Synthesis of a new series of biphenyl-substituted, fused 1,2,4-triazoles by oxidative cyclisation and Dimroth rearrangement

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A new series of 3-substituted-9-(1,1′-biphenyl-4-yl)-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo [4,3-*c*]pyrimidines and 2-substituted-9-(1,1′-biphenyl-4-yl)-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4] triazolo[1,5-*c*]pyrimidines were synthesised, as a new class of potent xanthine oxidase inhibitors, by oxidative cyclisation of 4-[2-(arylidene)hydrazinyl]-3-(1,1-biphenyl-4-yl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidines with $FeCl_3$ in ethanol and Dimroth rearrangement.

Keywords: hydrazones, nitrilimines, 1,5-electrocyclisation, heterocycles, Dimroth rearrangement

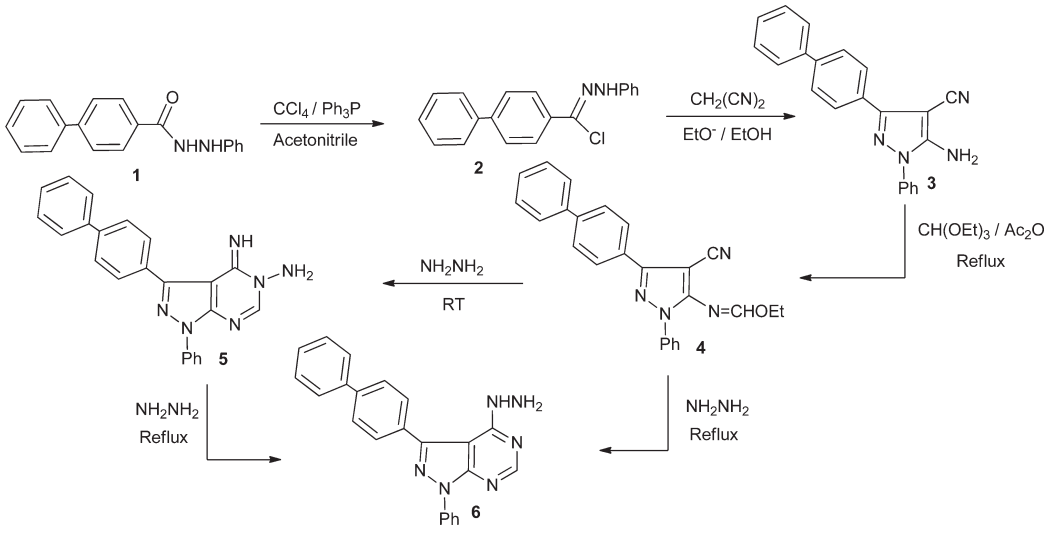
Fused 1,2,4-triazoles have interesting biological properties such as antimicrobial[1] and anxiolytic activities,[2] and can act also as adenosine[3,4] and benzodiazepine receptor antagonists.[5] In addition, some derivatives of pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*] pyrimidine and pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines exhibit pharmacological activities.[6] For example, several 3-and/or 5-substituted-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]-pyrimidines have been reported to be potent xanthine oxidase (XO) inhibitors.[6] Moreover, the introduction of a 1,1-biphenyl-4-yl group provides the heterocyclic nucleus with improved biological activity. For example, the 1,1-biphenyl-4-yl substituted compounds have been reported to be antimicrobial,[7,8] antihypertensive,[9,10] antidiabetic,[11] anti-inflammatory,[12–14] antiviral,[15] anticancer,[16] agents in addition to other activities. We now report the synthesis of the title compounds by a simple and convenient route. This route involves 1,5-electrocyclisation of nitrilimines generated *in situ* from *N*-(pyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazones **7a–f** to give the respective pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine derivatives **8a–f**. Dimroth rearrangement of the latter afforded the respective isomers, namely pyrazolo[4,3-*e*] [1,2,4]triazolo[1,5-*c*]pyrimidines **9a–f**.

Results and discussion

We hypothesised that the reaction of 3-(1,1-biphenyl-4-yl)-4-hydrazino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine **6** with aromatic aldehydes followed by oxidation and Dimroth rearrangement might be a potential approach for the synthesis of 3-substituted-9-(1,1-biphenyl-4-yl)-7-phenyl-7*H*-pyrazolo-[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **8a–f** and 2-substituted-9-(1,1-biphenyl-4-yl)-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4] triazolo[1,5-*c*]pyrimidines **9a–f** (Scheme 2). A variety of commercially available benzaldehydes and heteroaromatic aldehydes allow the introduction of chemical diversity at positions 2 and 3 of the heterocyclic nucleus.

The key starting material for the title compounds *i.e.* 3-(1,1-biphenyl-4-yl)-4-hydrazino-1-phenyl-1*H*-pyrazolo-[3,4-*d*]pyrimidine **6** was obtained from *N*-phenyl-1,1-biphenyl-4-carbohydrazide **1** as outlined in Scheme 1.

Hydrazide derivative **1** was converted to hydrazonoyl chloride **2** according to the method of Wolkoff.[17] Thus, CCl_4 was added dropwise to a refluxing solution of **1** and Ph_3P in dry acetonitrile to afford the expected product **2**. The structure of **2** was established on the basis of its spectral (MS, IR, ^{1}H NMR) data and elemental analysis. For example, the mass spectrum of **2** showed the molecular ion peak (M^+) at *m/z* 306, whilst the IR spectrum revealed the presence of the characteristic absorption bands for C=N– and N–H stretch at 1668 and 3305 cm^{-1} respectively. A singlet for the NH proton appeared at 9.90 ppm. Treatment of **2** with malononitrile in ethanol in the presence of sodium ethoxide at room temperature yielded the corresponding 5-amino-3-(1,1-biphenyl-4-yl)-1-phenyl-1*H*-pyrazole-4-carbonitrile **3**. Refluxing **3** with triethyl orthoformate in acetic anhydride for 7 h gave the imidoformate derivative **4**. Finally, treatment of **4** with an equivalent amount of hydrazine hydrate in ethanol at room temperature afforded the 4-iminopyrazolopyrimidine derivative **5** that rearranged to hydrazino derivative **6** upon treatment with excess hydrazine hydrate for 12 h. Also, **6** was accessible from a one-pot reaction by refluxing **4** with excess hydrazine hydrate for 3 h. The structures of the latter compounds were confirmed on the basis



Scheme 1

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of their elemental analysis and spectral data (see Experimental). The IR spectra of **3** and **4** exhibited absorption bands at 2210 and 2213 cm^{-1} assignable to C≡N stretch which disappeared in the IR spectrum of compound **6**. The ^{1}H NMR spectrum of compound **4** revealed the presence of a singlet at 8.65 ppm assignable to the N=CHO– proton which disappeared in the ^{1}H NMR spectrum of **6**. On the basis of these findings compound **6** was assigned a 4-hydrazino-1*H*-pyrazolo[3,4-*d*]pyrimidine structure. The rearrangement of **5** into **6** could be due to a Dimroth rearrangement which seems to occur through base-catalysed tandem ring opening and ring closure. This is consistent with a similar rearrangement that was reported recently.[18] Condensation of equimolar quantities of the hydrazino derivative **6** with a series of (hetero)aromatic aldehydes gave the corresponding hydrazones **7a–f** (Scheme 2).

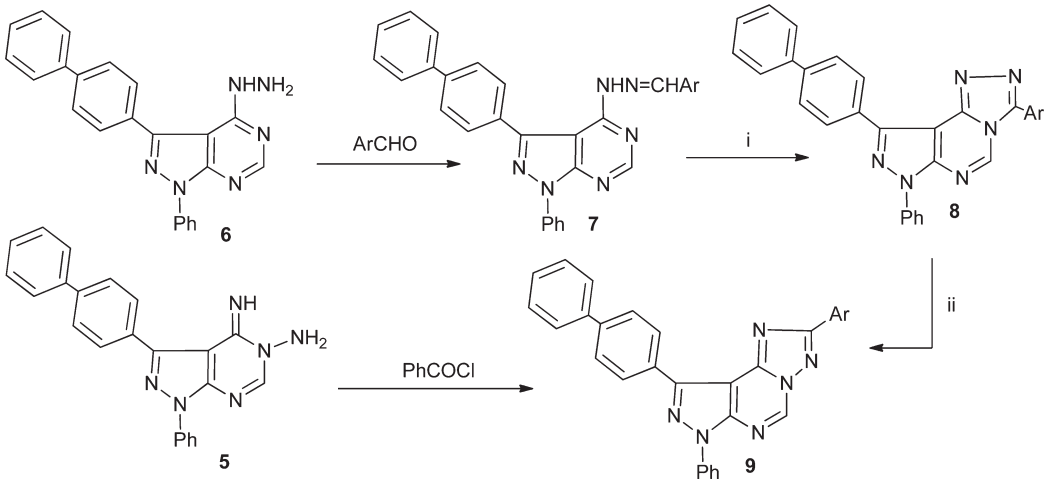
The elucidation of structures **7a–f** was based on spectral evidence and microanalysis (see Experimental). The mass spectra showed, in each case, the correct molecular ion peak. The IR spectra of **7a–f** revealed absorption bands in the 3100–3400 cm^{-1} region due to NH stretching absorptions. Their ^{1}H NMR spectra showed the presence of the hydrazone (–C=N–NH–) protons as singlets in the range 11.76–12.12 ppm. In addition, they exhibited multiplets in the 6.61–8.61 ppm region due to the aromatic protons as well as singlets at 8.36–8.67 ppm due to the hydrazone azomethine protons (–CH=N–). Subsequent oxidative intramolecular cyclisation of the hydrazones **7a–f** with $FeCl_3$ (4 equiv.) in ethanol at 45 °C provided the desired 3-substituted-9-(1,1-biphenyl-4-yl)-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **8a–f** in 40–75% yields. Characterisation of the products **8a–f** was based upon careful comparison of their IR and ^{1}H NMR spectra with those of the starting materials **7a–f**. Thus the IR spectra of **8a–f** showed the absence of NH bands that were present in the starting materials **7a–f**. An important characteristic feature in the ^{1}H NMR spectra of **8a–f** was the disappearance of the signals at δ 8.36–8.67 and 11.76–12.12 for the hydrazone and NH protons respectively that were present in the spectra of the intermediate hydrazones **7a–f**. The cyclisation of **7a–f** is reminiscent of related oxidative cyclisations of N-heteroarylaldehyde hydrazones with $FeCl_3$, which were reported to proceed by generation of the respective nitrilimines that undergo *in situ* 1,5-electrocyclisation to give the respective fused heterocycles.[19] Next, the Dimroth rearrangement of the 3-aryl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo [4,3-*c*]pyrimidines **8a–f** was examined. Treatment of **8a–f** with sodium acetate in refluxing ethanol yielded, in each case, a single product that was identified as the respective 2-aryl-7*H*-pyrazolo[4,3-*e*][1,2,4]-triazolo[1,5-*c*]pyrimidines **9a–f** (Scheme 2). The structures assigned to the latter products **9a–f** were consistent with their analytical and spectral (MS, ^{1}H NMR, IR) data (see Experimental). Rearrangement of **8** into **9** was evidenced by comparison of the ^{1}H NMR spectra of **8a–f** with those of **9a–f**. For example, the spectrum of **8a** revealed the pyrimidine H-5 proton signal as a singlet at δ 9.35, whereas the similar signal from **9a** was observed further downfield at δ 9.78. The downfield shift of the pyrimidine proton in **9a** can be attributed to proximity of the nitrogen atoms in the rearranged triazole ring. This feature is consistent with literature reports which indicate that the pyrimidine ring proton (H-5) in thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine is more deshielded than H-5 in thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine.[20]

The conversion of **8a–f** into **9a–f** is analogous to the rearrangement of 1,2,4-triazolo[4,3-*a*] pyrimidines in alkali to the isomeric 1,2,4-triazolo[1,5-*a*]pyrimidines.[20–25] To provide decisive evidence for this rearrangement, one of the products namely **9a**, was compared with an authentic sample prepared by alternate synthesis.[26] Thus, treatment of **5** with an equivalent quantity of benzoyl chloride in pyridine gave a single product which proved to be identical in all respects (m.p., mixed m.p., IR and ^{1}H NMR spectra) with that obtained above from the base-catalysed rearrangement of **8a** (Scheme 2).

In conclusion, we have successfully accomplished the facile and general synthesis of 3-substituted-9-(1,1-biphenyl-4-yl)-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **8a–f** and the isomeric 2-substituted-9-(1,1-biphenyl-4-yl)-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*] pyrimidines **9a–f** through heterocyclisation of hydrazones **7**, derived from **6** and aromatic aldehydes, and a subsequent Dimroth rearrangement.

Experimental

An electrothermal or Gallenkamp apparatus was used for melting point determinations. All synthesised compounds were dried over $CaCl_2$ in a desiccator. The IR spectra were measured on a Pye-Unicam SP300 instrument (KBr discs). The ^{1}H NMR spectra were recorded on a Varian Mercury VXR-300 spectrometer (300 MHz) in DMSO-d_6. MS were run on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometer at 70 eV. Elemental analyses were carried out by the Microanalytical Centre of Cairo University, Giza, Egypt. The starting biphenyl-4-carbonyl chloride was obtained from Aldrich Chemical Company.



i = $FeCl_3$ / EtOH / 45°C

ii = MeCOONa / heat

Ar = **a**) C_6H_5; **b**) 4-ClC_6H_4; **c**) 3,4-$(MeO)_2C_6H_3$; **d**) 1,3-benzodioxol-5-yl; **e**) 2-furyl; **f**) 2-thenyl.

Scheme 2

N-*Phenyl-1,1-biphenyl-4-carbohydrazide* (**1**): Biphenyl-4-carbonyl chloride (21.66 g, 0.1 mol) was added portionwise to a stirred solution of freshly distilled phenylhydrazine (19 mL, 0.1 mol) in pyridine (100 mL) over 30 min. When the addition was complete, the mixture was stirred for 3 h then poured onto cold HCl (300 mL, 10%). The precipitated solid was filtered, washed with dilute HCl and water. The product was crystallised from acetic acid and dried to give **1** as a white solid, yield 16.7 g (58%), m.p. 209–211 °C. IR ν_{max} (KBr): 3366, 3245, 3046, 1648, 1596, 744, 685 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.71–8.04 (m, 14 H, ArH), 10.40,10.41 (2s, 2H, –CONH–NH–Ph); MS *m/z* (%): 290 (M^++2, 1), 289 (M^++1, 10), 288 (M^+, 42), 181 (100), 153 (23), 152 (40), 77 (11). Anal. Calcd for $C_{19}H_{16}N_2O$ (288.35): C, 79.14; H, 5.59; N, 9.71. Found: C, 79.11; H, 5.62; N, 9.74%.

N-*Phenyl-1,1-biphenyl-4-ylcarbohydrazonoyl chloride* (**2**): CCl_4 (1.95 mL, 20 mmol) was added to a refluxing mixture of *N*-phenyl-1,1-biphenyl-4-carbohydrazide **1** (5.76 g, 20 mmol) and Ph_3P (6.55 g, 25 mmol) in acetonitrile (40 mL) that had been dried by passage through alumina column and introduced directly from the column into the reaction flask. The reaction mixture was refluxed for 2 h and after that stirred at room temperature for 12 h. The solid product was filtered, washed with water, crystallised from acetonitrile and dried to give **2** as yellow crystals yield 5.8 g (94.9%), m.p. 205–207 °C. IR ν_{max} (KBr): 3305, 3041, 1668, 1592, 754, 687 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.85–7.98 (m, 14 H, ArH), 9.90 (s, 1H, =NNH–); MS *m/z* (%): 309 (M^++3, 5), 308 (M^++2, 21), 307 (M^++1, 16), 306 (M^+, 63), 270 (65), 179 (26), 91 (100), 77 (5). Anal. Calcd for $C_{19}H_{15}ClN_2$ (306.80): C, 74.39; H, 4.93; N, 9.13. Found: C, 74.44; H, 4.95; N, 9.21%.

*5-Amino-3-(1,1-biphenyl-4-yl)-1-phenyl-1*H-*pyrazole-4-carbonitrile* (**3**): Malononitrile (0.33 g, 5 mmol) was added to an ethanolic solution of sodium ethoxide, prepared from sodium metal (0.11 g, 5 mmol) and absolute ethanol (15 mL), *N*-phenyl-1,1-biphenyl-4-ylcarbohydrazonoyl chloride **2** (1.53 g, 5 mmol) was added portionwise and the mixture was stirred for overnight. During this period the halide dissolved and the crude pyrazole derivative precipitated. The solid product was filtered, washed with water, crystallised from ethanol and dried to give **3** as a pale yellow solid, yield 1.42 g (85%), m.p. 188–190 °C. IR ν_{max} (KBr): 3430, 3394, 3024, 2210, 1626, 1598, 726, 689 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.82 (s, 2H, NH_2); 7.39–7.98 (m, 14H, ArH); MS *m/z* (%): 338 (M^++2, 4), 337 (M^++1, 27), 336 (M^+, 100), 335 (20), 153 (4), 152 (10), 77 (34). Anal. Calcd for $C_{22}H_{16}N_4$ (336.40): C, 78.55; H, 4.79; N, 16.65. Found: C, 78.63; H, 4.74; N, 16.85%.

*Ethyl [3-(1,1-biphenyl-4-yl)-4-cyano-1-phenyl-1*H-*pyrazol-5-yl]imidoformate* (**4**): Triethyl orthoformate (0.74 g, 5 mmol) was added to a solution of 5-amino-3-(1,1-biphenyl-4-yl)-1-phenyl-1*H*-pyrazole-4-carbonitrile **3** (1.68 g, 5 mmol) in acetic anhydride (3 mL); the mixture was refluxed for 7 h, then cooled. Methanol was added, the product solidified and was filtered, washed with water then crystallised from ethanol and dried to give the title compound as a white solid, yield 1.63 g (83%), m.p. 157–159 °C. IR ν_{max} (KBr): 3025, 2982, 2213, 1629, 732, 691 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.29–1.34 (t, 3H, CH_3); 4.31–4.38 (q, 2H, CH_2); 7.38–8.06 (m, 14 H, ArH); 8.65 (s, 1H, N=CHO-); MS *m/z* (%): 395 (M^++3, 1), 394 (M^++2, 5), 393 (M^++1, 30), 392 (M^+, 100), 336 (33), 335 (21), 152 (14), 77 (41). Anal. Calcd for $C_{25}H_{20}N_4O$ (392.46): C, 76.51; H, 5.14; N, 14.28. Found: C, 76.60; H, 4.98; N, 14.32%.

*3-(Biphenyl-4-yl)-4-imino-1-phenyl-1,4-dihydro-5*H-*pyrazolo[3,4-*d*]pyrimidin-5-amine* (**5**): Hydrazine hydrate 80% (1.5 mL) was added dropwise to a stirred mixture of ethyl [3-(1,1-biphenyl-4-yl)-4-cyano-1-phenyl-1*H*-pyrazol-5-yl] imidoformate **4** (1.96 g, 5 mmol) in ethanol (30 mL). The mixture was stirred at room temperature for 2 h. The precipitated solid was filtered, washed with water and crystallised from 1,4-dioxane to give **5** as a white solid, yield 1.79 g (95%), m.p. 203–204 °C. IR ν_{max} (KBr) 3424, 3314, 3139, 3050, 1640, 1600, 760, 687 cm^{-1}; ^1H NMR (DMSO-d_6): δ 5.72 (s, 2H, NH_2); 7.38–8.09 (m, 14H, ArH), 8.19 (s, 1H, H-6), 8.47 (s, 1H, NH); MS *m/z* (%): 378 (M^+, 7), 316 (8), 98 (17), 81(23), 80 (100), 79 (10). Anal Calcd for $C_{23}H_{18}N_6$ (378.44): C, 73.00; H, 4.79; N, 22.21. Found: C, 72.90; H, 4.71; N, 22.28%.

*3-(1,1-Biphenyl-4-yl)-4-hydrazino-1-phenyl-1*H-*pyrazolo[3,4-*d*]pyrimidine* (**6**): hydrazine hydrate (10 mL, 80%) was added to ethyl (3-(biphenyl-4-yl)-4-cyano-1-phenyl-1*H*-pyrazol-5-yl)imidoformate **4** (1.96 g, 5 mmol) in ethanol. The mixture was refluxed for 3 h, the precipitated solid was filtered and crystallised from 1,4-dioxane to give3-(biphenyl-4-yl)-4-hydrazino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine **6**, yield 1.52 g (81%) as a white solid, m.p. 216–218 °C. IR ν_{max} (KBr): 3426, 3194, 3030, 687, 759 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.85 (s, 3H, br. NH and NH_2), 7.35–8.25 (m, 14H, ArH), 7.92 (s, 1H, H-6); MS *m/z* (%): 379 (M^++1, 30), 378 (M^+, 100), 377 (57), 348 (47), 347 (15), 336 (13), 333 (10), 77 (74). Anal. Calcd for $C_{23}H_{18}N_6$ (378.44): C, 73.00; H, 4.79; N, 22.21. Found: C, 72.92; H, 4.78; N, 22.25%.

Synthesis of 3-(1,1-biphenyl-4-yl)-4-{2-[(hetero)arylidene]hydrazinyl}-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazones **7a–f***; general procedure*

Two drops of acetic acid were added to a mixture of 3-(1,1-biphenyl-4-yl)-4-hydrazino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine **6** (1.88 g, 5 mmol) and the appropriate aromatic aldehyde (5 mmol) in ethanol (50 mL), and the reaction mixture was refluxed for 2 h then cooled. The precipitate formed was filtered, washed with water, ethanol and finally crystallised from the appropriate solvent to give the corresponding hydrazone derivative **7a–f**. The various hydrazone derivatives **7a–f** prepared are listed below together with their physical constants and spectral data.

*4-[2-(Benzylidene)hydrazinyl]-3-(1,1-biphenyl-4-yl)-1-phenyl-1*H-*pyrazolo[3,4-*d*]pyrimidine* (**7a**): Yellow crystals, 71% yield, m.p. 226–228 °C; IR ν_{max} (KBr): 3341, 3050, 1639, 1584, 723, 683 cm^{-1}; ^1H NMR (DMSO-d_6): 7.41–8.59 (m, 19 H, ArH,), 8.13 (s, 1H, H-6), 8.51 (s, 1H, –N=CH); 12.07 (s, 1H, NH); MS *m/z* (%): 468 (M^++2, 6), 467 (M^++1, 7), 466 (M+, 9), 465 (39), 464 (100), 388 (25), 91 (58), 77 (66). Anal. Calcd for $C_{30}H_{22}N_6$ (466.55): C, 77.23; H, 4.75; N, 18.01. Found: C, 77.18; H, 4.66; N, 18.10%.

*3-(1,1-Biphenyl-4-yl)-4-[2-(4-chlorobenzylidene)hydrazinyl]-1-phenyl-1*H-*pyrazolo[3,4-*d*]pyrimidine* (**7b**): Yellow crystals, 85% yield, m.p. 235–237 °C; IR ν_{max} (KBr): 3309, 3037, 1636, 1589, 758, 686 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.40–8.57 (m, 18 H, ArH), 8.05 (s, 1H, H-6), 8.49 (s, 1H, –N=CH); 12.12 (s, 1H, NH); MS *m/z* (%): 502 (M^++1, 9), 501 (M^+, 66), 499 (57), 385 (100), 306 (90), 265 (94), 204 (95), 101 (90). Anal. Calcd for $C_{30}H_{21}ClN_6$ (501.00): C, 71.92; H, 4.23; N, 16.77. Found: C, 71.81; H, 4.18; N, 16.69%.

*3-(1,1-Biphenyl-4-yl)-4-[2-(3,4-dimethoxybenzylidene)hydrazinyl]-1-phenyl-1*H-*pyrazolo[3,4-*d*]pyrimidine* (**7c**): Yellow crystals, 86% yield, m.p. 250–252 °C; IR ν_{max} (KBr): 3333, 3034, 2952, 1637, 726, 687 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.83 and 3.88 (2s, 6H, $2OCH_3$), 7.03–8.61 (m, 17 H, ArH), 8.02 (s, 1H, H-6); 8.44 (s, 1H, –N=CH); 11.96 (s, 1H, NH); MS *m/z* (%): 529 (M^++3, 26), 528 (M^++2, 25), 527 (M^++1, 43), 526 (M^+, 36), 524 (25), 496 (39), 296 (36), 80 (100). Anal. Calcd for $C_{32}H_{26}N_6O_2$ (526.60): C, 72.99; H, 4.98; N, 15.96. Found: C, 73.06; H, 4.81; N, 16.03. %.

*4-[2-(1,3-Benzodioxolan-5yl)hydrazinyl]-3-(1,1-biphenyl-4-yl)-1-phenyl-1*H-*pyrazolo[3,4-*d*]pyrimidine* (**7d**): Yellow crystals, 87% yield, m.p. 242–244 °C; IR ν_{max} (KBr). 3350, 3037, 2896, 1641, 1592, 716, 682 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.10 (s, 2H, $–CH_2$), 6.64–8.59 (m, 17H, ArH), 7.83 (s, 1H, H-6), 8.40 (s, 1H, –N=CH); 12.03 (s, 1H, NH); MS *m/z* (%): 512 (M^++2, 6), 510 (M^+, 6), 98 (24), 82 (10), 81 (31), 80 (100). Anal. Calcd for $C_{31}H_{22}N_6O_2$ (510.56): C, 72.93; H, 4.34; N, 16.46. Found: C, 72.99; H, 4.31; N, 16.51%.

*3-(1,1-Biphenyl-4-yl)-4-[2-(2-furyl)hydrazinyl]-1-phenyl-1*H-*pyrazolo[3,4-*d*]pyrimidine* (**7e**): Yellow -brown crystals, 80% yield, m.p. 231–233 °C; IR ν_{max} (KBr): 3319, 3049, 1641, 1590, 740, 682 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.68–8.57 (m, 17 H, ArH), 7.89 (s, 1H, H-6), 8.36 (s, 1H, –N=CH); 11.89 (s, 1H, NH); MS *m/z* (%): 456 (M^+, 27), 455 (21), 454 (33), 363 (49), 154 (23), 77 (28), 64 (100), 51 (25). Anal. Calcd for $C_{28}H_{20}N_6O$ (456.51): C, 73.67; H, 4.42; N, 18.41. Found: C, 73.53; H, 4.37; N, 18.42%.

*3-(1,1-Biphenyl-4-yl)-4-[2-(2-thienyl)hydrazinyl]-1-phenyl-1*H-*pyrazolo[3,4-*d*]pyrimidine* (**7f**): Yellow crystals, 80% yield, m.p. 252–254 °C; IR ν_{max} (KBr): 3325, 3052, 1633, 1563, 726, 695 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.16–8.57 (m, 17 H, ArH), 8.02 (s, 1H, H-6), 8.67 (s, 1H, –N=CH); 11.76 (s, 1H, NH); MS *m/z* (%): 474 (M^++2, 58), 473 (M^++1, 66), 472 (M^+, 56), 395 (63), 389 (77), 279 (100), 242 (58), 236 (77). Anal. Calcd for $C_{28}H_{20}N_6S$ (472.58): C, 71.17; H, 4.27; N, 17.78. Found: C, 71.13; H, 4.22; N, 17.90%.

Synthesis of 3-(hetero)aryl-9-(1,1-biphenyl-4-yl)-7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo [4,3-c]pyrimidines **8a–f***; general procedure*

A solution of $FeCl_3$ (2 M, 10 mL) was added to a solution of the appropriate hydrazone **7a–f** (5 mmol) in ethanol (125 mL) and the mixture was stirred at 45 °C for 12 h. The precipitated solid was filtered, washed with water, ethanol and finally crystallised from DMF–EtOH to give the title compounds. The various derivatives **8a–f** prepared are given below together with their physical constants and spectral data.

*9-(1,1-Biphenyl-4-yl)-3,7-diphenyl-7*H-*pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine* (**8a**): White crystals, 67% yield, m.p. 274–275 °C; IR ν_{max} (KBr): 3051, 1623, 763, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.39–8.96 (m, 19 H, ArH), 9.35 (s, 1H, H-5); MS *m/z* (%): 467 (M$^+$+3, 9), 466 (M$^+$+2, 15), 465 (M$^+$+1, 41), 464 (M$^+$, 100), 387 (15), 234 (12), 153 (11) 77 (45). Anal. Calcd for $C_{30}H_{20}N_6$ (464.53): C, 77.57; H, 4.34; N, 18.09. Found: C, 77.53; H, 4.31; N, 18.11%.

*9-(1,1-Biphenyl-4-yl)-3-(4-chlorophenyl)-7-phenyl-7*H-*pyrazolo[4,3-*e*][1,2,4]triazolo [4,3-*c*]pyrimidine* (**8b**): Yellow crystals, 52% yield, m.p. 236–237 °C; IR ν_{max} (KBr): 3055, 1621, 758, 688 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.42–8.95 (m, 18 H, ArH), 9.36 (s, 1H, H-5); MS *m/z* (%): 501 (M$^+$+3, 14), 500 (M$^+$+2, 50), 499 (M$^+$+1, 43), 498 (M$^+$, 100), 421 (16), 345 (16), 152 (20), 77 (40). Anal. Calcd for $C_{30}H_{19}ClN_6$ (498.98): C, 72.21; H, 3.84; N, 16.84. Found: C, 72.12; H, 3.76; N, 16.90%.

*9-(1,1′-Biphenyl-4-yl)-3-(3,4-dimethoxyphenyl)-7-phenyl-7*H-*pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine* (**8c**): White crystals, 76% yield, m.p. 239–240 °C; IR ν_{max} (KBr): 3057, 2968, 1620, 735, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.88 and 3.89 (2s, 6H, 2OCH$_3$); 7.20–8.93 (m, 17 H, ArH), 9.33 (s, 1H, H-5); MS *m/z* (%): 527 (M$^+$+3, 25), 526 (M$^+$+2, 30), 525 (M$^+$+1, 52), 524 (M$^+$, 100), 509 (33), 493 (32), 340 (25), 310 (29). Anal. Calcd for $C_{32}H_{24}N_6O_2$ (524.59): C, 73.27; H, 4.61; N, 16.02. Found: C, 73.21; H, 4.54; N, 16.10%.

*3-(1,3-Benzodioxol-5-yl)-9-(1,1′-biphenyl-4-yl)-7-phenyl-7*H-*pyrazolo-[4,3-*e*][1,2,4]triazolo [4,3-*c*]pyrimidine* (**8d**): White crystals, 73% yield, m.p. 264–266 °C; IR ν_{max} (KBr): 3057, 2910, 1621, 735, 691 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 6.18 (s, 2H, –CH$_2$), 7.17–8.93 (m, 17H, ArH), 9.29 (s, 1H, H-5); MS *m/z* (%): 508 (M$^+$, 100), 468 (63), 181 (75), 77 (77). Anal. Calcd for $C_{31}H_{20}N_6O_2$ (508.54): C, 73.22; H, 3.96; N, 16.53. Found: C, 73.18; H, 3.87; N, 16.61%.

*9-(1,1′-Biphenyl-4-yl)-3-(2-furyl)-7-phenyl-7*H-*pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine* (**8e**): Pale brown crystals, 42% yield, m.p. 269–271 °C; IR ν_{max} (KBr): 3054, 1617, 760, 689 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 6.86–8.92 (m, 17H, ArH), 9.60 (s, 1H, H-5); MS *m/z* (%): 456 (M$^+$+2, 12), 455 (M$^+$+1, 44), 454 (M$^+$, 100), 377 (14), 301 (14), 152 (15), 77 (29). Anal. Calcd for $C_{28}H_{18}N_6O$ (454.50): C, 74.00; H, 3.99; N, 18.49. Found: C, 73.96; H, 3.93; N, 18.60%.

*9-(1,1′-Biphenyl-4-yl)-7-phenyl-3-(2-thienyl)-7*H-*pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine* (**8f**): Yellow crystals, 51% yield, m.p. 261–263 °C; IR ν_{max} (KBr): 3053, 1621, 755, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.36–8.92 (m, 17H, ArH), 9.54 (s, 1H, H-5); MS *m/z* (%): 472 (M$^+$+2, 16), 471 (M$^+$+1, 36), 470 (M$^+$, 100), 235 (10), 153 (8), 83 (7), 77 (32). Anal. Calcd for $C_{28}H_{18}N_6S$ (470.56): C, 71.47; H, 3.86; N, 17.86. Found: C, 71.42; H, 3.78; N, 17.93%.

Synthesis of 2-substituted-9-(1,1′-biphenyl-4-yl)-7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c] pyrimidines **9a–f***; general procedure*

To a solution of the appropriate **8a–f** derivative (5 mmol) in ethanol (250 mL) was added NaOAc (1.64 g, 10 mmol) and the mixture was refluxed for 6 h then cooled. The precipitated solid was filtered, washed with water, ethanol and finally crystallised from DMF to give the title compounds **9a–f**. The various derivatives prepared are given below:

*9-(1,1′-Biphenyl-4-yl)-2,7-diphenyl-7*H-*pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine* (**9a**): White crystals, 73% yield, m.p. 304–305 °C; IR ν_{max} (KBr): 3061, 1633, 758, 688 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.51–8.96 (m, 19 H, ArH), 9.78 (s, 1H, H-5); MS *m/z* (%): 464 (M$^+$, 100), 153 (25) 77 (58). Anal. Calcd for $C_{30}H_{20}N_6$ (464.53): C, 77.57; H, 4.34; N, 18.09. Found: C, 77.48; H, 4.44; N, 18.18%.

*9-(1,1′-Biphenyl-4-yl)-2-(4-chlorophenyl)-7-phenyl-7*H-*pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine* (**9b**): White crystals, 61% yield, m.p. >310 °C; IR ν_{max} (KBr): 3054, 1630, 753, 684 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.43–8.94 (m, 18 H, ArH), 9.79 (s, 1H, H-5); MS *m/z* (%): 498 (M$^+$, 79), 421 (82), 343 (79), 115 (91). Anal. Calcd for $C_{30}H_{19}ClN_6$ (498.98): C, 72.21; H, 3.84; N, 16.84. Found: C, 72.32; H, 3.78; N, 16.93%.

*9-(1,1′-Biphenyl-4-yl)-2-(3,4-dimethoxyphenyl)-7-phenyl-7*H-*pyrazolo[4,3-*e*][1,2,4]triazolo [1,5-*c*]pyrimidine* (**9c**): White crystals, 71% yield, m.p. 276–278 °C; IR ν_{max} (KBr): 3062, 2953, 1638, 758, 691 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.84 and 3.88 (2s, 6H, 2 × OCH$_3$); 7.10–8.90 (m, 17 H, ArH), 9.67 (s, 1H, H-5); MS *m/z* (%): 526 (M$^+$+2, 17), 525 (M$^+$+1, 39), 524 (M$^+$, 100), 506 (40), 152 (42), 77 (25). Anal. Calcd for $C_{32}H_{24}N_6O_2$ (524.59): C, 73.27; H, 4.61; N, 16.02. Found: C, 73.14; H, 4.57; N, 15.93%.

*2-(1,3-Benzodioxol-5-yl)-9-(1,1′-biphenyl-4-yl)-7-phenyl-7*H-*pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine* (**9d**): Pale yellow crystals, 78% yield, m.p. 309–311 °C; IR ν_{max} (KBr): 3064, 2908, 1632, 757, 684 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 6.16 (s, 2H, –CH$_2$), 7.12–8.93 (m, 17H, ArH), 9.72 (s, 1H, H-5); MS *m/z* (%): 510 (M$^+$+2, 75), 509 (M$^+$+1, 47), 508 (M$^+$, 49), 475 (100), 386 (67), 199 (78). Anal. Calcd for $C_{31}H_{20}N_6O_2$ (508.54): C, 73.22; H, 3.96; N, 16.53. Found: C, 73.15; H, 4.03; N, 16.42%.

*9-(1,1′-Biphenyl-4-yl)-2-(2-furyl)-7-phenyl-7*H-*pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine* (**9e**): Brown crystals, 80% yield, m.p. 279–281 °C; IR ν_{max} (KBr): 3078, 1628, 760,733, 688 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 6.79–8.85 (m, 17H, ArH), 9.72 (s, 1H, H-5); MS *m/z* (%): 454 (M$^+$, 13), 376 (13), 154 (14), 80 (62), 73 (100). Anal. Calcd for $C_{28}H_{18}N_6O$ (454.50): C, 74.00; H, 3.99; N, 18.49. Found: C, 74.06; H, 3.95; N, 18.58%.

*9-(1,1′-Biphenyl-4-yl)-7-phenyl-2-(2-thienyl)-7*H-*pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine* (**9f**): Yellow crystals, 88% yield, m.p. 310–312 °C; IR ν_{max} (KBr): 3056, 1630, 766, 692 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.29–8.89 (m, 17H, ArH), 9.72 (s, 1H, H-5); MS *m/z* (%): 472 (M$^+$+2, 18), 471 (M$^+$+1, 42), 470 (M$^+$, 100), 152 (15), 77 (22). Anal. Calcd for $C_{28}H_{18}N_6S$ (470.56): C, 71.47; H, 3.86; N, 17.86. Found: C, 71.59; H, 3.94; N, 17.75%.

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