An Efficient Two-Step Synthesis of Novel Thiazolo[2,3-*b*]pyrazolo[3,4-*f*][1,3,5]triazepines

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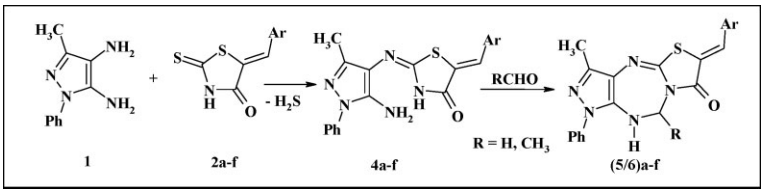

In an attempt to carry out a straightforward synthesis of thiazolopyrazolodiazepines from the reaction of 4,5-diamino-3-methyl-1-phenylpyrazole **1** with arylidene derivatives of rhodanine **2**, the unplanned (Z)-2′-[(5-amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5-arylidenethiazolidin-4-ones **4** were obtained as unique products. Nevertheless, the treatment of these compounds with aliphatic aldehydes in dimethylformamide provided the novel thiazolo[2,3-*b*]pyrazolo[3,4-*f*][1,3,5]triazepines **5** and **6** in good to excellent yields. All the structures of the obtained compounds were assigned on the basis of IR, 1D and 2D NMR measurements, mass spectrometry, and microanalysis.

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INTRODUCTION

In recent years, the synthesis and pharmacological properties of diverse systems containing heterocycles fused to a seven-membered diazepine ring have appeared in the literature [1]. Particularly, good CNS activity was reported for various pyrazolodiazepines [2], some of them acting as psychotropic agents [3].

It is known that the interaction of *ortho*-diamines with α,β-unsaturated carbonyl compounds constitutes one of the more expeditious procedures yielding diazepine systems fused to aromatic rings [4]. In this sense, we have successfully carried out several reactions between 4,5-diaminopyrazoles and diaminopyrimidines with chalcones and β-dimethylaminopropiophenone hydrochlorides as versatile approaches for the synthesis of new pyrazolo- and pyrimidodiazepine derivatives, respectively [5].

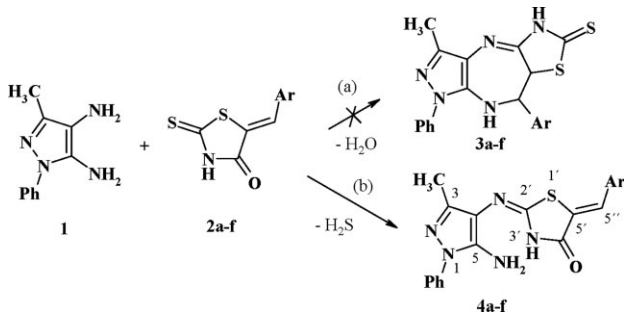
RESULTS AND DISCUSSION

Continuing with our studies directed toward the development of synthetic methodologies leading to fused pyrazole systems and in an attempt to obtain the new thiazolopyrazolodiazepines **3** for biological testing, we prepared a series of (Z)-arylidene derivatives of rhodanine **2a–f** (α,β-unsaturated carbonyl compounds) [6] to be reacted with 4,5-diamino-3-methyl-1-phenylpyrazole **1** as a direct procedure for the synthesis of our target compounds **3**, Scheme 1, approach (a).

To obtain the expected diazepines **3**, a mixture of diaminopyrazole **1** (1.5 mmol) and (Z)-5-(nitrobenzylidene)-2-thioxothiazolidin-4-one (**2a**) (Ar = 4-$NO_2C_6H_4$) (1.5 mmol) was heated at reflux for 15 h in the presence of ethanol (20 mL) as solvent and triethylamine (1 mL) as catalyst, according to previously reported procedures [7]. This reaction afforded a yellow solid, which after spectroscopic analysis (IR, ^{1}H and ^{13}C NMR and mass spectrum), corresponded unexpectedly to the imine compound **4a** (Ar = 4-$NO_2C_6H_4$) in 87% isolated yield, Scheme 1, approach (b), but not to the cyclo-condensed product **3a**.

The yellow solid exhibited all the signals expected for the proposed structure (**4a**). The IR spectrum showed mainly absorption bands at 3410, 3285, and 1700 cm^{-1} assigned to NH, NH_2, and C=O functionalities, respectively. The ^{1}H NMR of this compound features the following main signals: a broad singlet (2H) at 5.72 ppm assigned to the 5-NH_2 group, a singlet (1H) at 7.64 ppm assigned to 5″-H, and a broad singlet (1H) at 11.04 ppm assigned to 3′-NH. In fact, an H,H-NOESY effect was observed between both 5-NH_2 and 3′-NH groups in agreement with the proposed conformational structure. Without including the methyl carbon atoms, the relevant feature in

Scheme 1



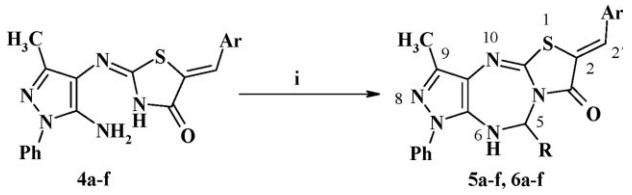
the ^{13}C NMR spectrum of this compound is that all signals appear at aromatic field (120.5–162.3 ppm), which is consistent with the proposed structure (**4a**). Finally, the molecular ion ($m/z = 420$), showed in mass spectrum confirmed that the formation process of this solid effectively involved the loss of a molecule of H_2S but not the loss of a molecule of H_2O, as expected for the synthesis of our compound **3**.

To evaluate the general character of this unplanned reaction, this approach was extended to the other 5-arylidene-2-thioxothiazolidin-4-ones (**2b–f**) with similar results, that is, yielding compounds **4b–f** as unique products involving in all the cases the loss of a molecule of H_2S, as shown in Scheme 1 and Table 1.

Trying to overcome the aforementioned failed attempt to obtain compounds **3**, we rationalized that according to NOESY experiments both 5-NH_2 and 3′-NH groups in **4** are certainly spatially nearby. Therefore, we considered the possibility of completing the cyclization process by treatment of compounds **4** with aldehydes, toward the formation of a novel, although slightly different from **3**, no less interesting triazepine system **5**. In this sense, the heating of compounds **4a–f** with an excess of formaldehyde in DMF at 70°C enabled us to obtain the novel pyrazolo[3,4-*f*]thiazolo[2,3-*b*][1,3,5]triazepines (**5a–f**) in 70 to 92% yield, as shown in Scheme 2 and Table 2.

In the ^1H NMR spectra of compounds **5**, the proton 2′-H appears as a singlet at $\delta = 7.65–7.77$ ppm. The signals for the 9-CH_3 protons of the pyrazole ring result in a singlet at $\delta = 2.19–2.22$ ppm. The two protons, 5-H and 6-NH, of the triazepine ring appear coupled between them, and the coupling constants are in the range of $J = 6.2–6.4$ Hz.

Scheme 2. i = HCHO for **5a–f** (R = H). i = CH_3CHO for **6a–f** (R = CH_3).



The analysis of ^{13}C, DEPT-135, and two-dimensional heteronuclear NMR spectra provided the final structural elucidation of compounds **5**. Thus, the signal for C-5 is in the range of $\delta = 56.4–63.9$ ppm. The HMBC experiments for all derivatives indicate three-bond correlations between 5-H and quaternary carbons C-10a and C-6a. Mass spectra of compounds **5** show well-defined molecular ions with a characteristic fragmentation pattern involving the loss of phenyl group.

The extension of this procedure to acetaldehyde provided the analog triazepine systems **6a–f** also in good yields, as shown in Table 2. It is worth mentioning that when the compounds **4** were treated with aryl aldehydes (*i.e.* benzaldehyde, 4-methylbenzaldehyde and 4-chlorobenzadehyde), under the same reaction conditions, the reaction was not observed. Probably, steric effects could be related to such lack of reactivity, and therefore, this procedure is limited to aliphatic aldehydes. In short, we have not yet concluded an explanation why monoamines reacts with the arylidene derivatives **2** involving the C=O functionality through its α,β-unsaturated moiety as previously reported [8], while the analog diamine **1** reacted exclusively by the C=S functionality without participation of the α,β-unsaturated moiety. Currently, we are working in other cases to try to give a satisfactory explanation to this matter.

In summary, we have developed a new and versatile indirect two-step method for the synthesis of novel thiazolopyrazolotriazepines **5** and **6**, *via* the initially unplanned iminopyrazoles **4**, followed by treatment with

Table 1

Physical and analytical data of compounds **4a–f**.

Compound	Ar	m.p. (°C)	Yield
4a	4-$O_2NC_6H_4$	287–288	87
4b	4-BrC_6H_4	265–267	82
4c	4-ClC_6H_4	261–263	70
4d	4-FC_6H_4	267–269	71
4e	4-$CH_3C_6H_4$	189–190	65
4f	4-$CF_3C_6H_4$	286–288	62

Table 2

Physical and analytical data of compounds (**5/6**)**a–f**.

Compound	Ar	m.p. (°C)	Yield (%)
(5/6)a	4-$O_2NC_6H_4$	291–293/262–264	72/92
(5/6)b	4-BrC_6H_4	248–250/262–264	70/94
(5/6)c	4-ClC_6H_4	310–312/254–256	70/88
(5/6)d	4-FC_6H_4	265–267/209–211	92/93
(5/6)e	4-$CH_3C_6H_4$	246–248/264–266	90/92
(5/6)f	4-$CF_3C_6H_4$	222–224/231–233	88/85

aliphatic aldehydes. The chemical and biological potential of the triazepines **5** and **6** described herein are currently under investigation.

EXPERIMENTAL

Melting points were measured using a Stuart SMP3 melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR 8400 instrument. The ^{1}H and ^{13}C NMR spectra were run on a Bruker DPX 400 spectrometer operating at 400 and 100 MHz, respectively, using dimethyl sulfoxide-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra were scanned on a Hewlett Packard HP Engine-5989 spectrometer (equipped with a direct inlet probe) operating at 70 eV. High-resolution mass spectra (HRMS) were recorded in a Waters Micromass AutoSpec NT spectrometer (STIUJA). The elemental analyses have been obtained using a LECO CHNS-900 and a Thermo Finnigan FlashEA1112 CHNS-O (STIUJA) elemental analyzers. Thin layer chromatography (TLC) was performed on a 0.2-mm precoated plates of silica gel 60GF$_{254}$ (Merck). The benzylidene derivatives of rhodanine were obtained according to methodology described in the work [6c].

General procedure for the synthesis of (*Z*)-2′-[(5-amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5′-arylidenethiazolidin-4-ones (4a–f). To a mixture of 4,5-diamino-3-methyl-1-phenylpyrazole **1** (1.5 mmol), ethanol (20 mL) and triethylamine (1 mL) was added to the corresponding 5-arylidene-2-thioxothiazolidin-4-one (1.5 mmol). The mixture was refluxed for 15 h. The formed precipitate was filtered off and washed with ethanol and recrystallized from ethanol.

(Z)-2′-[(5-Amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5′-(4-nitrobenzylidene)thiazolidin-4-one (4a). This compound was obtained as yellow solid (ethanol); IR (KBr): (NH, NH$_2$) 3410 and 3285, C=O 1700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H, 3-CH$_3$), 5.72 (s, 2H, NH$_2$), 7.34 (t, 1H, H$_p$-Ph, J = 7.5 Hz), 7.48 (t, 2H, H$_m$-Ph, J = 8.2 Hz), 7.50 (d, 2H, H$_o$-Ar, J = 8.2 Hz), 7.62 (d, 2H, H$_o$-Ph, J = 8.6 Hz), 7.64 (s, 1H, H-5″), 7.67 (d, 2H, H$_m$-Ar, J = 8.2 Hz), 11.04 ppm (s, 1H, 3′-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.3 (3-CH$_3$), 120.5 (C-4), 122.5 (C$_o$), 126.3 (C$_p$), 128.2 (C-5′), 128.5 (C-5″), 129.0 (C$_i$-Ar), 129.2 (C$_m$-Ph), 131.1 (C$_o$-Ar), 132.2 (C$_m$-Ar), 134.0 (C$_p$-Ar), 139.0 (C$_i$-Ph), 143.3 (C-5), 144.9 (C-2′), 147.0 (C-3), 162.3 ppm (C-4′); ms (EI, 70 eV) *m/z* (%): 420 (M$^+$, 100), 213 (39). *Anal*. Calcd for C$_{20}$H$_{16}$N$_6$O$_3$S: C, 57.13; H, 3.84; N, 19.99. Found: C, 57.01; H, 3.79; N, 19.91.

(Z)-2′-[(5-Amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5′-(4-bromobenzylidene)thiazolidin-4-one (4b). This compound was obtained as yellow solid (ethanol); IR (KBr): (NH, NH$_2$) 3442 and 3288, C=O 1698 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.05 (s, 3H, 3-CH$_3$), 5.68 (s, 2H, NH$_2$), 7.34 (t, 1H, H$_p$-Ph, J = 7.6 Hz), 7.49 (d, 2H, H$_m$-Ph, J = 8.3 Hz), 7.50 (d, 2H, Ho-Ar, J = 8.0 Hz), 7.63 (d, 2H, H$_o$-Ph, J = 8.7 Hz), 7.64 (s, 1H, H-5″), 7.68 (d, 2H, H$_m$-Ar, J = 8.0 Hz), 10.88 ppm (s, 1H, 3′-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.4 (3-CH$_3$), 120.3 (C-4), 122.4 (C$_o$-Ph), 122.9 (C$_i$-Ar), 126.2 (C$_p$-Ph), 128.0 (C-5″), 128.4 (C-5″), 129.1 (C$_m$-Ph), 131.3 (C$_o$-Ar), 132.2 (C$_m$-Ar), 133.1 (C$_p$-Ar), 139.0 (C$_i$-Ph), 143.2 (C-5), 143.5 (C-2′), 144.9 (C-3), 161.8 ppm (C-4′); ms (EI, 70 eV) *m/z* (%): 455 (M$^+$, 100), 213 (58). *Anal*. Calcd for C$_{20}$H$_{16}$BrN$_5$OS: C, 52.87; H, 3.55; N, 15.41. Found: C, 52.89; H, 3.49; N, 15.39.

(Z)-2′-[(5-Amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5′-(4-chlorobenzylidene)thiazolidin-4-one (4c). This compound was obtained as yellow solid (ethanol); IR (KBr): (NH, NH$_2$) 3410 and 3285, C=O 1700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.05 (s, 3H, 3-CH$_3$), 5.68 (s, 2H, NH$_2$), 7.33 (t, 1H, H$_p$-Ph, J = 7.6 Hz), 7.49 (d, 2H, H$_m$-Ph, J = 8.3 Hz), 7.50 (d, 2H, H$_o$-Ar, J = 8.3 Hz), 7.62 (d, 2H, H$_o$-Ph, J = 8.6 Hz), 7.64 (s, 1H, H-5″), 7.68 (d, 2H, H$_m$-Ar, J = 8.3 Hz), 10.96 ppm (s, 1H, 3′-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.3 (3-CH$_3$), 120.8 (C-4), 122.4 (C$_o$-Ph), 123.0 (C$_i$-Ar), 126.2 (C$_p$-Ph), 128.1 (C-5′), 128.4 (C-5″), 129.1 (C$_m$-Ph), 131.1 (C$_o$-Ar), 132.5 (C$_m$-Ar), 132.8 (C$_p$-Ar), 138.9 (C$_i$-Ph), 143.2 (C-5), 144.0 (C-2′), 144.9 (C-3), 162.0 ppm (C-4′); ms (EI, 70 eV) *m/z* (%): 409 (M$^+$, 100), 213 (39). *Anal*. Calcd for C$_{20}$H$_{16}$ClN$_5$OS: C, 58.61; H, 3.93; N, 17.09. Found: C, 58.56; H, 3.99; N, 17.00.

(Z)-2′-[(5-Amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5′-(4-fluorobenzylidene)thiazolidin-4-one (4d). This compound was obtained as yellow solid (ethanol); IR (KBr): (NH, NH$_2$) 3425 and 3290, C=O 1680 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H, 3-CH$_3$), 5.71 (s, 2H, NH$_2$), 7.34 (t, 1H, H$_p$-Ph, J = 6.2 Hz), 7.52 (d, 2H, H$_m$-Ph, J = 7.4 Hz), 7.55 (d, 2H, H$_o$-Ar, J = 8.7 Hz), 7.60 (d, 2H, H$_o$-Ph, J = 8.7 Hz), 7.69 (s, 1H, H-5″), 7.70 (dd, 2H, H$_m$-Ar, J = 5.29 Hz, J = 8.7 Hz), 10.89 ppm (s, 1H, 3′-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.3 (3-CH$_3$), 120.7 (C-4), 122.9 (C$_o$-Ph), 122.9 (C$_i$-Ar), 125.9 (C$_p$-Ph), 128.8 (C-5′), 129.0 (C-5″), 129.1 (C$_m$-Ph), 132.3 (d, $^3J_{C-F}$ = 8.0 Hz, C$_o$-Ar), 133.9 (d, $^2J_{C-F}$ = 22.0 Hz, C$_m$-Ar), 139.3 (d, $^1J_{C-F}$ = 242.0 Hz, C$_p$-Ar), 140.2 (C$_i$-Ph), 143.4 (C-5), 144.8 (C-2′), 144.9 (C-3), 163.2 ppm (C-4′); ms (EI, 70 eV) *m/z* (%): 393 (M$^+$, 100), 213 (47). *Anal*. Calcd for C$_{20}$H$_{16}$FN$_5$OS: C, 61.06; H, 4.10; N, 17.80. Found: C, 61.10; H, 4.02; N, 17.75.

(Z)-2′-[(5-Amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5′-(4-methylbenzylidene)thiazolidin-4-one (4e). This compound was obtained as yellow solid (ethanol); IR (KBr): (NH, NH$_2$) 3446 and 3286, C=O 1695 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H, 3-CH$_3$), 2.31 (s, 3H, CH$_3$Ar), 5.68 (s, 2H, NH$_2$), 7.29 (d, 2H, H$_o$-Ar, J = 8.1 Hz), 7.33 (t, 1H, H$_p$-Ph, J = 7.4 Hz), 7.43 (d, 2H, H$_m$-Ar, J = 8.1 Hz), 7.45 (d, 2H, H$_m$-Ph, J = 7.4 Hz), 7.51 (d, 2H, H$_o$-Ph, J = 6.4 Hz), 7.63 (s, 1H, H-5″), 10.82 ppm (s, 1H, 3′-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.4 (3-CH$_3$), 21.0 (CH$_3$Ar), 120.9 (C-4), 122.4 (C$_o$-Ph), 122.6 (C$_i$-Ar), 126.3 (C$_p$-Ph), 127.4 (C-5′), 127.6 (C$_p$-Ar), 127.9 (C$_m$-Ph), 129.2 (C-5″), 129.6 (C$_o$-Ar), 131.0 (C$_m$-Ar), 140.4 (C$_i$-Ph) 143.2 (C-5), 143.6 (C-2′), 144.9 (C-3), 162.4 ppm (C-4′); ms (EI, 70 eV) *m/z* (%): 389 (M$^+$, 100), 213 (69), 148 (32). *Anal*. Calcd for C$_{21}$H$_{19}$N$_5$OS: C, 64.76; H, 4.92; N, 17.98. Found: C, 64.70; H, 4.90; N, 17.95.

(Z)-2′-[(5-Amino-3-methyl-1-phenylpyrazol-4-yl)imino]-5′-(4-trifluoromethylbenzylidene)-thiazolidin-4-one (4f). This compound was obtained as yellow solid (ethanol); IR (KBr): (NH, NH$_2$) 3449 and 3296, C=O 1700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H, 3-CH$_3$), 5.70 (s, 2H, NH$_2$), 7.34 (t, 1H, H$_p$-Ph, J = 7.6 Hz), 7.50 (d, 2H, H$_m$-Ph, J = 7.7 Hz), 7.64 (d, 2H, H$_o$-Ph, J = 7.7 Hz), 7.74 (s, 1H, H-5″), 7.77 (d, 2H, H$_m$-Ar, J = 8.3 Hz), 7.84 (d, 2H, H$_o$-Ar, J = 8.3 Hz), 10.97 ppm (s, 1H, 3′-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ

11.3 (3-CH_3), 120.3 (C-4), 122.4 (C_o-Ph), 122.7 (C_i-Ar), 126.0 (C_p-Ph), 126.0 (q, $^3J_{C-F}$ = 5.2 Hz, C_m-Ar), 127.4 (C-5′), 127.9 (C_m-Ph), 128.5 (q, $^1J_{C-F}$ = 268.0 Hz, CF_3), 128.9 (q, $^2J_{C-F}$ = 31.2 Hz C_p-Ar), 129.2 ($C_{o'}$), 130.0 (C-5″), 138.9 (C_i-Ar), 143.2 (C-5), 143.5 (C-2′), 144.9 (C-3), 162.3 ppm (C-4′); ms (EI, 70 eV) *m/z* (%): 443 (M^+, 100), 213 (77), 145 (40). *Anal*. Calcd for $C_{21}H_{16}F_3N_5OS$: C, 56.88; H, 3.64; N, 15.79. Found: C, 56.82; H, 3.65; N, 15.84.

General procedure for the synthesis of (*Z*)-2-arylidene-9-methyl-7-phenyl-5-*R*-5,6-dihydropyrazolo[3,4-*f*][1,3]thiazolo [2,3-*b*][1,3,5]triazepin-3-ones (5a–f and 6a–f). A mixture of 2-(5-amino-3-methyl-1-phenylpyrazol-4-ylimino)-5-arylidenethiazolidin-4-one **4** (1 mmol), formaldehyde or acetaldehyde (2 mmol), and DMF (2.0 mL) was heated at 70°C for 2 h. The formed products were precipitated by adding water, filtered off under vacuum, washed with water and recrystallized from ethanol.

(Z)-9-Methyl-2-(4-nitrobenzylidene)-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-ona (5a). This compound was obtained as brown solid (ethanol); IR (KBr): NH 3371, C=O 1690 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 3H, 9-CH_3), 5.04 (d, 2H, H-5, *J* = 6.3 Hz), 7.18 (t, 1H, 6-NH, *J* = 6.2 Hz), 7.34 (t, 1H, H_p-Ph, *J* = 7.6 Hz), 7.48 (t, 2H, H_m-Ph, *J* = 8.4 Hz), 7.61 (d, 2H, H_o-Ph, *J* = 8.7 Hz), 7.77 (s, 1H, H-2′), 7.82 (d, 2H, H_o-Ar, *J* = 8.1 Hz), 8.30 ppm (d, 2H, H_m-Ar, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.1 (9-CH_3), 56.5 (C-5), 118.2 (C-9a), 122.5 (C_o-Ph), 124.1 (C_m-Ar), 125.9 (C-2′), 126.5 (C_p-Ph), 128.6 (C-2), 129.0 (C_m-Ph), 130.5 (C_o-Ar), 138.4 (C-6a), 138.5 (C_i-Ph), 139.9 (C_i-Ar), 142.5 (C-10a), 145.5 (C-9), 146.7 (C_p-Ar), 164.8 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 432 (M^+, 100), 225 (27), 131 (28). *Anal*. Calcd for $C_{21}H_{16}N_6O_3S$: C, 58.32; H, 3.73; N, 19.43. Found: C, 58.36; H, 3.67; N, 19.50.

(Z)-2-(4-Bromobenzylidene)-9-methyl-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (5b). This compound was obtained as red solid (ethanol); IR (KBr): NH 3394, C=O 1682 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, 9-CH_3), 5.02 (d, 2H, H-5, *J* = 6.0 Hz), 7.15 (t, 1H, 6-NH, *J* = 6.0 Hz), 7.34 (t, 1H, H_p-Ph, *J* = 7.5 Hz), 7.48 (t, 2H, H_m-Ph, *J* = 8.2 Hz), 7.53 (d, 2H, H_o-Ar, *J* = 8.0 Hz), 7.61 (d, 2H, H_o-Ph, *J* = 8.6 Hz), 7.66 (s, 1H, H-2′), 7.70 ppm (d, 2H, H_m-Ar, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.1 (9-CH_3), 56.4 (C-5), 118.3 (C-9a), 122.4 (C_o-Ph), 122.9 (C_p-Ar), 124.7 (C-2′), 126.4 (C_p-Ph), 127.4 (C-2), 129.0 (C_m-Ph), 131.5 (C_i-Ar), 132.1 (C_o-Ar), 132.8 (C_m-Ar), 138.4 (C-6a), 138.5 (C_i-Ph), 143.1 (C-10a), 145.4 (C-9), 165.1 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 465 (M^+, 83), 225 (52), 212 (52), 77 (100). *Anal*. Calcd for $C_{21}H_{16}BrN_5OS$: C, 54.09; H, 3.46; N, 15.02. Found: C, 54.00; H, 3.39; N, 15.10.

(Z)-2-(4-Chlorobenzylidene)-9-methyl-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (5c). This compound was obtained as red solid (ethanol); IR (KBr): NH 3382, C=O 1704 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, 9-CH_3), 5.02 (d, 2H, H-5, *J* = 5.9 Hz), 7.21 (t, 1H, 6-NH, *J* = 5.9 Hz), 7.33 (t, 1H, H_p-Ph, *J* = 7.6 Hz), 7.48 (t, 2H, H_m-Ph, *J* = 8.3 Hz), 7.60 (d, 2H, H_o-Ar, *J* = 8.2 Hz), 7.62 (d, 2H, H_o-Ph, *J* = 8.7 Hz), 7.64 (d, 2H, H_m-Ar, *J* = 8.3 Hz), 7.71 ppm (s, 1H, H-2′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.2 (9-CH_3), 56.5 (C-5), 118.3 (C-9a), 122.5 (C_o-Ph), 124.6 (C-2′), 124.7 (C_p-Ar), 126.4 (C_p-Ph), 127.3 (C-2), 129.0 (C_m-Ph), 129.3 (C_o-Ar), 131.5 (C_m-Ar), 132.6 (C_i-Ar), 134.1 (C_i-Ph), 138.5 (C-10a), 143.2 (C-6a), 145.4 (C-9), 165.1 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 421 (M^+, 100), 225 (30), 168 (40). *Anal*. Calcd for $C_{21}H_{16}ClN_5OS$: C, 59.78; H, 3.82; N, 16.60. Found: C, 59.75; H, 3.76; N, 16.50.

(Z)-2-(4-Fluorobenzylidene)-9-methyl-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (5d). This compound was obtained as orange solid (ethanol); IR (KBr): NH 3304, C=O 1677 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, 9-CH_3), 5.03 (d, 2H, H-5, *J* = 6.2 Hz), 7.13 (t, 1H, 6-NH, *J* = 6.2 Hz), 7.35 (t, 1H, H_p-Ph, *J* = 7.5 Hz), 7.37 (d, 2H, H_o-Ar, *J* = 8.9 Hz), 7.48 (t, 2H, H_m-Ph, *J* = 8.3 Hz), 7.61 (d, 2H, H_o-Ph, *J* = 8.7 Hz), 7.63 (dd, 2H, H_m-Ar, J_F = 5.38 Hz, *J* = 8.9 Hz), 7.72 ppm (s, 1H, H-2′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.1 (9-CH_3), 56.4 (C-5), 116.3 (d, $^3J_{C-F}$ = 8.0 Hz, C_o-Ar), 118.4 (C-9a), 122.5 (C_o-Ph), 123.5 (C-6a), 126.4 (C_p-Ph), 127.6 (C-2′), 128.9 (C_m-Ph), 130.3 (C_i-Ar), 132.1 (d, $^2J_{C-F}$ = 22.0 Hz, C_m-Ar), 138.5 (C_i-Ph), 143.3 (C-9), 145.4 (C-10a), 161.1 (C-2), 162.4 (d, $^1J_{C-F}$ = 248.0 Hz, C_p-Ar), 165.2 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 405 (M^+, 100), 225 (31), 152 (66). *Anal*. Calcd for $C_{21}H_{16}FN_5OS$: C, 62.21; H, 3.98; N, 17.27. Found: C, 62.27; H, 3.99; N, 17.37.

(Z)-9-Methyl-2-(4-methylbenzylidene)-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (5e). This compound was obtained as orange solid (ethanol); IR (KBr): NH 3357, C=O 1708 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H, 9-CH_3), 2.37 (s, 3H, CH_3Ar), 5.03 (d, 2H, H-5, *J* = 6.0 Hz), 6.82 (t, 1H, 6-NH, *J* = 6.0 Hz), 7.32 (t, 1H, H_p-Ph, *J* = 7.3 Hz), 7.34 (t, 2H, H_m-Ph, *J* = 7.1 Hz), 7.46 (d, 2H, H_o-Ph, *J* = 8.3 Hz), 7.48 (d, 2H, H_o-Ar, *J* = 7.7 Hz), 7.61 (d, 2H, H_m-Ar, *J* = 7.7 Hz), 7.65 ppm (s, 1H, H-2′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.4 (9-CH_3), 21.3 (CH_3Ar), 57.1 (C-5), 118.9 (C-10a), 123.0 (C_m-Ar), 123.5 (C_i-Ar), 126.8 (C_p-Ph), 129.3 (C-2′), 129.3 (C_o-Ph), 130.1 (C_o-Ar), 130.2 (C_m-Ph), 131.6 (C_i-Ph), 139.2 (C-2), 139.4 (C-6a), 140.2 (C_p-Ar), 143.9 (C-10a), 145.9 (C-9), 165.7 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 401 (M^+, 71), 225 (21), 148 (100), 77 (100). *Anal*. Calcd for $C_{22}H_{19}N_5OS$: C, 65.82; H, 4.77; N, 17.44. Found: C, 65.72; H, 4.71; N, 17.38.

(Z)-9-Methyl-7-phenyl-2-(4-trifluoromethylbenzylidene)-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (5f). This compound was obtained as orange solid (ethanol); IR (KBr): NH 3341, C=O 1689 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H, 9-CH_3), 5.81 (m, 2H, H-5), 7.14 (t, 1H, 6-NH), 7.33 (t, 1H, H_p-Ph, *J* = 7.5 Hz), 7.48 (t, 2H, H_m-Ph, *J* = 7.9 Hz), 7.58 (d, 2H, H_o-Ph, *J* = 8.3 Hz), 7.75 (s, 1H, H-2′), 7.80 (d, 2H, H_o-Ar, *J* = 8.3 Hz), 7.85 ppm (d, 2H, H_m-Ar, *J* = 8.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.2 (9-CH_3), 63.6 (C-5), 118.8 (C-9a), 123.1 (C_o-Ph), 125.7 (q, $^3J_{C-F}$ = 5.6 Hz C_m-Ar), 125.9 (q, $^1J_{C-F}$ = 274.0 Hz, CF_3,), 126.4 (q, $^2J_{C-F}$ = 30.6 Hz, C_p-Ar), 126.5 (C_p-Ph), 126.6 (C-2′), 129.2 (C-6a), 129.5 (C_i-Ar), 130.6 (C_m-Ph), 132.4 (C_o-Ar), 138.1 (C_i-Ph), 138.9 (C-2), 142.2 (C-10a), 145.8 (C-9), 165.05 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 455 (M^+, 100), 225 (20), 77 (34). *Anal*. Calcd for $C_{22}H_{16}F_3N_5OS$: C, 58.02; H, 3.54; N, 15.38. Found: C, 58.11; H, 3.60; N, 15.48.

(Z)-5,9-Dimethyl-2-(4-nitrobenzylidene)-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (6a). This compound was obtained as red solid (ethanol); IR (KBr): NH 3318, C=O 1691 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, 3H, 5-CH_3, *J* = 7.0 Hz), 2.21 (s, 3H, 9-CH_3), 5.81 (m, 1H, H-5), 7.16 (d, 1H, 6-NH, *J* = 6.1 Hz), 7.34 (t, 1H,

H_p-Ph, J = 7.9 Hz), 7.48 (t, 2H, H_m-Ph, J = 7.0 Hz), 7.58 (d, 2H, H_o-Ph, J = 7.9 Hz), 7.76 (s, 1H, H-2′), 7.83 (d, 2H, H_o-Ar, J = 7.9 Hz), 8.29 ppm (d, 2H, H_m-Ar, J = 7.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.6 (9-CH_3), 21.0 (5-CH_3), 63.7 (C-5), 118.7 (C-9a) 123.1 (C_o-Ph), 124.7 (C_m-Ar), 126.4 (C-2′), 127.1 (C_p-Ph), 128.7 (C-2), 129.6 (C_m-Ph), 131.0 (C_o-Ar), 136.5 (C-6a), 138.9 (C_i-Ph), 140.5 (C_p-Ar), 141.9 (C-10a), 145.80 (C-9), 147.3 (C_i-Ar), 164.9 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 446 (M^+, 100), 413 (30), 239 (20). *Anal.* Calcd for $C_{22}H_{18}N_6O_3S$: C, 59.18; H, 4.06; N, 18.82. Found: C, 59.10; H, 4.01; N, 18.90.

(Z)-2-(4-Bromobenzylidene)-5,9-dimethyl-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (6b). This compound was obtained as yellow solid (ethanol); IR (KBr): NH 3298, C=O 1688 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, 3H, 5-CH_3, J = 5.6 Hz), 2.23 (s, 3H, 9-CH_3), 5.84 (m, 1H, H-5), 6.81 (d, 1H, 6-NH, J = 6.2 Hz), 7.33 (t, 1H, H_p-Ph, J = 7.1 Hz), 7.48 (t, 2H, H_m-Ph, J = 7.3 Hz), 7.52 (d, 2H, H_o-Ar, J = 8.0 Hz), 7.62 (d, 2H, H_o-Ph, J = 8.2 Hz), 7.65 (s, 1H, H-2′), 7.74 ppm (d, 2H, H_m-Ar, J = 8.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.3 (9-CH_3), 20.9 (5-CH_3), 63.9 (C-5), 118.2 (C-9a), 122.3 (C_o-Ph), 123.0 (C_p-Ar), 124.6 (C-2′), 127.4 (C_p-Ph), 127.8 (C-2), 128.6 (C_m-Ph), 131.7 (C_i-Ar), 132.1 (C_o-Ar), 132.8 (C_m-Ar), 138.8 (C-6a), 139.3 (C_i-Ph), 143.1 (C-10a), 145.4 (C-9), 165.2 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 479 (M^+, 100), 481 (98), 239 (50), 168 (44), 77 (75). *Anal.* Calcd for $C_{22}H_{18}BrN_5OS$: C, 55.01; H, 3.78; N, 14.58. Found: C, 55.09; H, 3.83; N, 14.67.

(Z)-2-(4-Chlorobenzylidene)-5,9-dimethyl-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (6c). This compound was obtained as yellow solid (ethanol); IR (KBr): NH 3296, C=O 1687 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, 3H, 5-CH_3, J = 6.6 Hz), 2.23 (s, 3H, 9-CH_3), 5.82 (m, 1H, H-5), 7.13 (d, 1H, 6-NH, J = 5.0 Hz), 7.34 (t, 1H, H_p-Ph, J = 7.2 Hz), 7.49 (t, 2H, H_m-Ph, J = 7.4 Hz), 7.59 (d, 2H, H_o-Ph, J = 8.2 Hz), 7.62 (d, 2H, H_o-Ar, J = 8.2 Hz), 7.63 (d, 2H, H_m-Ar, J = 8.2 Hz), 7.71 ppm (s, 1H, H-2′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.1 (9-CH_3), 20.5 (5-CH_3), 56.5 (C-5), 118.4 (C-9a), 122.6 (C_o-Ph), 124.3 (C-2′), 126.6 (C_p-Ar), 127.4 (C_p-Ph), 129.1 (C-2), 129.3 (C_m-Ph), 131.3 (C_o-Ar), 132.6 (C_m-Ar), 134.1 (C_i-Ar), 135.9 (C_i-Ph), 138.5 (C-10a), 142.0 (C-6a), 145.2 (C-9), 164.7 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 435 (M^+, 100), 239 (52), 168 (47), 77 (86). *Anal.* Calcd for $C_{22}H_{18}ClN_5OS$: C, 60.62; H, 4.16; N, 16.06. Found: C, 60.55; H, 4.23; N, 16.15.

(Z)-5,9-Dimethyl-2-(4-fluorobenzylidene)-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (6d). This compound was obtained as yellow solid (ethanol); IR (KBr): NH 3398, C=O 1692 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, 3H, 5-CH_3, J = 6.6 Hz), 2.23 (s, 3H, 9-CH_3), 5.83 (m, 1H, H-5), 7.12 (d, 1H, 6-NH, J = 5.0 Hz), 7.34 (t, 1H, H_p-Ph, J = 6.1 Hz), 7.38 (d, 2H, H_o-Ar, J = 8.7 Hz), 7.49 (t, 2H, H_m-Ph, J = 8.1 Hz), 7.61 (d, 2H, H_o-Ph, J = 7.4 Hz), 7.68 (dd, 2H, H_m-Ar, J = 8.7 Hz, J = 5.38 Hz), 7.72 ppm (s, 1H, H-2′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.1 (9-CH_3), 20.5 (5-CH_3), 63.1 (C-5), 116.2 (d, $^2J_{C-F}$ = 21.0 Hz, C_o-Ar), 118.4 (C-9a), 122.6 (C_o-Ph), 123.1 (C-6a), 127.7 (C-2′), 127.8 (C_p-Ph), 128.6 (C-2), 129.1 (C_m-Ph), 131.0 (C_i-Ar), 132.1 (d, $^3J_{C-F}$ = 9.0 Hz, C_m-Ar), 138.5 (C_i-Ph), 142.2 (C-10a), 145.2 (C-9), 162.4 (d, $^1J_{C-F}$ = 248.0 Hz, C_p-Ar), 164.8 (C-3); ms (EI, 70 eV) *m/z* (%): 419 (M^+, 100), 239 (49), 152 (66), 77 (86). *Anal.* Calcd for $C_{22}H_{18}FN_5OS$: C, 62.99; H, 4.33; N, 16.70. Found: C, 62.91; H, 4.39; N, 16.78.

(Z)-5,9-Dimethyl-2-(4-methylbenzyliden)-7-phenyl-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]triazepin-3-one (6e). This compound was obtained as yellow solid (ethanol); IR (KBr): NH 3442, C=O 1701 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, 3H, 5-CH_3, J = 6.4 Hz), 2.24 (s, 3H, 9-CH_3), 2.39 (s, 3H, CH_3Ar), 5.83 (m, 1H, H-5), 7.10 (d, 1H, 6-NH, J = 5.0 Hz), 7.34 (t, 1H, H_p-Ph, J = 6.2 Hz), 7.35 (t, 2H, H_m-Ph, J = 7.4 Hz), 7.38 (d, 2H, H_o-Ph, J = 8.5 Hz), 7.49 (d, 2H, H_o-Ar J = 7.7 Hz), 7.61 (d, 2H, H_m-Ar, J = 7.7 Hz), 7.67 ppm (s, 1H, H-2′); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.1 (9-CH_3), 20.5 (5-CH_3), 21.3 (CH_3Ar), 62.9 (C-4), 118.5 (C-9a), 124.2 (C_m-Ar), 125.5 (C_i-Ar), 126.7 (C_p-Ph), 128.4 (C-2′), 129.3 (C_o-Ph), 130.1 (C_o-Ar), 131.2 (C_m-Ph), 131.6 (C_i-Ph), 139.7 (C-2), 141.0 (C-6a), 141.2 (C_p-Ar), 142.5 (C-10a), 145.2 (C-9), 165.7 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 415 (M^+, 100), 239 (46), 148 (57), 77 (73). *Anal.* Calcd for $C_{23}H_{21}N_5OS$: C, 66.48; H, 5.09; N, 16.85. Found: C, 66.39; H, 5.17; N, 16.84.

(Z)-5,9-Dimethyl-7-phenyl-2-(4-trifluoromethylbenzyli-dene)-5,6-dihydropyrazolo[3,4-f]thiazolo[2,3-b][1,3,5]tri-azepin-3-one (6f). This compound was obtained as orange solid (ethanol); IR (KBr): NH 3341, C=O 1689 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, 3H, 5-CH_3, J = 6.5 Hz), 2.21 (s, 3H, 9-CH_3), 5.04 (m, 1H, H-5), 7.17 (s, 1H, 6-NH), 7.34 (t, 1H, H_p-Ph, J =7.3 Hz), 7.49 (t, 2H, H_m-Ph, J = 7.8 Hz), 7.63 (d, 2H, H_o-Ph, J = 8.3 Hz), 7.77 (s, 1H, H-2′), 7.81 (d, 2H, H_o-Ar, J = 8.3 Hz), 7.87 ppm (d, 2H, H_m-Ar, J = 8.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.1 (9-CH_3), 21.0 (5-CH_3), 56.5 (C-5), 118.8 (C-9a), 122.2 (C_o-Ph), 125.3 (q, $^3J_{C-F}$ = 4.3 Hz, C_m-Ar), 125.8 (q, $^2J_{C-F}$ = 31.6 Hz, C_p-Ar), 126.0 (q, $^1J_{C-F}$ = 276.0 Hz, CF_3), 126.5 (C_p-Ph), 126.6 (C-2′), 127.0 (C-5a), 128.7 (C_i-Ar), 128.9 (C_m-Ph), 130.2 (C_o-Ar), 137.6 (C_i-Ph), 138.5 (C-2), 142.8 (C-10a), 145.5 (C-9), 164.9 ppm (C-3); ms (EI, 70 eV) *m/z* (%): 469 (M^+, 100), 239 (23), 145 (17). *Anal.* Calcd for $C_{23}H_{18}F_3N_5OS$: C, 58.84; H, 3.86; N, 14.92. Found: C, 58.91; H, 3.79; N, 14.99.

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