm. MS (70 eV) m/z (%): 450 (M^+, 94), 422 (9), 296 (17), 293 (100). Anal. Calcd. For $C_{21}H_{15}BrN_4O_3$: C, 55.89; H, 3.35; N, 12.42. Found: C, 55.76; H, 3.28; N, 12.51.

4.1.11. 9-Methoxy-6-phenyl-6,7,10,12-tetrahydroindeno[1,2-*e*]-pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (13)

The compound was obtained as an orange powder in a yield of 63%; mp 264 °C; FTIR (KBr) ν 3298 (NH); 1622 (C=O); 1592 (C=N and C=C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.58 (s, 3H, OCH_3), 5.32 (d, 1H, H-6, J = 4.6 Hz), 6.80–7.05 (m, 5H, Aryl), 7.45 (t, 1H, H-3, J = 7.4 Hz), 7.61 (d, 1H, H-4, J = 7.7 Hz), 7.68 (t, 1H, H-2, J = 7.6 Hz), 7.81 (d, 1H, H-7, J = 4.6 Hz), 8.20 (s, 1H, H-12), 8.31 (d, 1H, H-1, J = 7.9 Hz), 12.39 (s, 1H, H-10) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.6, 54.4, 101.5, 106.9, 118.2, 120.6, 126.4, 127.3, 129.0, 130.4, 131.5, 134.7, 137.8, 145.1, 148.6, 153.1, 153.8, 160.5, 190.4 ppm. MS (70 eV) m/z (%): 372 (M^+, 100), 344 (8), 295 (16), 215 (81). Anal. Calcd. For $C_{21}H_{16}N_4O_3$: C, 67.73; H, 4.33; N, 15.05. Found: C, 67.66; H, 4.28; N, 15.16.

4.1.12. 9-Methoxy-6-(4-methylphenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (14)

The compound was obtained as a red powder in a yield of 60%; mp 201 °C; FTIR (KBr) ν 3332 (NH); 1612 (C=O); 1581 (C=N and C=C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, *p*-CH_3), 3.84 (s, 3H, OCH_3), 5.36 (d, 1 H, H-6, J = 4.8 Hz), 7.02 (d, 2H, H-*o*, J = 8.0 Hz), 7.10 (d, 2H, H-*m*, J = 8.3 Hz), 7.18 (d, 1H, H-7, J = 4.0 Hz), 7.28 (t, 1H, H-2, J = 7.8 Hz), 7.33 (d, 1H, H-4, J = 7.0 Hz), 7.38 (t, 1H, H-3, J = 7.0 Hz), 7.59 (d, 1H, H-1, J = 7.3 Hz), 8.38 (s, 1H, H-12), 9.95 (s, 1H, H-10) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.5, 53.3, 54.4, 99.2, 105.6, 117.9, 119.8, 126.1, 128.9, 129.4, 129.6, 134.1, 134.5, 135.6, 137.1, 142.2, 148.9, 151.6, 152.4, 159.3, 187.3 ppm. MS (70 eV) m/z (%): 386 (M^+, 92), 358 (10), 295 (21), 229 (91). Anal. Calcd. For $C_{22}H_{18}N_4O_3$: C, 68.38; H, 4.70; N, 14.50. Found: C, 68.29; H, 4.57; N, 14.60.

4.1.13. 9-Methoxy-6-(4-methoxyphenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (15)

The compound was obtained as a dark-red powder in a yield of 63%; mp 264 °C; FTIR (KBr) ν 3360 (NH); 1619 (C=O); 1571 (C=N and C=C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.68 (s, 3H, *p*-OCH_3), 3.83 (s, 3H, OCH_3), 5.36 (d, 1H, H-6, J = 4.8 Hz), 6.78 (d, 2H, H-*o*, J = 8.3 Hz), 7.13 (d, 2H, H-*m*, J = 8.5 Hz), 7.16 (d, 1H, H-7, J = 4.8 Hz), 7.29 (t, 1H, H-2, J = 7.3 Hz), 7.33 (d, 1H, H-4, J = 7.0 Hz), 7.39 (t, 1H, H-3, J = 7.3 Hz), 7.59 (d, 1H, H-1, J = 7.0 Hz), 8.54 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.0, 54.4, 55.0, 99.2, 105.8, 113.8, 114.5, 117.9, 119.9, 127.3, 129.6, 130.8, 134.6, 137.1, 137.2, 149.0, 151.6, 152.5, 157.9, 159.3, 187.4 ppm. MS (70 eV) m/z (%): 402 (M^+, 89), 374 (7), 295 (17), 245 (88). Anal. Calcd. For $C_{22}H_{18}N_4O_4$: C, 65.66; H, 4.51; N, 13.92. Found: C, 65.78; H, 4.48; N, 14.06.

4.1.14. 10-Methyl-9-methylthio-6-(4-nitrophenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (16)

The compound was obtained as an orange powder in a yield of 63%; mp 269–270 °C; FTIR (KBr) ν 3340 (NH), 1640 (C=O), 1578 (C=N and C=C), 1532, 1339 (NO_2) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, SCH_3), 3.55 (s, 3H, CH_3), 5.45 (d, 2H, H-6, J = 4.6 Hz), 7.30 (d, 1H, H-4, J = 7.2 Hz), 7.34 (t, 1H, H-3, J = 6.8 Hz), 7.42 (t, 1H, H-2, J = 7.2 Hz), 7.44 (d, 2H, H-*m*, J = 8.4 Hz), 7.75 (d, 1H, H-1, J = 7.3 Hz), 7.83 (d, 2H, H-*o*, J = 8.4 Hz), 7.83 (d, 1H, H-7, J = 5.0 Hz), 8.87 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.1, 30.2, 53.0, 100.9, 104.4, 118.5, 120.10, 123.2, 123.9, 127.4, 129.9, 131.2, 134.0, 137.1, 142.7, 146.1, 152.4, 154.8, 158.0, 187.8 ppm. MS (70 eV) m/z (%): 447 (M^+, 100), 419 (8), 325 (12), 290 (81). Anal. Calcd. For $C_{22}H_{17}N_5O_4S$: C, 59.05; H, 3.83; N, 15.65; S, 7.17. Found: C, 59.13; H, 3.71; N, 15.73; S, 7.09.

4.1.15. 10-Methyl-9-methylthio-6-(4-chlorophenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (17)

The compound was obtained as an orange powder in a yield of 63%; mp 260–261 °C; FTIR (KBr) ν 3254 (NH), 1670 (C=O), 1580 (C=N and C=C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.49 (s, 3H, SCH_3), 3.42 (s, 3H, CH_3), 5.31 (d, 2H, H-6, J = 4.7 Hz), 7.18 (d, 2H, H-*o*, J = 8.4 Hz), 7.27 (d, 1H, H-4, J = 7.2 Hz), 7.30 (d, 2H, H-*m*, J = 8.4 Hz), 7.32 (t, 1H, H-3, J = 7.3 Hz), 7.40 (t, 1H, H-2, J = 6.8 Hz), 7.71 (d, 1H, H-1, J = 7.3 Hz), 7.77 (d, 1H, H-7, J = 4.5 Hz), 9.26 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.5, 54.3, 104.6, 105.8, 118.5, 119.3, 120.8, 127.5, 128.8, 131.0, 132.2, 136.6, 138.5, 146.3, 149.3, 152.3, 155.7, 162.0, 188.8 ppm. MS (70 eV) m/z (%): 436 (M^+, 100), 408 (10), 325 (16), 279 (79). Anal. Calcd. For $C_{22}H_{17}ClN_4O_2S$: C, 60.48; H, 3.92; N, 12.82; S, 7.34. Found: C, 60.39; H, 3.97; N, 12.77; S, 7.41.

4.1.16. 10-Methyl-9-methylthio-6-(4-bromophenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (18)

The compound was obtained as an orange powder in a yield of 66%; mp 250–251 °C; FTIR (KBr) ν 3268 (NH), 1652 (C=O), 1585 (C=N and C=C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H, SCH_3), 3.44 (s, 3H, CH_3), 5.31 (d, 2H, H-6, J = 4.9 Hz), 7.14 (d, 2H, H-*o*, J = 8.3 Hz), 7.29 (d, 1H, H-4, J = 6.9 Hz), 7.35 (t, 1H, H-3, J = 7.4 Hz), 7.41 (t, 1H, H-2, J = 7.2 Hz), 7.44 (d, 2H, H-*m*, J = 8.3 Hz), 7.69 (d, 1H, H-7, J = 5.0 Hz) 7.74 (d, 1H, H-1, J = 7.3 Hz) , 8.79 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.1, 30.2, 53.0, 100.9, 105.4, 118.3, 119.6, 120.0, 128.4, 130.9, 131.1, 131.3, 134.0, 137.1, 144.3, 146.9, 152.5, 154.6, 157.9, 187.8 ppm. MS (70 eV) m/z (%): 480 (M^+, 98), 452 (9), 324 (15), 323 (78). Anal. Calcd. For $C_{22}H_{17}BrN_4O_2S$: C, 54.89; H, 3.56; N, 11.64; S, 6.66. Found: C, 55.01; H, 3.49; N, 11.60; S, 6.71.

4.1.17. 10-Methyl-9-methylthio-6-(4-fluorophenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (19)

The compound was obtained as a red powder in a yield of 70%; mp 263–264 °C; FTIR (KBr) ν 3330 (NH), 1680 (C=O), 1563 (C=N and C=C) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.53 (s, 3H, SCH_3), 3.43 (s, 3H, CH_3), 5.34 (d, 2H, H-6, J = 4.8 Hz), 7.06 (d, 2H, H-*o*, J = 9.0 Hz), 7.27 (d, 1H, H-4, J = 6.5 Hz), 7.33 (t, 1H, H-3, J = 7.0 Hz), 7.41 (t, 1H, H-2, J = 7.5 Hz), 7.60 (d, 2H, H-*m*, J_F = 5.5 Hz, $J_{o\text{-}m}$ = 9.0 Hz), 7.68 (d, 1H, H-1, J = 4.8 Hz), 7.72 (d, 1H, H-7, J = 7.3 Hz), 8.77 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.5, 30.7, 53.3, 101.4, 106.3, 115.6, 115.8, 118.7, 120.5, 128.6, 130.3, 131.6, 134.6, 137.6, 141.6, 147.6, 153.0, 155.1, 158.4, 188.3 ppm. MS (70 eV) m/z (%): 420 (M^+, 100), 392 (6), 325 (12), 263 (80). Anal. Calcd. For $C_{22}H_{17}FN_4O_2S$: C, 62.84; H, 4.08; N, 13.33; S, 7.63. Found: C, 62.80; H, 3.99; N, 13.41; S, 6.58.

Crystallographic data for **22** were collected at 120 K on a Bruker Nonius Kappa Roper CCD area diffractometer using Mo-Kα X-ray radiation (λ = 0.71073 Å) and deposited at Cambridge Crystallographic data Center (CCDC reference: 692348).

4.1.18. 10-methyl-9-methylthio-6-phenyl-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (20)

The compound was obtained as an orange powder in a yield of 60%; mp 280–281 °C; FTIR (KBr) ν 3345 (NH), 1660 (C=O), 1570 (C=N and C=C) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.49 (s, 3H, SCH_3), 3.45 (s, 3H, CH_3), 5.33 (d, 2H, H-6, J = 4.8 Hz), 7.13 (t, 2H, H-*p*, J = 7.9 Hz), 7.21 (t, 2H, H-*o*, J = 8.5 Hz), 7.38 (d, 2H, H-*m*, J = 7.6 Hz), 7.20 (d, 1H, H-7, J = 5.0 Hz), 7.26 (d, 1H, H-4, J = 7.0 Hz), 7.33 (t, 1H, H-3, J = 6.8 Hz), 7.42 (t, 1H, H-2, J = 7.2 Hz), 7.70 (d, 1H, H-1, J = 7.3 Hz), 8.74 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.5, 30.7, 54.0, 100.0, 106.5, 118.6, 120.5, 126.7, 127.1, 129.0, 130.3, 131.6, 134.6, 137.7, 145.5, 147.6, 153.0, 155.0, 158.4, 184.6 ppm. MS (70 eV) m/z (%): 402 (M^+, 100), 374 (11), 325 (21), 245 (91). Anal. Calcd. For $C_{22}H_{18}N_4O_2S$: C, 65.65; H, 4.51; N, 13.92; S, 7.97. Found: C, 65.71; H, 4.43; N, 14.00; S, 7.81.

4.1.19. 10-methyl-9-methylthio-6-(4-methylphenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (21)

The compound was obtained as an orange powder in a yield of 61%; mp 255–256 °C; FTIR (KBr) ν 3360 (NH), 1635 (C=O), 1568 (C=N and C=C) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.10 (s, 3H, *p*-CH_3), 2.49 (s, 3H, SCH_3), 3.43 (s, 3H, CH_3), 5.30 (d, 2H, H-6, J = 4.8 Hz), 6.79 (d, 2H, H-*o*, J = 8.8 Hz), 7.09 (d, 2H, H-*m*, J = 8.8 Hz), 7.27 (d, 1H, H-4, J = 6.8 Hz), 7.33 (t, 1H, H-3, J = 7.0 Hz), 7.41 (t, 1H, H-2, J = 7.3 Hz), 7.71 (d, 1H, H-1, J = 4.8 Hz), 7.71 (d, 1H, H-7, J = 7.3 Hz), 8.72 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.5, 20.9, 30.7, 53.8, 101.6, 107.17, 114.5, 117.9, 120.6, 127.8, 130.1, 131.1, 134.8, 137.4, 138.9, 147.6, 152.9, 155.0, 158.6, 188.5 ppm. MS (70 eV) m/z (%): 416 (M^+, 100), 388 (7), 325 (13), 259 (78). Anal. Calcd. For $C_{23}H_{20}N_4O_2S$: C, 66.33; H, 4.84; N, 13.45; S, 7.70. Found: C, 66.41; H, 4.76; N, 13.52; S, 7.63.

4.1.20. 10-methyl-9-methylthio-6-(4-methoxyphenyl)-6,7,10,-12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (22)

The compound was obtained as a red powder in a yield of 63%; mp 280–281 °C; FTIR (KBr) ν 3210 (NH), 1690 (C=O), 1559 (C=N and C=C) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, SCH_3), 3.44 (s, 3H, CH_3), 3.50 (s, 3H, *p*-OCH_3), 5.28 (d, 2H, H-6, J = 4.5 Hz), 6.77 (d, 2H, H-*o*, J = 8.8 Hz), 7.12 (d, 2H, H-*m*, J = 8.5 Hz), 7.23 (d, 1H, H-7, J = 6.5 Hz), 7.29 (d, 1H, H-4, J = 7.0 Hz), 7.33 (t, 1H, H-3, J = 7.4 Hz), 7.41 (t, 1H, H-2, J = 4.8 Hz), 7.60 (d, 1H, H-1, J = 7.3 Hz), 8.47 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.5, 30.7, 53.3, 55.7, 101.4, 106.3, 115.6, 118.7, 120.5, 128.6, 130.2, 131.2, 134.6, 137.6, 141.6, 147.6, 153.0, 155.1, 158.4, 188.3 ppm. MS (70 eV) m/z (%): 432 (M^+, 100), 404 (8), 325 (11), 275 (62). Anal. Calcd. For $C_{23}H_{20}N_4O_3S$: C, 63.87; H, 4.66; N, 12.95; S, 7.41. Found: C, 63.79; H, 4.71; N, 12.92; S, 7.33.

4.1.21. 10-methyl-9-methylthio-6-(4-trifluoromethylphenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,-11-dione (23)

The compound was obtained as an orange powder in a yield of 69%; mp 284–285 °C; FTIR (KBr) ν 3232 (NH), 1658 (C=O), 1559 (C=N and C=C) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.47 (s, 3H, SCH_3), 3.50 (s, 3H, CH_3), 5.70 (d, 2H, H-6, J = 4.6 Hz), 7.34 (d, 2H, H-*o*, J = 8.3 Hz), 7.29 (d, 1H, H-4, J = 6.8 Hz), 7.30 (t, 1H, H-3, J = 7.3 Hz), 7.40 (d, 2H, H-*m*, J = 8.4 Hz), 7.39 (t, 1H, H-2, J = 7.0 Hz), 7.60 (d, 1H, H-1, J = 4.7 Hz), 7.74 (d, 1H, H-7, J = 7.3 Hz), 8.88 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.3, 55.6, 102.9, 104.9, 119.2, 122.6, 127.8, 129.6, 132.2, 133.5, 135.0, 137.9, 148.7, 152.0, 152.9, 155.2, 160.2, 188.7 ppm. MS (70 eV) m/z (%): 470 ($M^{\cdot+}$, 100), 442 (5), 325 (12), 313 (90). Anal. Calcd. For $C_{23}H_{17}F_3N_4O_2S$: C, 58.72; H, 3.64; N, 11.91; S, 6.82. Found: C, 58.81; H, 3.69; N, 11.86; S, 6.78.

4.1.22. 9-methoxy-10-methyl-6-(4-nitrophenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (24)

The compound was obtained as a red powder in a yield of 86%; mp 262 °C; FTIR (KBr) ν 3381 (NH), 1648 (C=O), 1570 (C=N and C=C), 1531, 1338 (NO_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.34 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 5.43 (d, 2H, H-6, J = 4.8 Hz), 7.30 (d, 1H, H-4, J = 6.8 Hz), 7.35 (t, 1H, H-3, J = 7.0 Hz), 7.43 (t, 1H, H-2, J = 7.4 Hz), 7.45 (d, 2H, H-*o*, J = 8.9 Hz), 7.74 (d, 1H, H-1, J = 7.2 Hz), 7.77 (d, 1H, H-7, J = 4.8 Hz), 8.12 (d, 2H, H-*m*, J = 8.9 Hz), 8.83 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.9, 53.0, 55.4, 99.1, 103.9, 118.3, 120.0, 123.8, 127.3, 129.8, 131.0, 134.2, 137.0, 146.0, 147.0, 150.9, 152.6, 156.7, 158.6, 187.5 ppm. MS (70 eV) m/z (%): 431 (M^+, 5), 403 (11), 303 (60), 181 (60), 155 (100). Anal. Calcd. For $C_{22}H_{17}N_5O_5$: C, 61.25; H, 3.97; N, 16.23. Found: C, 61.16; H, 4.03; N, 16.11.

4.1.23. 9-methoxy-10-methyl-6-(4-chlorophenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (25)

The compound was obtained as an orange powder in a yield of 72%; mp 267–268 °C; FTIR (KBr) ν 3340 (NH), 1636 (C=O), 1585 (C=N and C=C) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.28 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 5.30 (d, 2H, H-6, J = 4.8 Hz), 7.18 (d, 2H, H-*o*, J = 8.5 Hz), 7.26 (d, 1H, H-4, J = 5.5 Hz), 7.28 (d, 2H, H-*m*, J = 8.0 Hz), 7.32 (t, 1H, H-3, J = 7.5 Hz), 7.39 (t, 1H, H-2, J = 7.5 Hz), 7.61 (d, 1H, H-7, J = 4.5 Hz), 7.68 (d, 1H, H-1, J = 7.0 Hz), 8.69 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.4, 53.6, 55.9, 99.9, 105.6, 118.2, 120.5, 128.5, 128.8, 130.2, 131.4, 131.7, 134.9, 137.7, 144.4, 147.7, 151.4, 153.0, 159.2, 188.1 ppm. MS (70 eV) m/z (%): 420 (M^+, 60), 392 (9), 309 (12), 292 (100), 281 (53), 263 (58). Anal. Calcd. For $C_{22}H_{17}ClN_4O_3$: C, 62.79; H, 4.07; N, 13.31. Found: C, 62.83; H, 3.95; N, 13.26.

4.1.24. 9-methoxy-10-methyl-6-(4-bromophenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (26)

The compound was obtained as an orange powder in a yield of 64%; mp 272 °C; FTIR (KBr) ν 3341 (NH), 1634 (C=O), 1588 (C=N and C=C) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.32 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 5.30 (d, 2H, H-6, J = 4.6 Hz), 7.14 (d, 2H, H-*o*, J = 8.5 Hz), 7.28 (d, 1H, H-4, J = 6.9 Hz), 7.35 (t, 1H, H-3, J = 7.2 Hz), 7.43 (t, 1H, H-2, J = 7.6 Hz), 7.44 (d, 2H, H-*m*, J = 8.5 Hz), 7.62 (d, 1H, H-7, J = 4.8 Hz) 7.73 (d, 1H, H-1, J = 7.2 Hz) , 8.74 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.9, 53.0, 55.4, 99.1, 104.8, 118.2, 119.6, 119.9, 128.4, 129.8, 131.0, 131.3, 134.3, 137.0, 144.5, 147.2, 150.9, 152.6, 158.5, 187.4 ppm. MS (70 eV) m/z (%): 464 (M^+, 92), 449 (17), 436 (4), 309 (80), 281 (24). Anal. Calcd. For $C_{22}H_{17}BrN_4O_3$: C, 56.79; H, 3.68; N, 12.04; S, 6.66. Found: C, 56.82; H, 3.55; N, 11.94.

4.1.25. 9-methoxy-10-methyl-6-phenyl-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (27a)

The compound was obtained as an orange powder in a yield of 67%; mp 265 °C; FTIR (KBr) ν 3340 (NH), 1630 (C=O), 1579 (C=N and C=C) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.32 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 5.40 (d, 2H, H-6, J = 4.8 Hz), 7.18–7.22 (m, 5H, Aryl), 7.28 (d, 1H, H-4, J = 6.8 Hz), 7.32 (t, 1H, H-3, J = 7.3 Hz), 7.40 (t, 1H, H-2, J = 7.3 Hz), 7.59 (d, 1H, H-1, J = 7.3 Hz), 7.93 (d, 1H, H-7, J = 4.8 Hz), 8.45 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.7, 53.7, 55.1, 99.3, 105.5, 117.1, 119.8, 125.9, 126.3, 128.1, 129.4, 130.7, 134.3, 137.1,

144.8, 147.2, 150.7, 152.2, 158.6, 187.6 ppm. MS (70 eV) *m*/*z* (%): 386 (M^+, 39), 358 (8), 309 (13), 281 (5), 258 (9), 229 (100). Anal. Calcd. For $C_{22}H_{18}N_4O_3$: C, 68.38; H, 4.70; N, 14.50. Found: C, 68.30; H, 4.81; N, 14.62.

4.1.26. 5a-hydroxy-9-methoxy-10-methyl-6-phenyl-5a,6,7,10-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (27b)

The compound was obtained as orange crystals in a yield of 25%; mp 255 °C; FTIR (KBr) *ν* *3352–3338* (NH and OH), 1682 (C=O), 1579 (C=N and C=C) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.32 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 4.99 (d, 2H, H-6, *J* = 6.6 Hz), 6.49 (s, 1H, 5a-OH), 6.83 (d, 2H, H-*o*, *J* = 7.0 Hz), 6.98–7.07 (m, 3H, H-*m* and H-*p*), 7.39 (t, 1H, H-3, *J* = 7.9 Hz), 7.52 (d, 1H, H-4, *J* = 7.7 Hz), 7.63 (t, 1H, H-2, *J* = 7.9 Hz), 7.74 (d, 1H, H-1, *J* = 7.9 Hz), 8.16 (d, 1H, H-7, *J* = 6.6 Hz) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.6, 55.3, 62.4, 76.7, 106.1, 121.1, 122.8, 126.9, 127.3, 127.9, 129.2, 130.5, 135.4, 136.2, 139.7, 147.7, 152.4, 153.0, 161.0, 200.9 ppm. MS (70 eV) *m*/*z* (%): 420 (M^+, 11), 402 (11), 374 (39), 357 (16), 297 (90), 242 (62), 72 (100). Anal. Calcd. For $C_{22}H_{18}N_4O_4.H_2O$: C, 62.85; H, 4.79; N, 13.33. Found: C, 62.77; H, 4.86; N, 13.25.

Crystallographic data for **27b** were collected at 120 K on a Bruker Nonius Kappa Roper CCD area diffractometer using Mo-Kα X-ray radiation (λ = 0.71073 Å) and deposited at Cambridge Crystallographic data Center (CCDC reference: 692349).

4.1.27. 9-Methoxy-10-methyl-6-(4-methylphenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (28)

The compound was obtained as a red powder in a yield of 58%; mp 257 °C; FTIR (KBr) *ν* 3335 (NH), 1635 (C=O), 1584 (C=N and C=C) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.18 (s, 3H, *p*-CH_3), 3.32 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 5.36 (d, 2H, H-6, *J* = 4.8 Hz), 7.00 (d, 2H, H-*o*, *J* = 8.0 Hz), 7.09 (d, 2H, H-*m*, *J* = 7.8 Hz), 7.13 (d, 1H, H-7, *J* = 4.5 Hz), 7.29 (t, 1H, H-3, *J* = 7.0 Hz), 7.33 (d, 1H, H-4, *J* = 7.0 Hz), 7.40 (t, 1H, H-2, *J* = 7.3 Hz), 7.58 (d, 1H, H-1, *J* = 7.3 Hz), 8.42 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.0, 27.6, 53.3, 55.0, 99.0, 99.2, 105.7, 117.0, 119.7, 125.8, 128.6, 129.3, 130.6, 134.3, 135.4, 141.7, 147.1, 150.6, 152.1, 158.5, 187.4 ppm. MS (70 eV) *m*/*z* (%): 400 (M^+, 98), 372 (7), 309 (20), 272 (100), 243 (70). Anal. Calcd. For $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99. Found: C, 69.08; H, 4.89; N, 14.10.

4.1.28. 9-Methoxy-10-methyl-6-(4-methoxyphenyl)-6,7,10,12-tetrahydroindeno[1,2-*e*]pyrimido[4,5-*b*][1,4]diazepine-5,11-dione (29)

The compound was obtained as a red powder in a yield of 55%; mp 270–271 °C; FTIR (KBr) *ν* 3338 (NH), 1642 (C=O), 1580 (C=N and C=C) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.28 (s, 3H, CH_3), 3.63 (s, 3H, *p*-OCH_3), 3.86 (s, 3H, OCH_3), 5.27 (d, 2H, H-6, *J* = 4.8 Hz), 6.77 (d, 2H, H-*o*, *J* = 8.5 Hz), 7.09 (d, 2H, H-*m*, *J* = 8.5 Hz), 7.26 (d, 1H, H-4, *J* = 6.8 Hz), 7.32 (t, 1H, H-3, *J* = 7.3 Hz), 7.39 (t, 1H, H-2, *J* = 7.5 Hz), 7.50 (d, 1H, H-7, *J* = 4.8 Hz), 7.66 (d, 1H, H-1, *J* = 7.3 Hz), 8.60 (s, 1H, H-12) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.3, 53.8, 55.7, 55.8, 99.7, 106.6, 114.5, 117.8, 120.4, 127.8, 130.1, 131.3, 135.0, 137.7, 137.9, 147.9, 151.3, 152.9, 158.7, 159.2, 186.3, 188.1 ppm. MS (70 eV) *m*/*z* (%): 416 (M^+, 79), 388 (8), 309 (5), 288 (100), 281 (35), 259 (62). Anal. Calcd. For $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.84; N, 13.45. Found: C, 66.23; H, 4.90; N, 13.58.

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