Study of the Reaction of 5-Aryl-7-hydrazino-2-phenylpyrazolo[1,5-c]pyrimidines with 1,3-Dicarbonyl Compounds

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A novel synthetic method for the preparation of 5-aryl-7-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenylpyrazolo[1,5-*c*]-pyrimidines and 1-(5-aryl-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ols is provided by condensative cyclization of 5-aryl-7-hydrazino-2-phenylpyrazolo[1,5-*c*]pyrimidines with 1,3-dicarbonyl compounds. The study of the more reactive position for electrophilic substitusion reactions on such ring system was also achieved.

Keywords cyclization, electrophilic substitution, pyrazolylpyrazolopyrimidine, IR, NMR, mass spectrometry

Introduction

Pyrimidines and fused pyrimidines, are an integral part of DNA and RNA and play an essential role in several biological processes. Also, they have considerable chemical and pharmacological importance; particallarly, as nucleoside antibiotics, antibacterials, cardio vascular as well as agro chemical and veterin products.[1-9] Various pyrimidine derivaties have been reported to possess wide spread pharmacological properties such as analgesic, antiarrhythmic, and anticancer activities,[10-12] as well as, anti-inflammatory, antiparkinosnian, and androgenic anabolic activities.[13-18]

Moreover, pyrazole nucleus has pronounced pharmacological applications as anti-anxiety,[19,20] antipyretic, analgesic, and anti-inflammatory drugs.[21-23] Certain alkyl pyrazoles show significant bacteriostatic and fungicidal activities.[24]

Encouraged by the above observations and in continuation of our work for the syntheses of heterocyclic compounds from hydrazino heterocycles,[25-28] a new series of 5-aryl-7-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenylpyrazolo[1,5-*c*]pyrimidines and 1-(5-aryl-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ols were synthesized, with a view to explore the possibility of achieving better biological activities.

Experimental

Apparatus and materials

Melting points were determined on a Kofler Block and are uncorrected. Elemental analyses were carried out in the micro analytical laboratory of the faculty of science, Cairo University. The IR spectra of compounds were recorded on a Fourier Transform infrared 8400 spectrophotometer as potassium bromide pellets and frequencies are reported in cm^{-1}. The ^1H NMR spectra were recorded on a JEOL JNM ECA 500 MHZ and chemical shifts δ are relative to tetramethylsilane as an internal standard. Mass spectra were recorded at 70 eV with GCMS-QP 1000 EX. Reactions were routinely followed by thin layer chromatography (TLC) Merck Kiesel gel; 60-F254 precoated plastic plates, and spots were visualized using an ultraviolet (UV) lamp. All reagents of analytical grade were obtained from a commercial source and used without further purification.

5-Aryl-7-hydrazino-2-phenylpyrazolo[1,5-*c*]pyrimidines (1a—1d)

The compounds **1** were prepared from the respective acetylenic β-diketones as described earlier.[29,30]

5-Aryl-7-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenylpyrazolo[1,5-*c*]pyrimidines (3a—3d)

General procedure A mixture of a 5-aryl-7-hydrazino-2-phenylpyrazolo[1,5-*c*]pyrimidines (**1a**—**1d**, 1 g) and acetylacetone (10 mL) was heated under reflux for 1 h. The reaction mixture was evaporated under reduced pressure, EtOH was added and the product separated out was filtered, washed with EtOH and crystallized from EtOH to give the titled compounds **3a**—**3d** as colorless needles.

7-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2,5-diphenylpyrazolo[1,5-*c*]pyrimidine (3a) 1 g, yield 81%; m.p. 195—196 ℃; ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.44 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 6.18 (s, 1H, 1*H*-pyrazole-H), 6.99 (s, 1H, pyrazole-H), 7.87 (s, 1H, pyrimidine-H), 7.41—7.52 (m, 5H, aromatic-H), 7.99—8.11 (m, 5H, aromatic-H); IR (KBr) υ_{max}: 1624 (pyrazole ring C=N), 1535 (pyrimidine ring C=N), 1450 (C=C) cm^{-1}; MS *m*/*z* (%): 367 (M^++2, 9), 365 (M^+, 100), 351 (M^+−CH_2, 31), 337 (M^+−C_2H_4, 4), 323 (M^+−C_2H_4N, 21),

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297 ($M^+-C_4H_6N$, 4), 220 ($M^+-C_{10}H_{11}N$, 6), 193 ($M^+-C_{11}H_{12}N_2$, 6). Anal. calcd for $C_{23}H_{19}N_5$ (365.43): C 75.59, H 5.24, N 19.16; found C 75.50, H 5.20, N 19.15.

7-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-phenyl-5-*p*-tolylpyrazolo[1,5-*c*]pyrimidine (3b) 1 g, yield 83%; m.p. 200—201 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.41 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 6.16 (s, 1H, 1*H*-pyrazole-H), 6.94 (s, 1H, pyrazole-H), 7.81 (s, 1H, pyrimidine-H), 7.26—7.45 (m, 5H, aromatic-H), 7.96—7.99 (m, 4H, aromatic-H); IR (KBr) υ_{max}: 1618 (pyrazole ring C=N), 1535 (pyrimidine ring C=N), 1441 (C=C) cm^{-1}; MS *m*/*z* (%): 381 (M^++2, 12), 379 (M^+, 100), 365 (M^+-CH_2, 37), 351 ($M^+-C_2H_4$, 4), 337 ($M^+-C_2H_4N$, 21), 322 ($M^+-C_3H_7N$, 3), 296 ($M^+-C_5H_9N$, 4), 167 ($M^+-C_{13}H_{14}N_3$, 13). Anal. calcd for $C_{24}H_{21}N_5$ (379.50): C 75.97, H 5.58, N 18.46; found C 75.95, H 5.60, N 18.50.

5-(4-Methoxyphenyl)-7-(3,5-dimethyl-1*H*-pyrazolo-1-yl)-2-phenylpyrazolo[1,5-*c*]pyrimidine (3c) 1 g, yield 84%; m.p. 192—193 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.42 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.16 (s, 1H, 1*H*-pyrazole-H), 6.92 (s, 1H, pyrazole-H), 7.74 (s, 1H, pyrimidine-H), 6.98 (d, *J*=9.2 Hz, 2H, aromatic-H), 7.37—7.45 (m, 3H, aromatic-H), 7.97 (d, *J*=8.4 Hz, 2H, aromatic-H), 8.02 (d, *J*=8.5 Hz, 2H, aromatic-H); IR (KBr) υ_{max}: 1618 (pyrazole ring C=N), 1529 (pyrimidine ring C=N), 1450 (C=C) cm^{-1}; MS *m*/*z* (%): 380 (M^+-CH_3, 100), 354 ($M^+-C_2H_3N$, 34), 316 ($M^+-C_5H_5N$, 12), 303 ($M^+-C_7H_8$, 6), 275 ($M^+-C_7H_8N_2$, 30), 197 ($M^+-C_{14}H_{16}N$, 46). Anal. calcd for $C_{24}H_{21}N_5O$ (395.50): C 72.89, H 5.35, N 17.71; found C 72.90, H 5.33, N 17.68.

5-(4-Chlorophenyl)-7-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenylpyrazolo[1,5-*c*]pyrimidine (3d) 1 g, yield 84%; m.p. 181—182 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.41 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 6.16 (s, 1H, 1*H*-pyrazole-H), 6.97 (s, 1H, pyrazole-H), 7.81 (s, 1H, pyrimidine-H), 7.38—7.45 (m, 5H, aromatic-H), 7.97 (d, *J*=6.9 Hz, 2H, aromatic-H), 8.01 (d, *J*=9.2 Hz, 2H, aromatic-H); IR (KBr) υ_{max}: 1618 (pyrazole ring C=N), 1535 (pyrimidine ring C=N), 1440 (C=C) cm^{-1}; MS *m*/*z* (%): 401 (M^++1, 32), 399 (M^+−1, 100), 386 (M^+-CH_2, 9), 371 ($M^+-C_2H_5$, 4), 357 ($M^+-C_2H_5N$, 28), 330 ($M^+-C_3H_6N_2$, 4), 227 ($M^+-C_{10}H_{11}N_3$, 9), 192 ($M^+-C_{10}H_{11}ClN_3$, 7). Anal. calcd for $C_{23}H_{18}ClN_5$ (399.90): C 69.08, H 4.54, N 17.51; found C 69.00, H 4.50, N 17.61.

Ethyl 3-(2-(5-aryl-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)hydrazono)butanoates (4a—4d)

General procedure Ethyl acetoacetate (0.4 g, 3 mmol) was added to a suspension of 5-aryl-7-hydrazino-2-phenylpyrazolo[1,5-*c*]pyrimidines (**1a**—**1d**, 3 mmol) in ethanol (50 mL) and the reaction mixture was stirred overnight for 24 h at room temperature. The obtained product was filtered off, washed with EtOH and crystallized from $CHCl_3$/EtOH to give the titled compounds **4a**—**4d** as colorless needles.

Ethyl 3-(2-(2,5-diphenylpyrazolo[1,5-*c*]pyrimidin-7-yl)hydrazono)butanoate (4a) 1 g, yield 81%; m.p. 142—144 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.22 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 2.37 (s, 3H, CH_3), 3.55 (s, 2H, CH_2), 4.08 (q, *J*=6.9 Hz, 2H, CH_2CH_3), 7.09 (s, 1H, pyrazole-H), 7.38—7.67 (m, 6H, aromatic-H), 7.52 (s, 1H, pyrimidine-H), 8.04—8.08 (m, 4H, aromatic-H), 9.81 (s, 1H, exchangeable NH); IR (KBr) υ_{max}: 3344 (NH), 1732 (C=O), 1628 (pyrazole ring C=N), 1574 (pyrimidine ring C=N), 1450 (C=C) cm^{-1}; MS *m*/*z* (%): 413 (M^+, 38), 399 (M^+-CH_2, 4), 368 (M^+−OEt, 51), 326 ($M^+-C_2H_2CO_2Et$, 100), 299 ($M^+-C_6H_{10}O_2$, 29), 286 ($M^+-C_6H_9NO_2$, 42), 272 ($M^+-C_6H_9N_2O_2$, 33). Anal. calcd for $C_{24}H_{23}N_5O_2$ (413.47): C 69.72, H 5.61, N 16.94; found C 69.69, H 5.63, N 16.90.

Ethyl 3-(2-(2-phenyl-5-*p*-tolylpyrazolo[1,5-*c*]pyrimidin-7-yl)hydrazono)butanoate (4b) 1 g, yield 78%; m.p. 152—153 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.28 (t, *J*=7.4 Hz, 3H, CH_2CH_3), 2.25 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.61 (s, 2H, CH_2), 4.22 (q, *J*=7.4 Hz, 2H, CH_2CH_3), 6.76 (s, 1H, pyrazole-H), 7.25—7.50 (m, 5H, aromatic-H), 7.37 (s, 1H, pyrimidine-H), 7.99—8.01 (m, 4H, aromatic-H), 9.44 (s, 1H, exchangeable NH); IR (KBr) υ_{max}: 3443 (NH), 1734 (C=O), 1633 (pyrazole ring C=N), 1610 (pyrimidine ring C=N), 1451 (C=C) cm^{-1}; MS *m*/*z* (%): 428 (M^+, 45), 413 (M^+-CH_3, 4), 382 (M^+−EtOH, 55), 340 ($M^+-CH_3CO_2Et$, 100), 313 ($M^+-C_6H_{11}O_2$, 20), 300 ($M^+-C_6H_{10}NO_2$, 33), 285 ($M^+-C_6H_{11}N_2O_2$, 26), 270 ($M^+-C_7H_{14}N_2O_2$, 9). Anal. calcd for $C_{25}H_{25}N_5O_2$ (427.50): C 70.24, H 5.89, N 16.38; found C 70.20, H 5.91, N 16.41.

Ethyl 3-(2-(5-(4-methoxyphenyl)-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)hydrazono)-butanoate (4c) 1 g, yield 75%; m.p. 151—152 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.24 (t, *J*=8.4 Hz, 3H, CH_2CH_3), 2.36 (s, 3H, CH_3), 3.54 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 4.07 (q, *J*=6.9 Hz, 2H, CH_2CH_3), 6.98 (s, 1H, pyrazole-H), 7.43 — 7.62 (m, 5H, aromatic-H), 7.46 (s, 1H, pyrimidine-H), 8.03—8.12 (m, 4H, aromatic-H), 9.76 (s, 1H, exchangeable NH); IR (KBr) υ_{max}: 3468 (NH), 1742 (C=O), 1630 (pyrazole ring C=N), 1580 (pyrimidine ring C=N), 1459 (C=C) cm^{-1}; MS *m*/*z* (%): 444 (M^+, 36), 398 (M^+−EtOH, 85), 356 ($M^+-CH_3CO_2Et$, 81), 331 ($M^+-C_6H_9O_2$, 43), 329 ($M^+-C_6H_{11}O_2$, 24), 316 ($M^+-C_6H_{10}NO_2$, 100), 302 ($M^+-C_6H_{10}N_2O_2$, 85), 271 ($M^+-C_7H_{13}N_2O_3$, 33), 242 ($M^+-C_7H_{14}N_4O_3$, 26). Anal. calcd for $C_{25}H_{25}N_5O_3$ (443.50): C 67.70, H 5.68, N 15.79; found C 67.67, H 5.70, N 15.82.

Ethyl 3-(2-(5-(4-chlorophenyl)-2-phenylpyrazolo-[1,5-*c*]pyrimidin-7-yl)hydrazono)butanoate (4d) 1 g, yield 75%; m.p. 157—158 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.30 (t, *J*=7.4 Hz, 3H, CH_2CH_3), 2.25 (s, 3H, CH_3), 3.60 (s, 2H, CH_2), 4.22 (q, *J*=4.2 Hz, 2H, CH_2CH_3), 6.78 (s, 1H, pyrazole-H), 7.41—7.50 (m, 5H, aromatic-H), 7.36 (s, 1H, pyrimidine-H), 8.00 (d, *J*=7.3 Hz, 2H, aromatic-H), 8.03 (d, *J*=8.6 Hz, 2H, aromatic-H), 9.44 (s, 1H, exchangeable NH); IR (KBr) υ_{max}: 3435 (NH), 1730 (C=O), 1627 (pyrazole ring C=N),

1578 (pyrimidine ring C=N), 1451 (C=C) cm^{-1}; MS *m*/*z* (%): 450 (M^++2, 37), 448 (M^+, 79), 432 (M^+−CH_4, 8), 404 (M^+−C_3H_8, 48), 401 (M^+−C_2H_7O, 100), 362 (M^+−$CHCO_2Et$, 47), 333 (M^+−$C_6H_{11}O_2$, 38), 320 (M^+−$C_6H_{10}NO_2$, 39), 305 (M^+−$C_6H_{11}N_2O_2$, 41). Anal. calcd for $C_{24}H_{22}ClN_5O_2$ (447.90): C 64.35, H 4.95, N 15.64; found C 64.32, H 4.98, N 15.60.

1-(5-Aryl-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ols (6a—6d)

General procedure Ethyl 3-(2-(5-aryl-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)hydrazono)butanates **(4a—4d**, 1 g) and glacial acetic acid (20 mL) were heated under reflux for 2 h. Evaporation of the acetic acid under reduced pressure gave a residue which crystallized from $CHCl_3$/EtOH to give the titled compounds **6a—6d** as colorless needles.

1-(2,5-Diphenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ol (6a) 0.80 g, yield 73%; m.p. 270—272 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.47 (s, 3H, CH_3), 7.14 (s, 1H, pyrazole-H), 7.21—7.54 (m, 6H, aromatic-H), 7.43 (s, 1H, pyrazole-H), 7.64 (s, 1H, pyrimidine-H), 7.79 (d, *J*=5.1 Hz, 2H, aromatic-H), 8.17 (d, *J*=4.5 Hz, 2H, aromatic-H), 10.31 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3356 (OH), 1612 (pyrazole ring C=N), 1554 (pyrimidine ring C=N), 1442 (C=C) cm^{-1}; MS *m*/*z* (%): 367 (M^+, 2), 366 (M^+−1, 9), 350 (M^+−OH, 2), 339 (M^+−CO, 21), 298 (M^+−C_4H_5O, 6), 290 (M^+−C_6H_5, 6), 271 (M^+−$C_4H_4N_2O$, 2). Anal. calcd for $C_{22}H_{17}N_5O$ (367.40): C 71.92, H 4.66, N 19.06; found C 71.90, H 4.70, N 19.02.

1-(2-Phenyl-5-*p*-tolylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ol (6b) 0.80 g, yield 70%; m.p. 227—228 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.01 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 7.02 (s, 1H, pyrazole-H), 7.26—7.57 (m, 5H, aromatic-H), 7.41 (s, 1H, pyrazole-H), 7.57 (s, 1H, pyrimidine-H), 7.97 (d, *J*=7.7 Hz, 2H, aromatic-H), 8.07 (d, *J*=8.2 Hz, 2H, aromatic-H), 10.13 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3451 (OH), 1625 (pyrazole ring C=N), 1585 (pyrimidine ring C=N), 1440 (C=C) cm^{-1}; MS *m*/*z* (%): 380 (M^+−1, 1), 316 (M^+−C_4HO, 8), 315 (M^+−C_4H_2O, 8), 301 (M^+−C_4H_2NO, 6), 300 (M^+−C_4H_3NO, 3), 286 (M^+−C_6H_7O, 46). Anal. calcd for $C_{23}H_{19}N_5O$ (381.40): C 72.42, H 5.02, N 18.36; found C 72.39, H 5.00, N 18.40.

1-(5-(4-Methoxyphenyl)-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ol (6c) 0.80 g, yield 67%; m.p. 213—214 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.01 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 6.99 (s, 1H, pyrazole-H), 6.99—7.48 (m, 5H, aromatic-H), 7.40 (s, 1H, pyrazole-H), 7.50 (s, 1H, pyrimidine-H), 8.01 (d, *J*=8.4 Hz, 2H, aromatic-H), 8.07 (d, *J*=8.4 Hz, 2H, aromatic-H), 10.13 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3263 (OH), 1666 (pyrazole ring C=N), 1578 (pyrimidine ring C=N), 1447 (C=C) cm^{-1}; MS *m*/*z* (%): 397 (M^+, 1), 357 (M^+−CH_2O, 4), 331 (M^+−C_4H_2O, 100), 318 (M^+−C_5H_3O, 17), 316 (M^+−C_4H_3NO, 52), 287 (M^+−$C_5H_4NO_2$, 16). Anal. calcd for $C_{23}H_{19}N_5O_2$ (397.40): C 69.51, H 4.82, N 17.62; found C 69.49, H 4.80, N 17.66.

1-(5-(4-Chlorophenyl)-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ol (6d) 0.80 g, yield 66%; m.p. 242—243 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.01 (s, 3H, CH_3), 7.08 (s, 1H, pyrazole-H), 7.41 (s, 1H, pyrazole-H), 7.42—7.50 (m, 5H, aromatic-H), 7.66 (s, 1H, pyrimidine-H), 8.09 (d, *J*=8.6 Hz, 4H, aromatic-H), 10.14 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3451 (OH), 1652 (pyrazole ring C=N), 1558 (pyrimidine ring C=N), 1450 (C=C) cm^{-1}; MS *m*/*z* (%): 402 (M^+, 1), 377 (M^+−C_2H, 13), 366 (M^+−Cl, 1), 337 (M^+−C_4HO, 4), 336 (M^+−C_4H_2O, 9), 308 (M^+−$C_4H_2N_2O$, 6), 306 (M^+−$C_4H_4N_2O$, 19). Anal. calcd for $C_{22}H_{16}ClN_5O$ (401.80): C 65.76, H 4.01, N 17.43; found C 65.72, H 3.99, N 17.40.

5-Aryl-3-nitro-2-phenylpyrazolo[1,5-*c*]pyrimidin-7(6*H*)-ones (7a—7d)

General procedure A mixture of nitric acid (d 1.41, 1 mL) and sulfuric acid (d 1.84, 1 mL) in glacial acetic acid (10 mL) was gradually added to a suspension of 5-aryl-7-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenylpyrazolo[1,5-*c*]-pyrimidines (**3a—3d**, 1 mmol) in glacial acetic acid (10 mL) with stirring for 3 h at room temperature. The reaction mixture was then poured onto cold water with stirring and the yellow precipitated solids were filtered, washed with cold water, dried and crystallized from EtOH to give the titled compounds **7a—7d** as yellow needles.

3-Nitro-2,5-diphenylpyrazolo[1,5-*c*]pyrimidin-7(6*H*)-one (7a) 0.25 g, yield 76%; m.p. 301—302 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 7.26 (s, 1H, pyrimidine-H), 7.50—7.57 (m, 6H, aromatic-H), 7.70 (d, *J*=6.9 Hz, 2H, aromatic-H), 7.84 (d, *J*=7.7 Hz, 2H, aromatic-H), 12.72 (s, 1H, exchangeable NH); IR (KBr) υ_{max}: 3221 (NH), 1717 (C=O), 1620 (pyrazole ring C=N), 1562 (pyrimidine ring C=N), 1485 (C=C) cm^{-1}; MS *m*/*z* (%): 332 (M^+, 99), 302 (M^+−CH_2O, 7), 275 (M^+−CHN_2O, 4), 261 (M^+−CHN_3O, 11), 257 (M^+−$CHNO_3$, 5), 212 (M^+−C_7H_6NO, 13), 196 (M^+−$C_7H_6NO_2$, 28). Anal. calcd for $C_{18}H_{12}N_4O_3$ (332.31): C 65.06, H 3.64, N 16.86; found C 65.08, H 3.66, N 16.86.

3-Nitro-2-phenyl-5-*p*-tolylpyrazolo[1,5-*c*]pyrimidin-7(6*H*)-one (7b) 0.25 g, yield 71%; m.p. 179—180 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.45 (s, 3H, CH_3), 6.94 (s, 1H, pyrimidine-H), 7.25—7.28 (m, 2H, aromatic-H), 7.37—7.45 (m, 3H, aromatic-H), 7.81 (s, 1H, exchangeable NH), 7.96—7.99 (m, 4H, aromatic-H); IR (KBr) υ_{max}: 3213 (NH), 1739 (C=O), 1612 (pyrazole ring C=N), 1504 (pyrimidine ring C=N), 1443 (C=C) cm^{-1}; MS *m*/*z* (%): 346 (M^+, 100), 316 (M^+−CH_2O, 14), 300 (M^+−NO_2, 22), 272 (M^+−CNO_3, 26), 241 (M^+−C_7H_5O, 12), 210 (M^+−$C_7H_6NO_2$, 16), 182 (M^+−$C_7H_6N_3O_2$, 16). Anal. calcd for $C_{19}H_{14}N_4O_3$ (346.34): C 65.89, H 4.07, N 16.18; found C 65.90, H

4.05, N 16.17.

5-(4-Methoxyphenyl)-3-nitro-2-phenylpyrazolo-[1,5-*c*]pyrimidin-7(6*H*)-one (7c) 0.25 g, yield 69%; m.p. 172—173 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 3.82 (s, 3H, OCH_3), 7.10 (d, J=8.5 Hz, 2H, aromatic-H), 7.37 (s, 1H, pyrimidine-H), 7.47 (d, J=9.2 Hz, 2H, aromatic-H), 7.51—7.54 (m, 3H, aromatic-H), 7.65 (d, J=6.1 Hz, 2H, aromatic-H), 13.15 (s, 1H, exchangeable NH); IR (KBr) υ_{max}: 3211 (NH), 1736 (C=O), 1624 (pyrazole ring C=N), 1527 (pyrimidine ring C=N), 1447 (C=C) cm^{-1}; MS *m*/*z* (%): 364 (M^++2, 6), 349 (M^++2−CH_3, 3), 345 (M^+−OH, 8), 331 (M^+−CH_3O, 51), 302 (M^+−$C_2H_4O_2$, 14), 213 (M^+−$C_7H_5N_2O_2$, 11), 198 (M^+−$C_8H_8N_2O_2$, 15). Anal. calcd for $C_{19}H_{14}N_4O_4$ (362.34): C 62.98, H 3.89, N 15.46; found C 62.90, H 3.91, N 15.44.

5-(4-Chlorophenyl)-3-nitro-2-phenylpyrazolo[1,5-*c*]pyrimidin-7(6*H*)-one (7d) 0.25 g, yield 68%; m.p. 180—181 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.46 (s, 1H, pyrimidine-H), 7.55—7.59 (m, 3H, aromatic-H), 7.65 (d, J=8.6 Hz, 2H, aromatic-H), 8.05 (d, J=7.7 Hz, 2H, aromatic-H), 8.22 (d, J=8.6 Hz, 2H, aromatic-H), 8.48 (s, 1H, exchangeable NH); IR (KBr) υ_{max}: 3120 (NH), 1733 (C=O), 1616 (pyrazole ring C=N), 1535 (pyrimidine ring C=N), 1442 (C=C) cm^{-1}; MS *m*/*z* (%): 370 (M^++3, 10), 369 (M^++2, 11), 367 (M^+, 34), 337 (M^+−CH_2O, 10), 257 (M^+−$CHClNO_3$, 14), 232 (M^+−$C_7H_5NO_2$, 16), 230 (M^+−$C_7H_7NO_2$, 36), 203 (M^+−$C_7H_6N_3O_2$, 26), 189(M^+−$C_8H_6N_2O_3$, 17). Anal. calcd for $C_{18}H_{11}ClN_4O_3$ (366.76): C 58.95, H 3.02, N 15.28; found C 58.97, H 3.01, N 15.30.

1-(5-Aryl-3-nitro-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-4-nitro-1*H*-pyrazol-5-ols (8a—8d)

General procedure A mixture of nitric acid (d 1.41, 1 mL) and sulfuric acid (d 1.84, 1 mL) in glacial acetic acid (10 mL) was gradually added to a suspension of 1-(5-aryl-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ols (**6a**—**6d**, 1 mmol) in glacial acetic acid (10 mL) with stirring for 3 h at room temperature. The reaction mixture was then poured onto cold water with stirring and the yellow precipitated solids were filtered, washed with cold water, dried and crystallized from EtOH to give the titled compounds **8a**—**8d** as yellow needles.

1-(3-Nitro-2,5-diphenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-4-nitro-1*H*-pyrazol-5-ol (8a) 0.35 g, yield 76%; m.p. 178—180 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.47 (s, 3H, CH_3), 7.47—7.69 (m, 5H, aromatic-H), 7.59 (s, 1H, pyrimidine-H), 8.05 (d, J=7.7 Hz, 2H, aromatic-H), 8.34 (d, J=6.7 Hz, 2H, aromatic-H), 12.67 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3320 (OH), 1624 (pyrazole ring C=N), 1504 (pyrimidine ring C=N), 1467 (C=C) cm^{-1}; MS *m*/*z* (%): 457 (M^+, 1), 396 (M^+−CH_3NO_2, 1), 395 (M^+−CH_4NO_2, 1), 361 (M^+−$C_4H_2NO_2$, 5), 347 (M^+−C_4NO_3, 3), 332 (M^+−$C_4HN_2O_3$, 15), 316 (M^+−$C_4H_3N_3O_3$, 2), 315 (M^+−$C_4H_4N_3O_3$, 1). Anal. calcd for $C_{22}H_{15}N_7O_5$ (457.40): C 57.77, H 3.31, N 21.44; found C 57.79, H 3.28, N 21.47.

1-(3-Nitro-2-phenyl-5-*p*-tolylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-4-nitro-1*H*-pyrazol-5-ol (8b) 0.35 g, yield 74%; m.p. 137—138 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.37 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 7.32—7.68 (m, 5H, aromatic-H), 7.43 (s, 1H, pyrimidine-H), 8.03 (d, J=7.7 Hz, 2H, aromatic-H), 8.32 (d, J=6.9 Hz, 2H, aromatic-H), 12.60 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3459 (OH), 1636 (pyrazole ring C=N), 1544 (pyrimidine ring C=N), 1447 (C=C) cm^{-1}; MS *m*/*z* (%): 471 (M^+, 2), 420 (M^+−H_3O_3, 4), 401 (M^+−C_2NO_2, 12), 400 (M^+−C_2HNO_2, 17), 360 (M^+−C_4HNO_3, 3), 359 (M^+−$C_4H_2NO_3$, 2), 358 (M^+−$C_4H_3NO_3$, 2), 357 (M^+−$C_4H_4NO_3$, 2). Anal. calcd for $C_{23}H_{17}N_7O_5$ (471.40): C 58.60, H 3.63, N 20.80; found C 58.63, H 3.65, N 20.77.

1-(5-(4-Methoxyphenyl)-3-nitro-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-4-nitro-1*H*-pyrazol-5-ol (8c) 0.35 g, yield 71%; m.p. 177—178 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.47 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 7.05—7.64 (m, 5H, aromatic-H), 7.53 (s, 1H, pyrimidine-H), 8.04 (d, J=7.6 Hz, 2H, aromatic-H), 8.32 (d, J=6.8 Hz, 2H, aromatic-H), 12.65 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3462 (OH), 1625 (pyrazole ring C=N), 1566 (pyrimidine ring C=N), 1474 (C=C) cm^{-1}; MS *m*/*z* (%): 487 (M^+, 1), 316 (M^+−$C_5H_5N_3O_4$, 18), 302 (M^+−$C_6H_7N_3O_4$, 2), 301 (M^+−$C_6H_8N_3O_4$, 4), 207 (M^+−$C_{11}H_{10}N_3O_6$, 31). Anal. calcd for $C_{23}H_{17}N_7O_6$ (487.40): C 56.67, H 3.52, N 20.12; found C 56.70, H 3.50, N 20.14.

1-(5-(4-Chlorophenyl)-3-nitro-2-phenylpyrazolo-[1,5-*c*]pyrimidin-7-yl)-3-methyl-4-nitro-1*H*-pyrazol-5-ol (8d) 0.35 g, yield 71%; m.p. 164—165 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.47 (s, 3H, CH_3), 7.31—7.52 (m, 5H, aromatic-H), 7.53 (s, 1H, pyrimidine-H), 7.94 (d, J=7.7 Hz, 2H, aromatic-H), 8.11—8.22 (m, 2H, aromatic-H), 12.79 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3459 (OH), 1634 (pyrazole ring C=N), 1551 (pyrimidine ring C=N), 1474 (C=C) cm^{-1}; MS *m*/*z* (%): 492 (M^+, 1), 398 (M^+−$CClNO_2$, 4), 366 (M^+−$CClNO_4$, 7), 320 (M^+−$C_4H_4N_4O_4$, 14), 316 (M^+−$C_4H_2ClN_3O_3$, 36), 301 (M^+−$C_4HClN_3O_4$, 12). Anal. calcd for $C_{22}H_{14}ClN_7O_5$ (491.80): C 53.72, H 2.87, N 19.93; found C 53.75, H 2.89, N 19.90.

5-Aryl-7-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-iodo-2-phenylpyrazolo[1,5-*c*]pyrimidines (9a, 9c, 9d)

General procedure A solution of iodine monochloride (0.2 g, 1.2 mmol) in acetic acid (10 mL) was gradually added to a suspension of 5-aryl-7-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenylpyrazolo[1,5-*c*]pyrimidines (**3a**, **3c**, **3d**, 1 mmol) in acetic acid (10 mL) with stirring for 3 h at room temperature. The reaction mixture was then poured onto crushed ice and the precipitated 5-aryl-7-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-iodo-2-phenylpyrazolo-[1,5-*c*]pyrimidines (**9a**, **9c**, **9d**)

were filtered, washed with water, dried and crystallized from EtOH as colorless needles.

7-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-iodo-2,5-diphenylpyrazolo[1,5-*c*]pyrimidine (9a) 0.4 g, yield 82%; m.p. 213—214 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.22 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.23 (s, 1H, 1*H*-pyrazole-H), 7.46—7.53 (m, 6H, aromatic-H), 7.85 (d, J=6.7 Hz, 2H, aromatic-H), 8.11 (s, 1H, pyrimidine-H), 8.19 (d, J=7.7 Hz, 2H, aromatic-H); IR (KBr) υ_{max}: 1620 (pyrazole ring C=N), 1540 (pyrimidine ring C=N), 1446 (C=C) cm^{-1}; MS *m*/*z* (%): 493 (M^++2, 8), 492 (M^++1, 27), 491 (M^+, 100), 477 (M^+-CH_2, 8), 463 ($M^+-C_2H_4$, 8), 449 ($M^+-C_2H_4N$, 37), 364 (M^+−I, 46), 349 (M^+-CH_3I, 15), 322 ($M^+-C_3H_6I$, 29). Anal. calcd for $C_{23}H_{18}IN_5$ (491.33): C 56.22, H 3.69, N 14.25; found C 56.25, H 3.71, N 14.23.

7-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-iodo-5-(4-methoxyphenyl)-2-phenylpyrazolo[1,5-*c*]pyrimidine (9c) 0.4 g, yield 77%; m.p. 227—228 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.21 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.22 (s, 1H, 1*H*-pyrazole-H), 7.05 (d, J=8.5 Hz, 2H, aromatic-H), 7.47—7.53 (m, 3H, aromatic-H), 7.84 (d, J=6.9 Hz, 2H, aromatic-H), 7.95 (s, 1H, pyrimidine-H), 8.14 (d, J=9.2 Hz, 2H, aromatic-H); IR (KBr) υ_{max}: 1622 (pyrazole ring C=N), 1542 (pyrimidine ring C=N), 1444 (C=C) cm^{-1}; MS *m*/*z* (%): 523 (M^++2, 7), 521 (M^+, 100), 507 (M^+-CH_2, 15), 479 ($M^+-C_2H_4N$, 19), 394 (M^+−I, 77), 378 (M^+-CH_4I, 25), 353 ($M^+-C_3H_5I$, 19), 351 ($M^+-C_2H_5IN$, 25). Anal. calcd for $C_{24}H_{20}IN_5O$ (521.35): C 55.29, H 3.87, N 13.43; found C 55.31, H 3.85, N 13.45.

5-(4-Chlorophenyl)-7-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-iodo-2-phenylpyrazolo[1,5-*c*]pyrimidine (9d) 0.4 g, yield 75%; m.p. 219—220 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.38 (s, 3H, CH_3), 2.45 (s,3H, CH_3), 6.15 (s, 1H, 1*H*-pyrazole-H), 7.77 (s, 1H, pyrimidine-H), 7.45—7.47 (m, 5H, aromatic-H), 7.98—8.06 (m, 4H, aromatic-H); IR (KBr) υ_{max}: 1603 (pyrazole ring C=N), 1535 (pyrimidine ring C=N), 1406 (C=C) cm^{-1}; MS *m*/*z* (%): 528 (M^++2, 18), 526 (M^+, 100), 512 (M^+-CH_2, 6), 483 ($M^+-C_2H_5N$, 3), 447 ($M^+-C_3H_7Cl$, 6), 401 ($M^+-C_5H_8N_4$, 17), 399 (M^+−I, 30), 383 ($M^+-C_8H_{11}Cl$, 13), 357 ($M^+-C_9H_{11}ClN$, 9). Anal. calcd for $C_{23}H_{17}ClIN_5$ (525.77): C 52.54, H 3.26, N 13.32; found C 52.51, H 3.24, N 13.30.

5-Aryl-3-iodo-7-(4-iodo-3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenylpyrazolo[1,5-*c*]pyrimidines (10a—10c)

General procedure A solution of iodine monochloride (0.4 g, 2.4 mmol) in acetic acid (10 mL) was gradually added to a suspension of 5-aryl-7-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenylpyrazolo[1,5-*c*]pyrimidines (**3a**—**3c**, 1 mmol) in acetic acid (10 mL) with stirring for 3 h at room temperature. The reaction mixture was then poured onto crushed ice and the precipitated 5-aryl-3-iodo-7-(4-iodo-3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenylpyrazolo[1,5-c]pyrimidines (**10a** — **10c**) were filtered, washed with water, dried and crystallized from EtOH as colorless needles.

3-Iodo-7-(4-iodo-3,5-dimethyl-1*H*-pyrazol-1-yl)-2,5-diphenylpyrazolo[1,5-*c*]pyrimidine (10a) 0.45 g, yield 72%; m.p. 243—244 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.22 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 7.47—7.53 (m, 6H, aromatic-H), 7.84 (d, J=7.7 Hz, 2H, aromatic-H), 8.12 (s, 1H, pyrimidine-H), 8.19 (d, J=6.1 Hz, 2H, aromatic-H); IR (KBr) υ_{max}: 1620 (pyrazole ring C=N), 1542 (pyrimidine ring C=N), 1442 (C=C) cm^{-1}; MS *m*/*z* (%): 618 (M^++1, 100), 603 (M^+-CH_2, 3), 577 ($M^+-C_2H_2N$, 6), 491 (M^++1−I, 68), 463 ($M^+-C_2H_3I$, 7), 450 ($M^+-C_3H_4I$, 34), 363 (M^+-I_2, 12), 348 ($M^+-CH_3I_2$, 7), 335 ($M^+-C_2H_4I_2$, 10). Anal. calcd for $C_{23}H_{17}I_2N_5$ (617.22): C 44.76, H 2.78, N 11.35; found C 44.74, H 2.80, N 11.38.

3-Iodo-7-(4-iodo-3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenyl-5-*p*-tolylpyrazolo[1,5-*c*]pyrimidine (10b) 0.45 g, yield 71%; m.p. 199—200 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.39 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 7.30 (d, J=8.4 Hz , 2H, aromatic-H), 7.46—7.48 (m, 3H, aromatic-H), 7.78 (s, 1H, pyrimidine-H), 7.97—8.03 (m, 4H, aromatic-H); IR (KBr) υ_{max}: 1612 (pyrazole ring C=N), 1549 (pyrimidine ring C=N), 1439 (C=C) cm^{-1}; MS *m*/*z* (%): 632 (M^++1, 100), 617 (M^+-CH_2, 3), 591 ($M^+-C_2H_2N$, 5), 540 ($M^+-C_7H_7$, 22), 490 (M^+-CH_2I, 54), 464 ($M^+-C_2H_2IN$, 38), 449 ($M^+-C_3H_5IN$, 3), 413 ($M^+-C_7H_7I$, 16), 378 (M^++1−I_2, 97). Anal. calcd for $C_{24}H_{19}I_2N_5$ (631.30): C 45.66, H 3.03, N 11.09; found C 45.69, H 3.00, N 11.08.

3-Iodo-7-(4-iodo-3,5-dimethyl-1*H*-pyrazol-1-yl)-5-(4-methoxyphenyl)-2-phenylpyrazolo[1,5-*c*]-pyrimidine (10c) 0.45 g, yield 69%; m.p. 224—225 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.30 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 7.18—8.20 (m, 9H, aromatic-H), 7.90 (s, 1H, pyrimidine-H); IR (KBr) υ_{max}: 1607 (pyrazole ring C=N), 1518 (pyrimidine ring C=N), 1412 (C=C) cm^{-1}; MS *m*/*z* (%): 648 (M^++1, 13), 522 (M^++2−I, 100), 507 (M^+−CHI, 14), 480 ($M^+-C_2H_2IN$, 6), 443 ($M^+-C_6H_5I$, 2), 395 ($M^+-C_6H_9IN_2O$, 41), 379 ($M^+-CH_2I_2$, 14), 352 ($M^+-C_2H_3I_2N$, 11). Anal. calcd for $C_{24}H_{19}I_2N_5O$ (647.20): C 44.54, H 2.96, N 10.82; found C 44.51, H 2.99, N 10.80.

4-Iodo-1-(5-aryl-3-iodo-2-phenylpyrazolo[1,5-c]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ols (11a—11d)

General procedure A solution of iodine monochloride (0.4 g, 2.4 mmol) in acetic acid (10 mL) was gradually added to a suspension of (5-aryl-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ols (**6a**—**6d**, 1 mmol) in acetic acid (10 mL) with stirring for 3 h at room temperature. The reaction mixture was then poured onto crushed ice and the precipitated 5-aryl-4-iodo-1-(3-iodo-2-phenylpyra-zolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ols (**11a** — **11d**) were filtered, washed with water, dried and crystallized from EtOH as colorless needles.

4-Iodo-1-(3-iodo-2,5-diphenylpyrazolo[1,5-*c*]-pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ol (11a) 0.45 g, yield 73%; m.p. 202—204 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.47 (s, 3H, CH_3), 7.13—7.50 (m, 6H, aromatic-H), 7.63 (s, 1H, pyrimidine-H), 7.79 (d, J=7.4 Hz, 2H, aromatic-H), 8.21 (d, J=8.2 Hz, 2H, aromatic-H), 10.38 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3210 (OH), 1620 (pyrazole ring C=N), 1551 (pyrimidine ring C=N), 1450 (C=C) cm^{-1}; MS *m*/*z* (%): 621 (M^++2, 27), 364 (M^+−HI_2, 14), 363 (M^+−H_2I_2, 62), 333 (M^+−CH_4I_2O, 9), 287 (M^+−$C_6H_6I_2$, 20), 247 (M^+−$C_8H_8I_2N$, 12). Anal. calcd for $C_{22}H_{15}I_2N_5O$ (619.20): C 42.67, H 2.44, N 11.31; found C 42.70, H 2.46, N 11.29.

4-Iodo-1-(3-iodo-2-phenyl-5-*p*-tolylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ol (11b) 0.45 g, yield 71%; m.p. 199—200 ℃; IR (KBr) υ_{max}: 3220 (OH), 1612 (pyrazole ring C=N), 1555 (pyrimidine ring C=N), 1447 (C=C) cm^{-1}; MS *m*/*z* (%): 635 (M^++2, 7), 633 (M^+, 11), 618 (M^+−CH_3, 7), 601 (M^+−CH_3OH, 3), 599 (M^+−CH_6O, 17), 584 (M^+−C_2H_9O, 6), 334 (M^+−$C_{11}H_{10}INO$, 26), 300 (M^+−$C_6H_7I_2$, 100). Anal. calcd for $C_{23}H_{17}I_2N_5O$ (633.20): C 43.63, H 2.71, N 11.06; found C 43.60, H 2.75, N 11.10.

4-Iodo-1-(3-iodo-5-(4-methoxyphenyl)-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ol (11c) 0.45 g, yield 69%; m.p. 211—212 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.47 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.05—8.18 (m, 9H, aromatic-H), 7.53 (s, 1H, pyrimidine-H), 9.61 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3240 (OH), 1605 (pyrazole ring C=N), 1551 (pyrimidine ring C=N), 1408 (C=C) cm^{-1}; MS *m*/*z* (%): 506 (M^+−CH_4I, 24), 359 (M^+−$C_{10}H_{11}IO_2$, 22), 350 (M^+−$C_{11}H_{10}INO$, 39), 331 (M^+−$C_{11}H_{13}INO_2$, 22), 317 (M^+−$C_6H_6I_2$, 82), 301 (M^+−$C_6H_6I_2O$, 31), 288 (M^+−$C_8H_{11}I_2$, 34), 286 (M^+−$C_7H_9I_2O$, 29), 246 (M^+−$C_9H_9I_2O_2$, 22). Anal. calcd for $C_{23}H_{17}I_2N_5O_2$ (649.20): C 42.55, H 2.64, N 10.79; found C 42.57, H 2.60, N 10.82.

1-(5-(4-Chlorophenyl)-3-iodo-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-4-iodo-3-methyl-1*H*-pyrazol-5-ol (11d) 0.45 g, yield 69%; m.p. 204—205 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.01 (s, 3H, CH_3), 7.40 (s, 1H, pyrimidine-H), 7.44—7.56 (m, 5H, aromatic-H), 7.98 (d, J=7.6 Hz, 2H, aromatic-H), 8.16 (d, J=8.4 Hz, 2H, aromatic-H), 10.17 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3468 (OH), 1625 (pyrazole ring C=N), 1576 (pyrimidine ring C=N), 1462 (C=C) cm^{-1}; MS *m*/*z* (%): 506 (M^+−$C_9H_{10}NO$, 49), 504 (M^+−C_8H_5ClN, 100), 464 (M^+−C_2H_4ClI, 28), 462 (M^+−CH_2ClIO, 61), 446 (M^+−CH_4ClINO, 11), 432 (M^+−$C_4H_3IN_2O$, 15), 377 (M^+−C_9H_7ClI, 6), 335 (M^+−CH_2ClI_2O, 6), 319 (M^+−CH_4ClI_2NO, 10), 305 (M^+−$CH_4ClI_2N_2O$, 45). Anal. calcd for $C_{22}H_{14}ClI_2N_5O$ (653.60): C 40.43, H 2.16, N 10.71; found C 40.45, H 2.20, N 10.74.

5-Aryl-3-bromo-7-(4-bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenylpyrazolo[1,5-*c*]pyrimidines (12a—12d)

General procedure A solution of bromine (0.12 mL, 2.4 mmol) in acetic acid (10 mL) was gradually added to a suspension of 5-aryl-7-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenylpyrazolo[1,5-*c*]pyrimidines (**3a**—3**d**, 1 mmol) in acetic acid (10 mL) with stirring for 3 h at room temperature. The precipitated 5-aryl-3-bromo-7-(4-bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenylpyrazolo[1,5-*c*]pyrimidines (**12a** — **12d**) were filtered, washed with water, dried and crystallized from EtOH as colorless needles.

3-Bromo-7-(4-bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)-2,5-diphenylpyrazolo[1,5-c]pyrimidine (12a) 0.4 g, yield 77%; m.p. 215—216 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.24 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 7.45—7.53 (m, 6H, aromatic-H), 7.89 (d, J=7.7 Hz, 2H, aromatic-H), 8.19 (d, J=6.7 Hz, 2H, aromatic-H), 8.22 (s, 1H, pyrimidine-H); IR (KBr) υ_{max}: 1624 (pyrazole ring C=N), 1543 (pyrimidine ring C=N), 1447 (C=C) cm^{-1}; MS *m*/*z* (%): 527 (M^++4, 4), 525 (M^++2, 38), 523 (M^+, 100), 509 (M^+−CH_2, 4), 482 (M^+−C_2H_3N, 9), 446 (M^+−C_6H_5, 10), 445 (M^+−C_6H_6, 63), 428 (M^+−CH_3Br, 11), 363 (M^+−C_5H_6BrN, 11). Anal. calcd for $C_{23}H_{17}Br_2N_5$ (523.22): C 52.80, H 3.27, N 13.39; found C 52.78, H 3.30, N 13.40.

3-Bromo-7-(4-bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)-2-phenyl-5-*p*-tolylpyrazolo[1,5-*c*]pyrimidine (12b) 0.4 g, yield 74%; m.p. 217—218 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.39 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.29 (d, J=7.9 Hz, 2H, aromatic-H), 7.45—7.49 (m, 3H, aromatic-H), 7.81 (s, 1H, pyrimidine-H), 7.99 (d, J=8.0 Hz, 2H, aromatic-H), 8.04 (d, J=7.7 Hz, 2H, aromatic-H); IR (KBr) υ_{max}: 1616 (pyrazole ring C=N), 1529 (pyrimidine ring C=N), 1439 (C=C) cm^{-1}; MS *m*/*z* (%): 541 (M^++4, 4), 539 (M^++2, 38), 537 (M^+, 100), 523 (M^+−CH_2, 4), 496 (M^+−C_2H_3N, 10), 459 (M^+−Br, 85), 457 (M^+−Br, 74), 442 (M^+−CH_3Br, 14), 418 (M^+−C_3H_3Br, 28), 416 (M^+−C_3H_3Br, 26). Anal. calcd for $C_{24}H_{19}Br_2N_5$ (537.20): C 53.65, H 3.56, N 13.04; found C 53.57, H 3.53, N 13.00.

3-Bromo-7-(4-bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)-5-(4-methoxyphenyl)-2-phenyl-pyrazolo[1,5-*c*]-pyrimidine (12c) 0.4 g, yield 73%; m.p. 201—202 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.56 (s, 6H, $2CH_3$), 3.60 (s, 3H, OCH_3), 7.59 (s, 1H, pyrimidine-H), 7.14—7.93 (m, 5H, aromatic-H), 8.19 (d, J=7.7 Hz, 2H, aromatic-H), 8.21 (d, J=7.6 Hz, 2H, aromatic-H); IR (KBr) υ_{max}: 1609 (pyrazole ring C=N), 1539 (pyrimidine ring C=N), 1437 (C=C) cm^{-1}; MS *m*/*z* (%): 557 (M^++4, 4), 555 (M^++2, 40), 553 (M^+, 100), 539 (M^+−CH_2, 4), 512 (M^+−C_2H_3N, 7), 475 (M^+−Br, 63), 473 (M^+−Br, 53), 458 (M^+−CH_3Br, 10), 431 (M^+−$C_7H_{10}O$, 17). Anal. calcd for $C_{24}H_{19}Br_2N_5O$ (553.20): C 52.10, H 3.46, N 12.66; found C 52.12, H 3.44, N 12.63.

3-Bromo-7-(4-bromo-3,5-dimethyl-1*H*-pyrazol-1-

yl)-5-(4-chlorophenyl)-2-phenyl-pyrazolo[1,5-*c*]-pyrimidine (12d) 0.4 g, yield 71%; m.p. 222—223 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.39 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.83 (s, 1H, pyrimidine-H), 7.45—7.49 (m, 5H, aromatic-H), 8.03—8.06 (m, 4H, aromatic-H); IR (KBr) υ_{max}: 1616 (pyrazole ring C=N), 1539 (pyrimidine ring C=N), 1433 (C=C) cm^{-1}; MS *m*/*z* (%): 561 (M^++4, 14), 559 (M^++2, 51), 557 (M^+, 100), 543 (M^+−CH_2, 4), 516 (M^+−C_2H_3N, 11), 480.5 (M^+−C_2H_3ClN, 39), 400 (M^+−C_2H_3BrClN, 4). Anal. calcd for $C_{23}H_{16}Br_2ClN_5$ (557.70): C 49.54, H 2.89, N 12.56; found C 49.56, H 2.90, N 12.52.

4-Bromo-1-(5-aryl-3-bromo-2-phenylpyrazolo[1,5-*c*]-pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ols (13a — 13d)

General procedure A solution of bromine (0.12 mL, 2.4 mmol) in acetic acid (10 mL) was gradually added to a suspension of 1-(5-aryl-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ols (**6a**—**6d**, 1 mmol) in acetic acid (10 mL) with stirring for 3 h at room temperature. The precipitated 4-bromo-1-(5-aryl-3-bromo-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ols (**13a**—**13d**) were filtered, washed with water, dried and crystallized from EtOH as colorless needles.

4-Bromo-1-(3-bromo-2,5-diphenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ol (13a) 0.40 g, yield 75%; m.p. 221—223 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.47 (s, 3H, CH_3), 7.29—8.23 (m, 10H, aromatic-H), 7.55 (s, 1H, pyrimidine-H), 10.69 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3348 (OH), 1616 (pyrazole ring C=N), 1554 (pyrimidine ring C=N), 1447 (C=C) cm^{-1}; MS *m*/*z* (%): 445 (M^+−Br, 10), 444 (M^+−HBr, 7), 366 (M^+−C_4HBrNO, 20), 365 (M^+−C_4H_2BrNO, 8), 364 (M^+−C_4H_3BrNO, 19). Anal. calcd for $C_{22}H_{15}Br_2N_5O$ (525.20): C 50.31, H 2.88, N 13.33; found C 50.30, H 2.90, N 13.35.

4-Bromo-1-(3-bromo-2-phenyl-5--*p*-tolylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ol (13b) 0.40 g, yield 74%; m.p. 168—170 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.47 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 7.29—7.57 (m, 5H, aromatic-H), 7.56 (s, 1H, pyrimidine-H), 7.66 (d, *J*=6.2 Hz, 2H, aromatic-H), 7.86 (d, *J*=6.1 Hz, 2H, aromatic-H), 9.63 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3430 (OH), 1680 (pyrazole ring C=N), 1585 (pyrimidine ring C=N), 1442 (C=C) cm^{-1}; MS *m*/*z* (%): 540 (M^++1, 1), 539 (M^+, 1), 538 (M^+−1, 1), 521 (M^+−H_2O, 66), 458 (M^+−HBr, 32), 443 (M^+−CH_4Br, 36), 299 (M^+−$C_4H_2Br_2NO$, 25), 282 (M^+−$C_4H_5Br_2N_2O$, 16). Anal. calcd for $C_{23}H_{17}Br_2N_5O$ (539.20): C 51.23, H 3.18, N 12.99; found C 51.20, H 3.20, N 13.00.

4-Bromo-1-(3-bromo-5-(4-methoxyphenyl)-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ol (13c) 0.40 g, yield 71%; m.p. 176—178 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.47 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 7.01—7.87 (m, 9H, aromatic-H), 7.53 (s, 1H, pyrimidine-H), 9.58 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3320 (OH), 1686 (pyrazole ring C=N), 1593 (pyrimidine ring C=N), 1442 (C=C) cm^{-1}; MS *m*/*z* (%): 557 (M^++2, 1), 555 (M^+, 2), 541 (M^+−CH_2, 59), 523 (M^+−CH_3OH, 25), 494 (M^+−$C_2H_5O_2$, 59), 474 (M^+−HBr, 24), 459 (M^+−CH_4Br, 100), 443 (M^+−CH_4BrO, 21), 395 (M^+−Br_2, 18), 381 (M^+−CH_2Br_2, 16), 364 (M^+−CH_3Br_2O, 17). Anal. calcd for $C_{23}H_{17}Br_2N_5O_2$ (555.20): C 49.75, H 3.09, N 12.61; found C 49.77, H 3.11, N 12.64.

4-Bromo-1-(3-bromo-5-(4-chlorophenyl)-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ol (13d) 0.40 g, yield 71%; m.p. 237—238 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.47 (s, 3H, CH_3), 7.48 — 7.54 (m, 3H, aromatic-H), 7.55 (s, 1H, pyrimidine-H), 7.66 (d, *J*=7.7 Hz, 2H, aromatic-H), 7.78 (d, *J*=6.9 Hz, 2H, aromatic-H), 7.83 (d, *J*=6.9 Hz, 2H, aromatic-H), 12.25 (s, 1H, exchangeable aromatic C-OH); IR (KBr) υ_{max}: 3468 (OH), 1641 (pyrazole ring C=N), 1582 (pyrimidine ring C=N), 1435 (C=C) cm^{-1}; MS *m*/*z* (%): 546 (M^+−CH_2, 52), 544 (M^+−CH_4, 95), 541 (M^+−H_3O, 100), 465 (M^+−CH_3Br, 7), 463 (M^+−HBrO, 15), 383 (M^+−HBr_2O, 11). Anal. calcd for $C_{22}H_{14}Br_2ClN_5O$ (559.60): C 47.22, H 2.52, N 12.51, found C 47.25, H 2.50, N 12.48.

Results and discussion

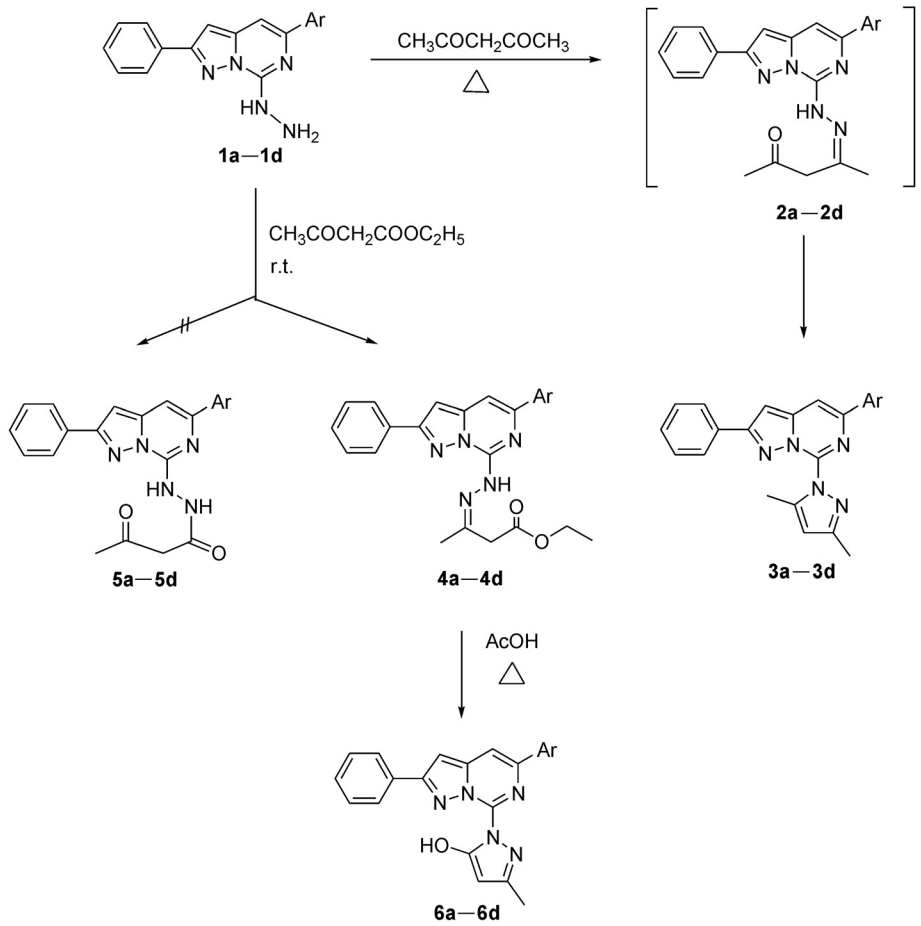
Condensation of 5-aryl-7-hydrazino-2-phenylpyrazolo[1,5-*c*]pyrimidines (**1a**—**1d**), which were readily obtained from ethyl phenylpropiolate,[29,30] with 1,3-dicarbonyl compounds was studied. Thus, treatment of **1a**—**1d** with acetylacetone under reflux for 1 h afforded the respective dehydrative cyclized products **3a**—**3d** rather than the hydrazone derivatives **2a**—**2d** as confirmed from their spectral and elemental analyses. Their ^{1}H NMR spectra showed the absence of both NH and NH_2 protons as well as the CH_2 protons of the starting materials. Moreover, a new characteristic singlet signals corresponding to the two methyl groups as well as H-4 of the newly synthesized pyrazole ring moity were assigned at δ_H 2.41—2.47 and 6.16—6.18, respectively. The singlets at δ_H 6.92—6.99 and 7.74—7.87 were due to H-3 and H-4 of the pyrazolopyrimidine moiety (Scheme 1).

On the other hand, condensation of **1a**—**1d** with equimolar amounts of ethyl acetoacetate at room temperature in ethanol afforded the respective hydrazone derivatives ethyl 3-(2-(5-aryl-2-phenylpyrazolo[1,5-*c*]-pyrimidin-7-yl)hydrazono)butanoates **4a**—**4d** rather than the respective hydrazides **5a**—**5d** as confirmed from their spectral analyses. Their IR spectra showed a characteristic sharp absorption band at 1730—1742 cm^{-1} for ester carbonyl group whereas, that of NH was absorbed at 3435—3468 cm^{-1}. Furthermore, the ^{1}H NMR spectra of **4a**—**4d** showed a characteristic signals of the ethyl ester group that resonated as triplet at δ_H

1.22—1.30 and a quartet at δ_H 4.07—4.22 corresponding to CH_3 and CH_2 protons, respectively, in agreement with the formation the hydrazone **4a**—**4d** rather than hydrazide **5a**—**5d** that also, was confirmed from the presence of only one exchangeable NH proton at δ_H 9.44—9.81. Moreover, the assignment of singlet signal at δ_H 3.54—3.61 characteristic for the methylene protons confirmed the assigned hydrazone structure rather than the cyclized products **6a**—**6d**. Furthermore, the MS spectra of **4a**—**4d** also confirmed the assigned structure (cf. Experimental). Cyclization of **4a**—**4d** was attempted by boiling in glacial acetic acid for 2 h to give 1-(5-aryl-2-phenylpyrazolo[1,5-*c*]pyrimidin-7-yl)-3-methyl-1*H*-pyrazol-5-ols (**6a**—**6d**). Their structures were achieved from their elemental analyses and spectral data. Their IR spectra showed the absence of absorption bands characteristic for ester and NH groups, which were also disappeared from their ^{1}H NMR spectra. Also, singlet of the methylene protons was omitted and instead two characteristic singlets of H-4 of the cyclized pyrazole ring and its C5-OH proton were assigned at δ_H 6.99—7.14 and 10.13—10.31, respectively.

In the present investigation the nitration and halogenation reactions on both compounds **3a**—**3d** and **6a**—**6d** were studied with the aim that introduction of such substituted groups may enhance their biological properties as well as study the more reactive position for electrophilic substitution reactions on such ring system. Thus, nitration of **3a**—**3d** with a mixture nitric acid and sulfuric acid in glacial acetic acid at room temperature gave the unexpected 5-aryl-3-nitro-2-phenylpyrazolo-[1,5-*c*]pyrimidin-7(6*H*)ones (**7a**—**7d**) as confirmed from their spectral data. The MS spectra of compounds **7a**—**7d** showed a molecular ion peak in agreement with losing of dimethylpyrazole moiety and introduction of only one nitro group. Moreover, the ^{1}H NMR spectra showed the absence of both signals of the two methyl groups. Furthermore, an exchangeable NH proton was assigned at δ_H 7.81—13.15 and only a singlet signal of the pyrimidine unit was resonated at δ_H 6.94—7.46 which confirmed that nitration reaction took place at pyrazole ring as well as an oxidative cleavage of the 3,5-dimethylpyrazole moiety took place to give **7a**—**7d**. The amidic carbonyl absorption at 1717—1739 cm^{-1} also, supports the assigned structure. On the other hand, under similar reaction conditions, nitration of **6a**—**6d**

Scheme 1 Synthesis of pyrazolylpyrazolopyrimidines



Ar = C_6H_5 (**a**), *p*-MeC_6H_4 (**b**), *p*-$MeOC_6H_4$ (**c**), *p*-ClC_6H_4 (**d**)

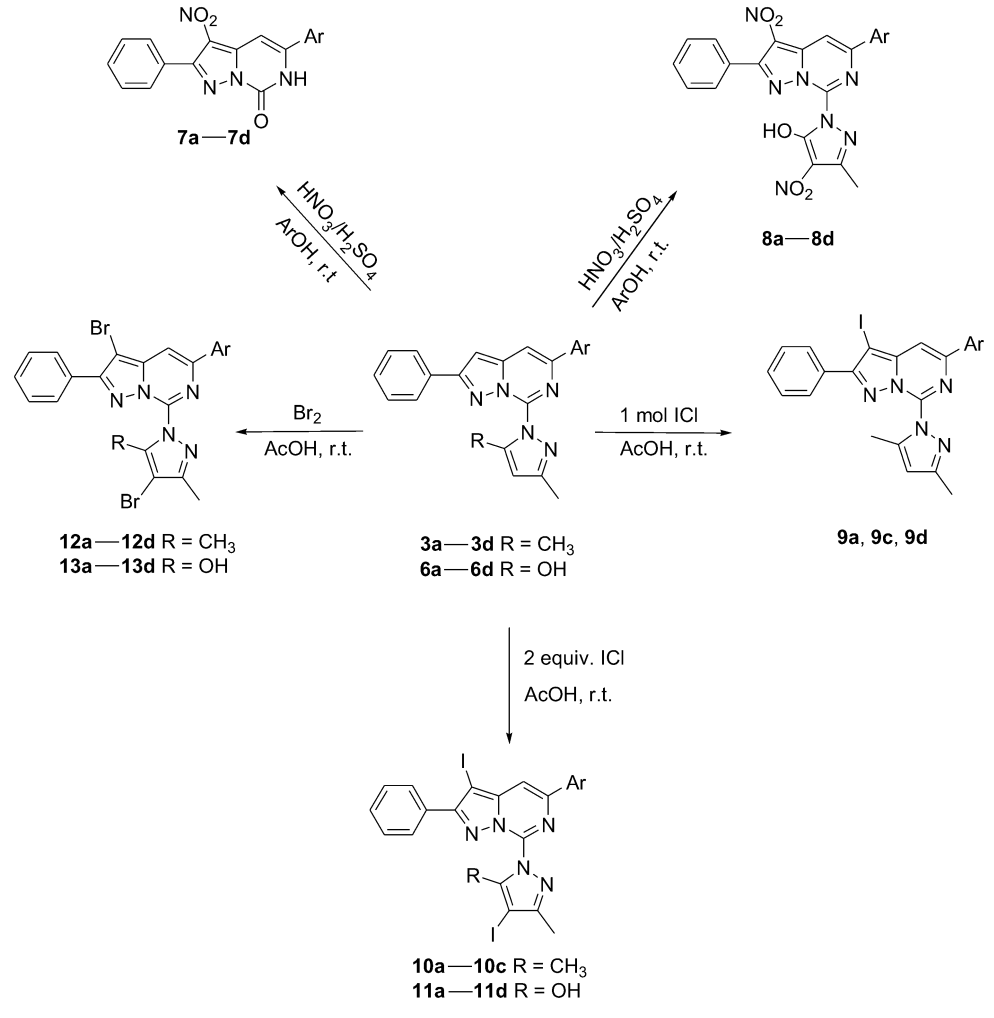
afforded the respective dinitro derivatives **8a**—**8d** as established from their spectral analyses. Their mass spectra showed a molecular ion peaks (*m*/*z* 457—492) in agreement with the introduction of two nitro groups; whereas, their ^{1}H NMR spectra showed the disappearance of singlet signals corresponding to the two pyrazoles ring protons and the presence of an exchangeable aromatic C-OH at δ_H 12.60—12.79 and only a singlet signal of the pyrimidine unit at δ_H 7.43—7.59 (Scheme 2).

Iodination of **3a**, **3c**, **3d** with 1 mol equiv. of iodine monochloride in acetic acid at room temperature gave the respective monoiodo derivatives; 5-aryl-7-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-iodo-2-phenylpyrazolo-[1,5-*c*]pyrimidines (**9a**, **9c**, **9d)**, whereas with excess of ICl compounds **3a**—**3c** and **6a**—**6d** afforded the diiodo derivatives **10a**—**10c** and **11a**—**11d**, respectively. Alternatively, bromination of **3a**—**3d** as well as **6a**—**6d** with excess bromine in glacial acetic acid at room temperature also afforded the dibromides **12a**—**12d** and **13a**—**13d**, respectively. The structures of the synthesized products **9**—**13** were established from their mass spectra, ^{1}H NMR spectra as well as their elemental analyses (cf. Experimental). The introduction of monoiodo group at C-3 of the pyrazolopyrimidine moiety rather than C-4 of the pyrazole side chain proves that it is the more reactive position to electrophilic substitution reaction. Furthermore, the pyrazole ring is also more reactive to electrophilic substitution reaction rather than the pyrimidine ring since the second electrophilic substitution step took place at the side chain pyrazole ring moiety, with the formation of either dinitro, diiodo or dibromo derivatives.

Conclusions

In conclusion, a library of functionalized pyrazolylpyrazolopyrimidines and their substituted analogs has been successively achieved. The strategy for constructing the target compounds is based on the heterocyclisation of 5-aryl-7-hydrazino-2-phenylpyrazolo-[1,5-*c*]pyrimidines (**1a**—**1d**)[29,30] with three-carbon donors such as acetylacetone and ethyl acetoacetate.

Scheme 2 Electrophilic substitution reactions of pyrazolylpyrazolopyrimidines



Ar = C_6H_5 (**a**), *p*-Me-C_6H_4 (**b**), *p*-MeO-C_6H_4 (**c**), *p*-ClC_6H_4 (**d**)

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