Tetrahedron 65 (2009) 644–647

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis and tautomeric structure of 6-arylhydrazono 1*H*-pyrazolo[3′,4′:4,5]-pyrimido[1,6-*b*][1,2,4]triazepines

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ARTICLE INFO

Article history:
Received 17 September 2008
Received in revised form 19 October 2008
Accepted 6 November 2008
Available online 12 November 2008

Keywords:
Azo-hydrazone tautomerism
Heterocycles
Pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*]triazepine

ABSTRACT

A simple synthetic strategy is described for synthesis of the hitherto unreported 6-arylhydrazono-1,3-diphenyl-7-methyl-1*H*-pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazepin-5(6*H*)-ones **5a–j**. The acid dissociation constants were determined for the series prepared and were correlated by the Hammett equation using the enhanced substituent constants. The results of such a correlation together with the spectral data indicated that the studied compounds exist predominantly in the hydrazone tautomeric form.

1. Introduction

In continuation of our studies on the synthesis and elucidation of the tautomeric structures of arylazo heterocycles,[1–8] we wish to report herein the synthesis of a series of the title azo dyes, which have not been reported hitherto. In addition it was thought interesting to elucidate the actual tautomeric structure of such dyes as they can have one or more of four possible tautomeric forms (Fig. 1). The knowledge of the actual tautomeric form(s) of azo dyes in solution and the solid phase is an important factor for their industrial and biological applications. Our interest in arylazo heterocycles is due to the fact that many of such dyes have found many applications in industry including: hair dyeing, disperse dyes, ink-jet inks, and laser material.[9–15]

2. Results and discussion

The starting 1,3-diphenyl-7-methyl-1*H*-pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazepin-5(6*H*)-one **3** has not been reported hitherto. It was prepared in this study by condensation of ethyl acetoacetate **2** with 5-amino-1,3-diphenyl-4,5-dihydro-4-imino-1*H*-pyrazolo[3,4-*d*]pyrimidine **1**.[16] Although the reaction of **1** with **2** can lead to **3** and/or its isomer namely 1,3-diphenyl-5-methyl-1*H*-pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*]triazepin-7(8*H*)-one **4**, the latter isomeric structure was discarded (Scheme 1). This is because reactions of ethyl acetoacetate with imino-aminoheterocycles thus far studied were reported to be regioselective and lead to products that result from nucleophilic attack of the =NH and the N–NH_2 groups at the ester and keto carbonyl groups of the keto ester, respectively, to give the corresponding fused 2-oxo-1,2,4-triazepine derivatives.[17–21] The structure of the product **3** was confirmed by its spectra (MS, ^{1}H NMR, and IR) together with elemental analysis. The ^{1}H NMR spectra revealed four characteristic signals near δ 2.31, 4.21, 7.43–8.75, 9.62 assignable to CH_3, CH_2, C_6H_5, and CH protons, respectively. Its IR spectrum revealed band at 1716 (CO) cm^{-1}. Its mass spectrum shows the molecular ion peak at *m*/*z* 368. A further evidence for the assigned structure **3** is provided by its ^{13}C NMR spectrum, which revealed the signal for the ring carbonyl carbon at δ 173.85. This value suggests that the nitrogen atom adjacent to the carbonyl carbon is sp^2 hybridized.

In aqueous ethanol in the presence of sodium hydroxide, compound **3** reacted with diazotized anilines and afforded the respective arylazo derivatives **5** (Scheme 1). The assigned structure **5** was confirmed by an alternative synthesis of the products **5a**, **5d**, and **5h** as typical examples of the series prepared. Thus, treatment of **1** with each of the compounds **6a**, **6d**, and **6h**[22] in dioxan in presence of triethylamine gave the products **5a**, **5d**, and **5h** that proved identical in all respects (mp, mixed mp, IR, UV) with those obtained above from the coupling of **3** with the respective diazotized anilines (Scheme 1). The mass spectra of the latter products revealed the molecular ion peaks at the expected *m*/*z* values and their elemental analysis data were consistent with their assigned structures. Their IR spectra showed, in each case, one carbonyl band in the region 1708–1655 cm^{-1} and one NH band in the region 3433–3062 cm^{-1}. The observed wavenumber of the CO stretching band in compounds **5** seems to result from the possible

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doi:10.1016/j.tet.2008.11.018

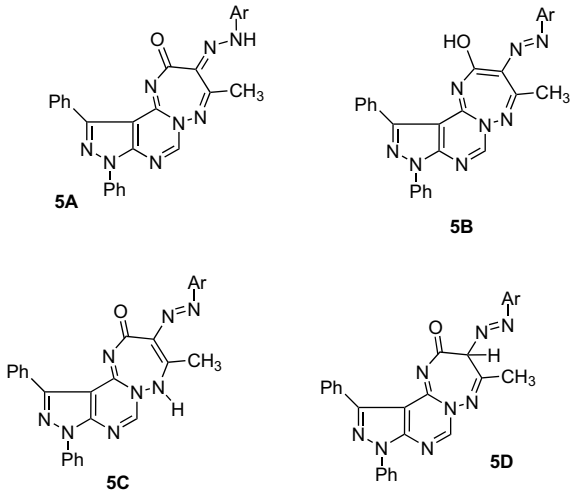
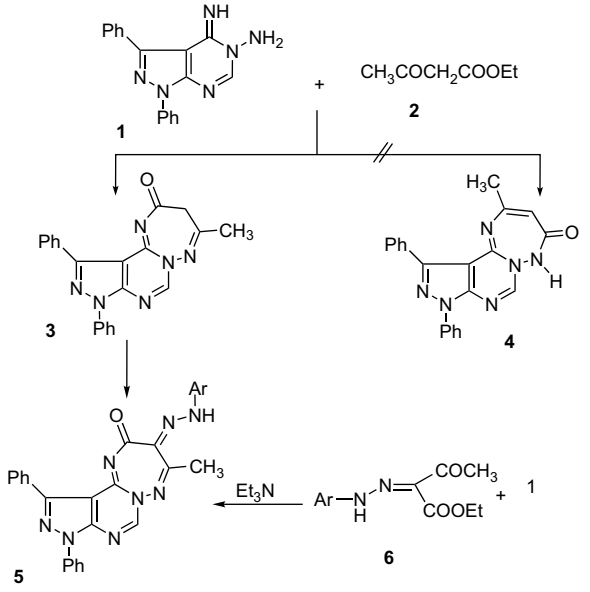


Figure 1.

strong chelation with the hydrazone NH and conjugation with the C=N double bond as required by the hydrazone form **5A** (Fig. 1).[23] These data seem to be consistent with tautomeric form **5A** for the compounds prepared (Fig. 1).

The electronic absorption spectral data of the studied compounds **5a–j** are summarized in Table 1. As shown, each of compounds **5** in dioxan exhibits two characteristic absorption bands in the regions 387–316 and 294–233 nm. Such an absorption pattern is similar to that of typical hydrazone chromophore.[3,24] Furthermore, the spectra of **5d**, taken as a typical example of the series studied, in solvents of different polarities showed little, if any, shift (Table 1). This finding while it suggests that compounds **5** exist in one tautomeric form, it excludes the azo tautomeric forms **5B–D** (Fig. 1).

To provide further evidence for the assignment of the tautomeric structure **5A** for the products prepared **5**, their acid dissociation constants, pK_a's, were determined and their correlation by the



Scheme 1.

Table 1
UV spectra and acid dissociation constants[b] of 6-arylahydrazono-1,3-diphenyl-7-methyl-1*H*-pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazepin-5(6*H*)-ones **5a–j** in dioxan

Compd. No.	λ_{max} (log ε)	pK_a ($\pm s$)	σ^-_x
4a	375 (4.80), 272 (5.16)	8.42 (0.02)	−0.27
4b	380 (4.58), 273 (4.63)	8.00 (0.03)	−0.17
4c	316 (4.08), 294 (4.05), 254 (4.61)	7.88 (0.04)	−0.07
4d[a]	374 (4.47), 233 (5.40)	7.83 (0.05)	0.0
4e	358 (4.91), 292 (4.74), 273 (4.80)	7.12 (0.02)	0.23
4f	385 (4.96), 279 (5.35)	6.75 (0.02)	0.37
4g	372 (4.62), 272 (5.03)	5.93 (0.02)	0.71
4h	387 (5.00), 291 (4.57), 272 (4.83)	4.64 (0.03)	1.28
4i	381 (4.59), 269 (5.08)	6.08 (0.05)	0.68
4j	373 (4.54), 272 (4.97)	5.56 (0.02)	0.84

[a] Solvent: λ_{max} (log ε): acetic acid 380 (4.69), 273 (5.14); chloroform 379 (4.75), 204 (5.40); DMF 372 (4.54), 255 (5.40); ethanol 374 (4.52), 215 (5.00).
[b] pK_a in dioxan–water (4:1 v/v) solution at 25 °C and μ=0.10.

Hammett equation was examined.[3–7] The acid dissociation constants for the series **5a–j** were determined potentiometrically at 25 °C in 80% dioxan–water mixture (v/v). In all determinations the ionic strength μ was kept constant at 0.1. From the pH-titrant volume data, the acid dissociation constants of the compounds studied were calculated (see Section 3) and the results are summarized in Table 1. When the pK_a values were plotted versus *Hammett* substituent constants σ_x,[22] all the substituents fall on the correlation line except the substituents with −R effect, namely the *p*-NO_2, *p*-CH_3CO, and *p*-EtOCO groups, which are capable of direct interaction with the negatively charged reaction site. However, when the pK_a data were plotted versus σ^-_x constants,[22] better correlation was obtained. The equation of the regression line obtained is:

$$pK_a = 7.701 - 2.445\sigma^-_x;\ r = 0.996;\ s = \pm 0.04$$

This excellent correlation indicates that the parameter r^- in the Humffray–Ryan equation:[25] $pK_a = pK^0_a + \rho\{\sigma_x + r^-(\sigma^-_x - \sigma_x)\}$, which gives the contribution of the resonance effect of the substituent varied, is close to unity for the series **5a–j** studied.

The foregoing linear correlation between pK_a values and σ^-_x constants and the values of ρ and r^- found to provide further evidence that the studied compounds **5** exist predominantly in the hydrazone form **5A**. This is because the values of ρ (2.445) and r^-=1.00 are similar to those reported for ionization of phenols (ρ=2.67; r^-=1.00) and anilinium ions (ρ=2.77; r^-=1.00) in 50% ethanol–water mixture.[26–28] This finding indicates that the negative charge in the anion formed by deprotonation of **5** is largely localized on the *N*-atom adjacent to the benzene bearing the substituent. Thus, it is not unreasonable to conclude that the observed linear correlation of the dissociation constants with the enhanced Hammett substituent constant indicates that the hydrazone tautomeric form **5A** prevails under the conditions of the measurement of pK_a's.

In conclusion, we have encountered a novel series of 6-arylhydrazono-1,3-diphenyl-7-methyl-1*H*-pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazepin-5(6*H*)-ones **5** and both their spectral data and LFER correlations of their acidity constants indicate collectively that such compounds exist predominantly in the hydrazone tautomeric form **5A**.

3. Experimental

3.1. General

Melting points were determined on a Gallenkamp apparatus. IR spectra were recorded in potassium bromide using Perkin–Elmer FTIR 1650 and Pye-Unicam SP300 infrared spectrophotometers. ^{1}H NMR and ^{13}C NMR spectra were recorded in deuterated dimethyl sulfoxide using a Varian Gemini 300 NMR spectrometer. Mass

spectra were recorded on a GCMS-QP 1000 EX Shimadzu and GCMS 5988-A HP spectrometers. Electronic absorption spectra were recorded on Perkin–Elmer Lambada 40 spectrophotometer. Elemental analyses were carried out using German made Elementar vario LIII CHNS analyzer at the Microanalytical Laboratory of Cairo University, Giza, Egypt. 5-Amino-1,3-diphenyl-4,5-dihydro-4-imino-1*H*-pyrazolo[3,4-d]pyrimidine **1**[16] and ethyl 2-arylhydrazonoacetoacetate **6**[22] were prepared as previously described.

3.2. 1,3-Diphenyl-7-methyl-1*H*-pyrazolo[3′,4′:4,5]pyrimido-[1,6-*b*][1,2,4]triazepin-5(6*H*)-one (3)

A mixture of **1** (3.01 g, 10 mmol) and ethyl acetoacetate **2** (2.0 g, 15 mmol) was heated to reflux for 30 h, then cooled. The oil residue was treated with methanol. The solid formed was collected by filtration and crystallized from *N*,*N*-dimethylformamide to give compound **3** as pale yellow solid, (1.29 g, 35%). Mp >300 °C. ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 4.21 (s, 2H, CH_2), 7.43–8.75 (m, 10H, Ar–H), 9.62 (s, 1H, pyrimidine-H); ^{13}C NMR (DMSO-d_6) δ 173.85, 148.40, 140.53, 137.91, 129.28, 128.74, 127.66, 127.31, 122.46, 122.38, 120.79, 120.70, 120.66, 120.56, 115.16, 29.81, 19.80; IR (KBr) ν_{max} 1716 (CO) cm^{-1}. MS *m*/*z* (%) 369 (M^++1, 4), 368 (M^+, 32), 350 (13), 281 (58), 228 (21), 187 (17), 152 (30), 126 (100), 116 (43), 111 (60), 102 (44), 91 (78), 77 (17). Anal. Calcd for $C_{21}H_{16}N_6O$ (368.40): C, 68.47; H, 4.38; N, 22.81. Found: C, 68.24; H, 4.13; N, 22.62%.

3.3. 6-Arylhydrazono-1,3-diphenyl-7-methyl-1*H*-pyrazolo-[3′,4′:4,5] pyrimido[1,6-*b*][1,2,4]triazepin-5(6*H*)-ones (5a–j)

3.3.1. Method A

To a stirred solution of compound **3** (0.92 g, 2.5 mmol) in ethanol (20 mL) was added sodium hydroxide (0.1 g, 2.5 mmol) and the mixture was cooled in an ice bath to 0–5 °C. To the resulting solution, while being stirred, was added dropwise over a period of 20 min a solution of the appropriate arenediazonium chloride, prepared as usual by diazotizing the respective aniline (2.5 mmol) in hydrochloric acid (6 M, 1.5 mL) with sodium nitrite (1 M, 2.5 mL). The whole mixture was then left in a refrigerator overnight. The precipitated solid was filtered, washed with water and finally crystallized from ethanol to give the respective hydrazone **5**.

3.3.2. Method B

A mixture of **1** (0.76 g, 2.5 mmol) with ethyl 2-arylhydrazono-3-oxobutanoate **6** (5 mmol) in dioxan (30 mL) and triethylamine (0.35 mL) was heated to reflux for 10 h, then cooled. The solid formed was collected by filtration and crystallized from the appropriated solvent to give the corresponding compounds **5a**, **5d**, and **5h**, which were found identical in all respects with that produced by method A.

3.3.3. 6-(4-Methoxyphenylhydrazono)-1,3-diphenyl-7-methyl-1H-pyrazolo[3′,4′:4,5]pyrimido[1,6-b][1,2,4]triazepin-5(6H)-one (**5a**)

Red solid, (0.78 g, 62%), mp 210–212 °C (ethanol–dioxan). ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.08 (d, *J*=8 Hz, 2H, ArH), 7.38–7.59 (m, 10H, ArH), 7.80 (d, *J*=8 Hz, 2H, ArH), 8.34 (s, 1H, pyrimidine-H), 11.0 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 193.60, 164.05, 159.82, 152.30, 147.71, 144.88, 140.09, 137.50, 131.04, 130.79, 129.82, 128.23, 128.09, 127.57, 127.47, 127.41, 125.66, 121.32, 119.35, 116.20, 67.09, 13.21; IR (KBr) ν_{max} 3395, 1658 cm^{-1}. MS *m*/*z* (%) 504 (M^++2, 36), 503 (M^++1, 51), 502 (M^+, 51), 369 (52), 368 (81), 299 (14), 196 (17), 141 (4), 102 (25), 90 (89), 77 (85), 76 (100). Anal. Calcd for $C_{28}H_{22}N_8O_2$ (502.54): C, 66.92; H, 4.41; N, 22.30. Found: C, 66.60; H, 4.21; N, 22.17%.

3.3.4. 6-(4-Methylphenylhydrazono)-1,3-diphenyl-7-methyl-1H-pyrazolo[3′,4′:4,5]pyrimido[1,6-b][1,2,4]triazepin-5(6H)-one (**5b**)

Orange solid, (0.82 g, 70%), mp 248–250 °C (ethanol). ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 7.01 (d, *J*=9 Hz, 2H, ArH), 7.15 (d, *J*=9 Hz, 2H, ArH), 7.34–7.76 (m, 10H, ArH), 8.23 (s, 1H, pyrimidine-H), 10.35 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 193.01, 164.68, 157.75, 156.25, 146.70, 139.36, 137.87, 135.83, 134.54, 130.31, 129.72, 129.28, 128.30, 127.73, 127.61, 125.86, 123.24, 121.99, 121.84, 119.91, 21.31, 14.44; IR (KBr) ν_{max} 3301, 1666 cm^{-1}. MS *m*/*z* (%) 488 (M^++2, 34), 487 (M^++1, 96), 486 (M^+, 100), 444 (59), 368 (38), 367 (42), 341 (24), 338 (30), 106 (32), 91 (40), 77 (27). Anal. Calcd for $C_{28}H_{22}N_8O$ (486.54): C, 69.12; H, 4.56; N, 23.03. Found: C, 69.02; H, 4.31; N, 23.16%.

3.3.5. 6-(3-Methylphenylhydrazono)-1,3-diphenyl-7-methyl-1H-pyrazolo-[3′,4′:4,5]pyrimido[1,6-b][1,2,4]triazepin-5(6H)-one (**5c**)

Red solid, (0.61 g, 50%), mp 242–244 °C (ethanol). ^{1}H NMR (DMSO-d_6) δ 2.46 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 7.38–8.27 (m, 14H, ArH), 8.50 (s, 1H, pyrimidine-H), 11.18 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 195.42, 164.72, 161.67, 152.20, 149.58, 147.00, 139.49, 139.32, 137.99, 136.24, 134.74, 133.19, 129.24, 129.19, 128.31, 128.18, 128.06, 127.04, 124.74, 123.96, 122.91, 114.93, 24.73, 20.37; IR (KBr) ν_{max} 3417, 1681 cm^{-1}. MS *m*/*z* (%) 487 (M^++1, 1), 486 (M^+, 1), 369 (1), 368 (1), 187 (2), 146 (64), 131 (16), 120 (2), 105 (100), 104 (86), 77 (53). Anal. Calcd for $C_{28}H_{22}N_8O$ (486.54): C, 69.12; H, 4.56; N, 23.03. Found: C, 69.30; H, 4.19; N, 22.95%.

3.3.6. 1,3-Diphenyl-7-methyl-6-(phenylhydrazono)-1H-pyrazolo-[3′,4′:4,5]pyrimido[1,6-b][1,2,4]triazepin-5(6H)-one (**5d**)

Orange solid, (0.80 g, 68%), mp 228–230 °C (dioxan–ethanol). ^{1}H NMR (DMSO-d_6) δ 2.63 (s, 3H, CH_3), 7.76–7.79 (m, 15H, ArH), 8.24 (s, 1H, pyrimidine-H), 10.35 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 194.10, 164.69, 157.75, 156.25, 146.70, 139.36, 137.87, 136.25, 135.83, 134.54, 130.31, 129.72, 128.30, 127.61, 125.86, 121.99, 120.23, 119.21, 118.67, 116.31, 14.45; IR (KBr) ν_{max} 3240, 1708 cm^{-1}. MS *m*/*z* (%) 474 (M^++2, 17), 473 (M^++1, 66), 472 (M^+, 80), 429 (33), 367 (40), 340 (35), 338 (33), 286 (14), 127 (15), 92 (32), 77 (100). Anal. Calcd for $C_{27}H_{20}N_8O$ (472.51): C, 68.63; H, 4.27; N, 23.71. Found: C, 68.42; H, 4.06; N, 23.50%.

3.3.7. 6-(4-Chlorophenylhydrazono)-1,3-diphenyl-7-methyl-1H-pyrazolo[3′,4′:4,5]pyrimido[1,6-b][1,2,4]triazepin-5(6H)-one (**5e**)

Orange solid, (0.90 g, 71%), mp >300 °C (dioxan). ^{1}H NMR (DMSO-d_6) δ 2.57 (s, 3H, CH_3), 7.36–7.48 and 7.58–7.69 (m, 10H, ArH), 7.53 (d, *J*=8 Hz, 2H, ArH), 8.05 (d, *J*=8 Hz, 2H, ArH), 8.22 (s, 1H, pyrimidine-H), 9.89 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 193.43, 162.33, 151.34, 149.12, 147.32, 141.37, 138.12, 132.09, 131.36, 129.26, 129.13, 128.95, 128.68, 128.19, 127.30, 127.24, 126.75, 121.78, 117.63, 116.64, 13.82; IR (KBr) ν_{max} 3394, 1705 cm^{-1}. MS *m*/*z* (%) 508 (M^++2, 33), 507 (M^++1, 38), 506 (M^+, 100), 367 (30), 339 (40), 302 (62), 287 (48), 198 (51), 111 (3), 77 (20). Anal. Calcd for $C_{27}H_{19}ClN_8O$ (506.96): C, 63.97; H, 3.78; N, 22.10. Found: C, 63.69; H, 3.61; N, 21.95%.

3.3.8. 6-(3-Chlorophenylhydrazono)-1,3-diphenyl-7-methyl-1H-pyrazolo[3′,4′:4,5]pyrimido[1,6-b][1,2,4]triazepin-5(6H)-one (**5f**)

Dark red solid, (0.72 g, 57%), mp 150–152 °C (ethanol). ^{1}H NMR (DMSO-d_3) δ 2.34 (s, 3H, CH_3), 7.39–8.02 (m, 14H, ArH), 9.01 (s 1H, pyrimidine-H), 11.10 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 193.00, 160.12, 159.29, 156.39, 155.00, 149.62, 145.29, 140.26, 139.11, 137.53, 131.09, 130.33, 129.60, 128.40, 128.21, 127.45, 124.63, 122.05, 121.40, 119.44, 118.05, 115.26, 13.21; IR (KBr) ν_{max} 3433, 1680 cm^{-1}. MS *m*/*z* (%) 508 (M^++2, 34), 507 (M^++1, 83), 506 (M^+, 100), 491 (31), 481 (23), 479 (30), 368 (30), 339 (57), 338 (30), 312 (43), 286 (78), 77 (57). Anal. Calcd for $C_{27}H_{19}ClN_8O$ (506.96): C, 63.97; H, 3.78; N, 22.10. Found: C, 63.76; H, 3.52; N, 22.40%.

*3.3.9. 6-(3-Nitrophenylhydrazono)-1,3-diphenyl-7-methyl-1H-pyrazolo[3′,4′:4,5]pyrimido[1,6-b][1,2,4]triazepin-5(6H)-one (**5g**)*

Dark yellow solid, (0.66 g, 51%), mp 296–298 °C (dioxan). ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3H, CH_3), 7.34–7.83 (m, 14H, ArH), 8.23 (s 1H, pyrimidine-H), 11.09 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 191.95, 165.38, 159.15, 156.85, 151.31, 149.70, 145.31, 140.10, 139.23, 137.53, 131.11, 130.75, 129.78, 128.02, 127.50, 127.47, 123.56, 122.31, 121.48, 119.65, 118.21, 116.30, 14.16; IR (KBr) ν_{max} 3301, 1655 cm^{-1}. MS *m*/*z* (%) 519 (M^++2, 4), 518 (M^++1, 6), 517 (M^+, 7), 369 (1), 260 (83), 232 (6), 218 (16), 208 (19), 142 (96), 132 (22), 121 (10), 106 (100), 105 (97), 77 (52). Anal. Calcd for $C_{27}H_{19}N_9O_3$ (517.51): C, 62.67; H, 3.70; N, 24.36. Found: C, 62.45; H, 3.61; N, 24.45%.

*3.3.10. 6-(4-Nitrophenylhydrazono)-1,3-diphenyl-7-methyl-1H-pyrazolo[3′,4′:4,5]pyrimido[1,6-b][1,2,4]triazepin-5(6H)-one (**5h**)*

Orange solid, (0.88 g, 68%), mp 268–270 °C (dioxan). ^{1}H NMR (DMSO-d_6) δ 2.49 (s, 3H, CH_3), 7.40–8.29 (m, 10H, ArH), 8.60 (d, *J*=7 Hz, 2H, ArH), 8.74 (d, *J*=7 Hz, 2H, ArH), 9.77 (s 1H, pyrimidine-H), 11.74 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 194.05, 162.50, 154.49, 152.83, 146.70, 140.50, 137.66, 130.81, 129.15, 129.07, 128.62, 128.49, 127.63, 127.20, 125.52, 123.19, 122.24, 120.60, 114.72, 114.34, 25.52; IR (KBr) ν_{max} 3433, 1693 cm^{-1}. MS *m*/*z* (%) 518 (M^++1, 18), 517 (M^+, 67), 516 (35), 367 (36), 339 (25), 338 (43), 312 (13), 287 (11), 154 (11), 127 (17), 116 (15), 77 (100), 76 (34). Anal. Calcd for $C_{27}H_{19}N_9O_3$ (517.51): C, 62.67; H, 3.70; N, 24.36. Found: C, 62.41; H, 3.29; N, 24.16%.

*3.3.11. 6-(4-Acetylphenylhydrazono)-1,3-diphenyl-7-methyl-1H-pyrazolo[3′,4′:4,5]pyrimido[1,6-b][1,2,4]triazepin-5(6H)-one (**5i**)*

Red solid, (0.72 g, 56%), mp 118–120 °C (ethanol). ^{1}H NMR (DMSO-d_6) δ 2.50 (s, 3H, CH_3), 2.64 (s, 3H, $COCH_3$), 7.41 (d, *J*=7 Hz, 2H, ArH), 7.56–8.00 (m, 10H, ArH), 8.20 (d, *J*=7 Hz, 2H, ArH), 8.68 (s, 1H, pyrimidine-H), 13.56 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 194.50, 194.41, 168.00, 149.90, 144.65, 129.89, 129.77, 129.57, 129.20, 128.99, 128.88, 128.74, 128.51, 128.19, 127.85, 126.97, 123.01, 122.75, 120.65, 120.63, 113.61, 25.68, 14.00; IR (KBr) ν_{max} 3062, 1678 cm^{-1}. MS *m*/*z* (%) 515 (M^++1, 3), 514 (M^+, 6), 342 (33), 325 (100), 324 (11), 272 (12), 104 (4), 98 (54), 84 (18), 77 (45). Anal. Calcd for $C_{29}H_{22}N_8O_2$ (514.55): C, 67.69; H, 4.31; N, 21.78. Found: C, 67.51; H, 4.03; N, 21.64%.

*3.3.12. 6-(4-Ethoxycarbonylphenylhydrazono)-1,3-diphenyl-4-methyl-1H-pyrazolo[3′,4′:4,5]pyrimido[1,6-b][1,2,4]triazepin-5(6H)-one (**5j**)*

Red solid, (0.58 g, 42%), mp 158–160 °C (ethanol). ^{1}H NMR (DMSO-d_6) δ 1.37 (t, *J*=7 Hz, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.35 (q, *J*=7 Hz, 2H, CH_2), 7.45–7.62 (m, 10H, ArH), 7.99 (d, *J*=8 Hz, 2H, ArH), 8.32 (d, *J*=8 Hz, 2H, ArH), 8.65 (s 1H, pyrimidine-H), 10.75 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 193.49, 162.34, 157.00, 151.37, 151.09, 149.80, 144.00, 141.41, 138.08, 132.05, 131.51, 129.17, 129.01, 128.70, 128.24, 127.22, 126.85, 123.12, 121.86, 117.67, 116.67, 61.10, 25.35, 13.83; IR (KBr) ν_{max} 3386, 1720, 1680 cm^{-1}. MS *m*/*z* (%) 545 (M^++1, 7), 544 (M^+, 15), 434 (23), 395 (40), 368 (24), 351 (23), 325 (34), 287 (53), 271 (33), 142 (27), 116 (22), 103 (40), 92 (23), 77 (100). Anal. Calcd for $C_{30}H_{24}N_8O_3$ (544.58): C, 66.17; H, 4.44; N, 20.58. Found: C, 66.21; H, 4.19; N, 20.77%.

3.4. pK_a Determination of compounds 5a–j

The acid dissociation constants of compounds **5** were determined potentiometrically in 80% dioxan–water mixtures at 25±0.1 °C and ionic strength (KNO_3) of 0.1. A Meetrohm 686 titroprocessor equipped with 665 Dosimat was used. The electrode and the titroprocessor were calibrated with standard Beckman buffer solutions of pH 4.01 and 7.00. The pH meter reading B recorded in dioxan–water solution was converted to hydrogen ion concentration [H^+] by means of the relation of van Uitert and Haas[28] namely:

$$-\log[H^+] = B + \log U_H$$

where $\log U_H$ is the correction factor for the solvent composition and ionic strength used for which *B* is read. The value of $\log U_H$ was found to be 0.48. A carbonate-free sodium hydroxide titrant was prepared and standardized against potassium hydrogen phthalate solution.

The experimental procedure followed in the determination of pK_a values and their calculations, by the method of least squares, from the titrant volume-pH data using the relation: $pK_a = pH_i - \log V_i/(V_e - V_i)$, is similar to that previously described.[4,6,29] In this equation, pH_i is the corrected pH value of the solution when the volume of the added titrant is V_i and V_e is the volume of the titrant at the equivalence point. The calculations of the pK_a values were carried out using computer program MINIQUAD-75.[30] The pK_a values obtained were reproducible to within ±0.02 pK_a unit. The results are summarized in Table 1.

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