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Michael Cyclization of Polarized Systems: Synthesis and *in vitro* Anti-Diabetic Evaluation of Some Novel Pyrimidine, Pyridine, Pyrazole and Pyrazolo[3,4-*b*]pyridine Derivatives

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Abstract: Various interesting heterocycle skeletons were synthesized *via* Michael type addition reaction with 1,2; 1,3-bidentate nitrogen and carbon nucleophiles. Cycloaddition of different α,β–unsaturated systems afforded bromopyrimidinone **3**/**5**, bromothiazine **4** and bromopyrazole **6a**/**6b** pyrazole-1-carboxylate **8**, pyridinylmethanone **9**, nicotinonitrile **10**, pyrazolopyridine **11a**/**11b**, pyran-3-carbonitrile **12**/**13**, chromenopyridine **14** and *N*-butyrylpyrazolyl-1-butanone **15** derivatives. The structures of the synthesized compounds were elucidated based on IR, NMR and mass spectral analyses. Group of the newly synthesized compounds were screened for their anti-diabetic activities, whereas compounds **8** and **11b** exhibited promising anti-diabetic activities at micro molar concentration against α-glucosidase inhibitor with IC_{50} values ranging between 13.80-500 μM. On the other hand compound **10** showed a week effect as compared to the standard anti-diabetic agent.

Keywords: pyrimidine, nicotinonitrile, pyrazolopyridine, chromenopyridine, anti-diabetic.

INTRODUCTION

NITROGEN-containing heterocyclic molecules constitute the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals, which are vital for enhancing quality of life.[1–11] In this respect and various approaches for the preparation of these privileged structures with drug-like properties have been developed on various synthetic strategies. Pyrimidines, as the most important nitrogen-containing heterocyclic compounds, are of chemical and pharmacological interest. Many studies have been shown that compounds containing the pyrimidine ring possess antidiabetic, antibacterial, antifungal, antimalarial, and anticonvulsant activities,[12–16] and anticancer activities,[17,18] and many of pyrimidine compounds were reported to act as calcium channel blockers,[19] and as potential central nervous system (CNS) depressants.[20,21] Also, Pyrazoline derivatives widely occur in the environment, in the form of alkaloids, vitamins and pigments as constituents of plant and animal cell. Considerable attention has been carried out on the pyrazolines and substituted pyrazolines due to their inspiring biological activities such as antibacterial, antifungal,[22–24] antidepressant,[25–28] anticonvulsant,[29] and antitumor,[30] properties. The pyrazoline, a versatile moiety is present as the core constituent in a variety of leading drugs such as Sildenafil, Celebrex, and Rimonabant etc. The fact that α,β-unsaturated carbonyl compounds are push-pull olefins, and Michael acceptors permits them as adaptable intermediates in the synthesis of many azole and azine molecules.[31] Changes in their structure have offered a high degree of diversity that has proven useful for the development of new therapeutic agents having improved potency and lowered toxicity. Based on the above considerations and in continuation of our research on biologically potent heterocyclic derivatives,[32–38] herein, we report the synthesis, structural elucidation and anti-diabetic activity of some new azoles and azines prepared from commercially available reagents.

EXPERIMENTAL

All melting points were determined using a Stuart melting point apparatus by the open capillary tube method and are uncorrected. IR spectra were recorded on a FT-IR JASCO 6100 instrument in KBr phase. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian spectrometer (300 MHz) in DMSO-*d6* as solvent, using TMS as internal standard and chemical shifts are expressed as δ ppm. The mass spectra were recorded by ISQ LT single quadrupole mass spectrometer. *In vitro* antimicrobial activities were carried out at the Regional Center for Mycology and Biotechnology, Al-Azhar University, Egypt. Elemental analyses were performed by the Micro Analytical Center, Cairo University, Egypt and are within 0.4 % of the theoretical values. The starting materials 2,3-dibromo-1,3-diphenylpropan-1-one (**1a**), 2,3-dibromo-1-(4-chlorophenyl)-3-(2-methoxyphenyl)propan-1-one (**1b**), 1-(4-chlorophenyl)-3-(2-methoxyphenyl)prop-2-en-1-one (**7a)** and 1-(4-chlorophenyl)-3-(2-hydroxyphenyl)prop-2-en-1-one (**7b)** was prepared as described in the literature.[31] The progress of the reaction and the purity of the compounds were routinely monitored on TLC by pre-coated aluminum silica gel 60F_{254} thin layer plates obtained from Merck (Germany) eluting with petroleum ether/ethyl acetate. The yields of all products were not optimized. All reagents used were obtained from commercial sources. All solvents were of analytical grade and used without further purification.

Synthesis of Phenyl(2-phenyl-3,4-dihydro-2*H*-1,4-benzothiazin-3-yl)methanone (2)

A mixture of 2,3-dibromo-1,3-diphenylpropan-1-one (**1a**) (3.68 g, 10 mmol) and 2-aminobenzenethiol (1.25 g, 10 mmol) in methanol (30 mL) was stirred at r.t. for 30 min, then refluxed for 1 h. After removal of the solvent under vacuum, water was added. The precipitated solid was filtered off, washed with water, dried and recrystallized from methanol to give **2**. Yield 80 % (2.65 g); green crystals; m.p. 160–162 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3347 (NH), 3059, 3025 (CH aromatic), 2922, 2875 (CH aliphatic), 1677 (C=O), 1589 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ / ppm: 8.31–7.37 (m, 14H, Ar-H), 6.69 (d, 1H, *J* = 11.32 Hz, SCH), 5.78 (d, 1H, *J* = 11.32 Hz, CH-Ar), 3.61 (s, 1H, NH); ^{13}C NMR spectrum (75 MHz, DMSO-d_6) δ / ppm: 192.03, 144.60, 138.84, 137.92, 135.13, 134.07, 133.68, 131.18, 129.59, 129.64, 129.44, 129.31, 129.24, 128.96, 128.46, 128.35, 127.83, 122.46, 51.26, 46.77; MS *m* / *z*: 333 (M^+ + 2), 332 (M^+ + 1), 331 (M^+), 330 (M^+ – 1), 229 (M^+ – 2), 69(100); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{21}H_{17}NOS$ (*M*r = 331.43) are: C, 76.10; H, 5.17; N, 4.23. Found: C, 76.32; H, 5.34; N, 4.72.

General Procedure for Synthesis of Pyrimidin-2(1*H*)-one 3, Thiazine 4, Dihydropyrimidin-2(1*H*)-one 5, Pyrazole 6a and 6b Derivatives

A mixture of 2,3-dibromo ketone derivative **1a**/**1b** (10 mmol), urea, thiourea, semicarbazide (0.75 g, 10 mmol) or hydrazine hydrate 99 % (15 mmol) in presence of AcONa (10 g) in AcOH (30 mL) was refluxed for 5–7 hours. Water was added after removal of the solvent under vacuum. The solid precipitated was filtered off, washed with water, dried and recrystallized from the proper solvent to give **3**, **4**, **5**, **6a** and **6b**, respectively.

5-BROMO-6-(4-CHLOROPHENYL)-4-(2-METHOXYPHENYL)PYRIMIDIN-2(1*H*)-ONE (3)

Yield 57 % (2.23 g); green crystals; recrystallized from benzene; m.p. 146–148 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3430 (NH), 3113, 3063 (CH aromatic), 2925, 2852 (CH aliphatic), 1653 (C=O), 1586 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6) δ / ppm: 8.07 (s, 1H, NH), 8.06–7.06 (m, 8H, Ar–H), 3.79 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-*d6*) δ / ppm: 189.33 (C=O), 156.41 (C=N), 138.01, 137.15, 134.37, 134.03, 131.44, 131.26, 128.80, 124.28, 123.48, 113.65, 111.29 (aromatic carbons), 56.17 (OCH_3); MS *m* / *z*: 394 (1.53) (M^+ + 2), 392 (2.00) (M^+), 161(100); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{17}H_{12}BrClN_2O_2$ (*M*r = 391.64) are: C, 52.13; H, 3.09; N, 7.15. Found: C, 51.91; H, 2.99; N, 6.82.

5-BROMO-4-(4-CHLOROPHENYL)-6-(2-METHOXYPHENYL)-3,6-DIHYDRO-2*H*-1,3-THIAZIN-2-IMINE (4)

Yield 67 % (2.74 g); yellow crystals; recrystallized from petroleum ether 60 / 80; m.p. 124–126 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3417 (NH), 2923, 2852 (CH aliphatic), 1658 (C=N), 1591 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ / ppm: 8.21-7.04 (m, 10H, Ar-H + D_2O exchangeable NH), 3.88 (s, 3H, OCH_3), 3.78 (s, 1H, Ar-CH); ^{13}C NMR (75 MHz, DMSO-*d6*) δ / ppm: 187.84, 157.34, 138.14, 136.94, 136.07, 134.41, 131.44, 130.42, 130.24, 128.77, 125.06, 122.58, 114.03, 113.62, 112.51, 56.17 (OCH_3), 56.07 (ArCH); MS *m* / *z*: 411(2.61) (M^+ + 2), 409 (5.64) (M^+), 69 (100); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{17}H_{14}BrClN_2OS$ (*M*r = 409.72) are: C, 49.83; H, 3.44; N, 6.84. Found: C, 49.52; H, 3.04; N, 6.52.

3-AMINO-5-BROMO-6-(4-CHLOROPHENYL)-4-(2-METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONE (5)

Yield 75 % (3.06 g); colorless crystals; recrystallized from petroleum ether 60 / 80; m.p. 162–164 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3450 (NH), 3287, 3221 (NH_2), 2962, 2928, 2846 (CH aliphatic), 1677 (C=O), 1590 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ / ppm: 8.23–7.03 (m, 8H, Ar-H), 6.60 (s, 3H, D_2O exchangeable, NH + NH_2), 3.76 (s, 3H, OCH_3), 3.53 (s, 1H, CH); ^{13}C NMR (75 MHz, DMSO-*d6*) δ/ppm: 156.78, 154.33,

145.95, 143.95, 133.19, 131.42, 130.38, 128.25, 127.66, 126.78, 122.41, 114.63, 112.34, 91.68, 55.94 (ArCH), 54.90 (OCH_3); MS (*m* / *z*, %): 329, 328 (M^+ – Br), 102 (100); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{17}H_{15}BrClN_3O_2$ (M_r = 408.67) are: C, 49.96; H, 3.70; N, 10.28. Found: C, 49.79; H, 3.81; N, 10.61.

4-BROMO-3,5-DIPHENYL-1*H*-PYRAZOLE (6a)

Yield 83 % (2.48 g); colorless crystals; recrystallized from petroleum ether 60 / 80; m.p. 202–204 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3445 (NH), 3095, 3063, 3003 (CH aromatic), 1608 (C=N), 1578 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ / ppm: 13.35 (1H, s, D_2O exchangeable, NH), 7.89–7.17 (10H, m, Ar–H); ^{13}C NMR spectrum (75 MHz, DMSO-d_6) δ / ppm: 151.34, 143.37 (pyrazole carbons), 133.67, 129.33, 128.93, 128.57, 128.05, 127.39, 125.10, 124.68 (aromatic carbons), 99.54 (C–Br); MS *m* / *z*: 301 (M^+ + 2), 299 (M^+), 223, 222 (M^+ – C_6H_5), 221, 220 (100), 219 (M^+ – Br); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{15}H_{11}BrN_2$ (M_r = 299.16) are: C, 60.22; H, 3.71; N, 9.36. Found: C, 60.56; H, 4.01; N, 9.12.

4-BROMO-3-(4-CHLOROPHENYL)-5-(2-METHOXYPHENYL)-1*H*-PYRAZOLE (6b)

Yield 80 % (2.91 g); colorless crystals; recrystallized from benzene; m.p. 190–192 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3280 (NH), 3140 (CH aromatic), 2980, 2922, 2838 (CH aliphatic), 1580 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6) δ / ppm: 7.98–7.10 (m, 9H, Ar–H + D_2O exchangeable NH), 3.92 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-*d6*) δ / ppm: 155.02, 131.95, 131.38, 129.53, 128.69, 126.71, 114.21, 112.14, 102.84 (aromatic carbons), 55.84 (OCH_3); MS *m* / *z*: 365 (M^+ + 2), 364 (M^+ + 1), 363 (M^+), 362 (M^+ – 1), 361 (M^+ – 2), 174(100); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{16}H_{12}BrClN_2O$ (M_r = 363.63) are: C, 52.85; H, 3.33; N, 7.70. Found: C, 52.52; H, 3.26; N, 7.97.

Synthesis of *Tert*-butyl 5-(4-chlorophenyl)-3-(2-methoxyphenyl)-2,3-dihydro-1*H*-pyrazole-1-carboxylate (8)

A mixture of **7a** (2.72 g, 10 mmol), *tert*-carbazate (10 mmol) in ethanol (30 mL) was heated under reflux for 5 h. The reaction mixture was concentrated under reduced pressure, cooled and ice cold water was added. The product formed was filtered off, washed with water, dried and recrystallized from petroleum ether 60 / 80 to give **8**. Yield 60 % (2.32 g); yellow crystals; m.p. 136–138 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3426 (NH), 3257, 3045 (CH aromatic), 2975, 2928 (CH aliphatic), 1707(C=O), 1604 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ / ppm: 10.81 (s, 1H, D_2O exchangable, NH), 8.36–6.93 (m, 9H, Ar-H and ethenylic CH), 3.80 (s, 3H, OCH_3), 2.18 (s, 1H, methinyl CH), 1.46 (s, 9H, *tert*-butyl); ^{13}C NMR (75 MHz, DMSO-*d6*) δ/ppm: 157.20 (C=O), 152.43, 138.58, 130.63, 128.14, 127.55, 125.14, 122.71, 120.52, 111.57, 79.20, 55.50 (s, 3H, OCH_3), 28.03 (s, 9H, CH_3); MS *m* / *z*: 389 (M^+ + 2), 387 (M^+), 54(100); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{21}H_{23}ClN_2O_3$ (M_r = 386.87) are: C, 65.20; H, 5.99; N, 7.24. Found: C, 64.91; H, 5.88; N, 6.94.

Synthesis of (4-Chlorophenyl)[6-(4-chlorophenyl)-2,4-bis(2-methoxyphenyl)-3-pyridinyl]methanone (9)

A mixture of **7a** (2.72 g, 10 mmol) and ammonium acetate (10 g) in acetic acid (30 mL) was refluxed for 1 h. After removal of the solvent under vacuum, ice cold water was added and the resultant solution was neutralized with diluted HCl. The solid formed was filtered off, washed with water, dried and recrystallized from methanol to give **9**. Yield 50 % (2.70 g); colorless crystals; m.p. 170–172 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3065 (CH aromatic), 2923, 2830 (CH aliphatic), 1658 (C=O), 1601 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6) δ / ppm: 8.27–7.09 (m, 17H, Ar-H and CH pyridine), 3.83 (s, 6H, $2OCH_3$); ^{13}C NMR (75 MHz, DMSO-*d6*) δ / ppm: 154.48 (C=O), 148.30 (C=N), 137.51, 134.01, 130.50, 128.75, 128.55, 120.90, 119.64, 111.95 (aromatic carbons), 55.72 (OCH_3); MS *m* / *z*: 541 (M^+), 115 (100); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{32}H_{23}Cl_2NO_3$ (M_r = 540.43) are: C, 71.12; H, 4.29; N, 2.59. Found: C, 70.82; H, 4.09; N, 2.26.

General Procedure for Synthesis of Nicotinonitrile 10,Pyrazolopyridine 11a and 11b Derivatives

A mixture of **7a**/**7b** (10 mmol) with malononitrile and/or *N*-phenyl pyrazolone derivative (10 mmol) in acetic acid (30 mL) in presence of ammonium acetate (10 g) was refluxed for 10 h. After removal of the solvent under vacuum, water was added and the resultant solution was neutralized with diluted HCl. The precipitated solid was filtered off, washed with water, dried and recrystallized from the proper to give **10**, **11a** and **11b**, respectively.

2-AMINO-4-(4-CHLOROPHENYL)-6-(2-METHOXYPHENYL)NICOTINONITRILE (10)

Yield 65 % (2.18 g); recrystallized from acetic acid; orange crystals; m.p. 218–220 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3449, 3348, 3226 (NH...NH_2), 3073, 3026 (CH aromatic), 2970, 2937 (CH aliphatic), 2217 (CN), 1632 (C=N), 1599 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ / ppm: 8.12–6.93 (m, 9H, Ar–H and CH pyridine), 3.80 (s, 3H, OCH_3), 3.36 (s, 2H, D_2O exchangable, NH_2); ^{13}C NMR (75 MHz, DMSO-*d6*) δ / ppm: 155.61, 154.71, 149.98, 134.02, 130.55, 130.51, 128.53, 128.12, 127.99, 125.16, 120.13, 111.13, 55.42, 55.35, 41.06; MS *m* / *z*: 338 (M^+ + 2), 337 (M^+ + 1), 336 (M^+), 40 (100); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{19}H_{14}ClN_3O$ (M_r = 335.78) are: C, 67.96; H, 4.20; N, 12.51. Found: C, 67.35; H, 4.46; N, 12.64.

6-(4-CHLOROPHENYL)-4-(2-METHOXYPHENYL)-3-METHYL-1-PHENYL-1*H*-PYRAZOLO[3,4-*B*]PYRIDINE (11a)

Yield 75 % (3.19 g); recrystallized from methanol; yellow crystals; m.p. 178–180 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3073, 3001 (CH aromatic), 2954, 2926, 2828 (CH aliphatic), 1600 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6) δ / ppm: 8.27-7.09 (m, 14H, Ar–H and CH pyridine), 3.84 (s, 6H, 2CH$_3$); ^{13}C NMR (75 MHz, DMSO-*d6*) δ / ppm: 176.57, 156.33, 154.45, 148.26, 137.48, 133.98, 130.46, 128.71, 128.51, 127.08, 120.87, 120.45, 119.61, 111.91 (aromatic carbon), 55.69 (OCH$_3$), 40.33 (CH$_3$); MS *m* / *z*: 428 (M$^+$ + 2), 427 (M$^+$ + 1), 426 (M$^+$), 131 (100); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{26}H_{20}ClN_3O$ (M_r = 425.90) are: C, 73.32; H, 4.73; N, 9.87. Found: C, 73.02; H, 4.33; N, 9.57.

2-[6-(4-CHLOROPHENYL)-3-METHYL-1-PHENYL-1H-PYRAZOLO[3,4-B]PYRIDIN-4-YL]PHENOL (11b)

Yield 61 % (2.51 g); recrystallized from methanol / water; brown crystals; m.p. 312–314 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3428 (OH), 3065 (CH aromatic), 2859 (CH aliphatic), 1601 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6) δ / ppm: 11.58 (s, 1H, D$_2$O exchangable, OH), 8.15–7.20 (m, 14H, Ar-H and CH pyridine), 2.16 (s, 3H, CH$_3$); MS *m* / *z*: 413 (M$^+$ + 2), 411 (M$^+$), 83 (100); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{25}H_{18}ClN_3O$ (M_r = 411.88) are: C, 72.90; H, 4.40; N, 10.20. Found: C, 72.15; H, 4.56; N, 9.85.

Synthesis of 6-(4-Chlorophenyl)-4-(2-hydroxyphenyl)-2-imino-3,4-dihydro-2*H*-pyran-3-carbonitrile (12)

A mixture of **7b** (2.58 g, 10 mmol), malononitrile (0.66 g, 10 mmol) and ten drops of TEA in DMF (30 mL) was heated under reflux for 9 h, and then cooled, poured into ice-cold water and acidified with acetic acid. The precipitated solid was filtered off, dried and recrystallized from methanol to give **12**.

Yield 48 % (1.56 g); brown crystals; m.p. 268–270 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3429 (OH), 3235 (NH), 3074 (CH aromatic), 2202 (CN), 1601 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6) δ / ppm: 8.98 (s, 1H, OH), 8.86 (s, 1H, NH), 8.02–7.06 (m, 9H, Ar-–H and CH pyran), 3.45 (d, 1H, *J* = 6.9 Hz, CH), 3.40 (d, 1H, *J* = 7.2 Hz, CH); MS *m* / *z*: 326 (M$^+$ + 2), 324 (M$^+$), 323 (M$^+$ – 1), 43(100); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{18}H_{13}ClN_2O_2$ (*M*r = 324.76) are: C, 66.57; H, 4.03; N, 8.63. Found: C, 66.58; H, 3.96; N, 8.37.

General Procedure for Synthesis of Pyran-3-carbonitrile 13 and Chromenopyridine 14

A mixture of **7b** (2.58 g, 10 mmol) and/or cyanoacetamide, malonamide (10 mmol) in 50 mL ethoxide solution [prepared by dissolving (0.46 g, 20 mmol) of Na in 50 mL abs. ethanol] was heated under reflux for 7 h. After removal of the solvent under vacuum, water was added and the alkaline solution was neutralized with diluted HCl. The product formed was filtered off, washed with cold water, dried and recrystallized from the proper solvent to give **13** and **14**, respectively.

6-(4-CHLOROPHENYL)-4-(2-HYDROXYPHENYL)-2-OXO-2*H*-PYRAN-3-CARBONITRILE (13)

Yield 55 % (1.78 g); green crystals; recrystallized from methanol; m.p. 320–322 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3409 (OH), 3038 (CH aromatic), 2226 (CN), 1771 (C=O), 1614 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ / ppm: 10.10 (s, 1H, OH), 8.50–6.79 (m, 8H, Ar-H); MS *m* / *z*: 326 (M$^+$ + 2), 325 (M$^+$ + 1), 324 (M$^+$), 323(100) (M$^+$ – 1); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{18}H_{10}ClNO_3$ (*M*r = 323.72) are: C, 66.78; H, 3.11; N, 4.33. Found: C, 67.12; H, 3.26; N, 4.65.

2-(4-CHLOROPHENYL)-4*H*-CHROMENO[3,4-*C*]PYRIDINE-4,5(3*H*)-DIONE (14)

Yield 60 % (1.94 g); colorless crystals; recrystallized from acetic acid; m.p. 350–352 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3433 (NH), 3068, 3035 (CH aromatic), 1777, 1638 (C=O), 1616 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ / ppm: 12.42 (s, 1H, D$_2$O exchangable, NH), 8.50-7.36 (m, 9H, Ar-H and 1H, pyridone-H1); MS *m* / *z*: 326 (M$^+$ + 2), 325 (M$^+$ + 1), 324 (M$^+$), 323 (100) (M$^+$ – 1); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{18}H_{10}ClNO_3$ (M_r = 323.73) are: C, 66.78; H, 3.11; N, 4.33. Found: C, 66.49; H, 3.15; N, 4.52.

Synthesis of 1-[2-Butyryl-5-(4-chlorophenyl)-3-(2-hydroxyphenyl)-2,3-dihydro-1*H*-pyrazol-1-yl]-1-butanone (15)

A mixture of **7b** (2.72 g, 10 mmol) and hydrazine hydrate 99 % (15 mmol) in butyric acid (20 mL) was refluxed for 10 h. The reaction mixture was concentrated under reduced pressure, cooled and neutralized with 5 % sodium carbonate solution. The separated solid was filtered off, washed with water, dried and recrystallized from methanol to give **15**. Yield 72 % (2.97 g); yellowish crystals; m.p. 178–180 °C; IR (KBr) $\tilde{\nu}$ / cm^{-1}: 3226 (OH), 3190 (CH aromatic), 2962, 2877 (CH aliphatic), 1638 (C=O), 1594 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ / ppm: 9.62 (s, 1H, OH), 7.79–6.67 (m, 8H, Ar–H), 5.67–5.62 (d, 1H, *J* = 4.8 Hz, enaminic CH), 3.82–3.72 (t, 4H, *J* = 12 Hz, 2CO$\underline{CH_2}$CH$_2$CH$_3$), 3.02-2.94 (d, 1H, *J* = 4.8, Ar-CH), 2.79–2.63 (m, 4H, 2CH$_2\underline{CH_2}$CH$_3$), 0.93 (t, 6H, *J* = 7.5 Hz, 2CH$_3$); MS *m* / *z*: 415 (M$^+$ + 2), 413 (M$^+$), 370 (100); *Anal.* Calcd mass fractions of elements, *w* / %, for $C_{23}H_{25}ClN_2O_3$ (M_r = 412.90) are: C, 66.90; H, 6.10; N, 6.78. Found: C, 66.65; H, 5.75; N, 6.45.

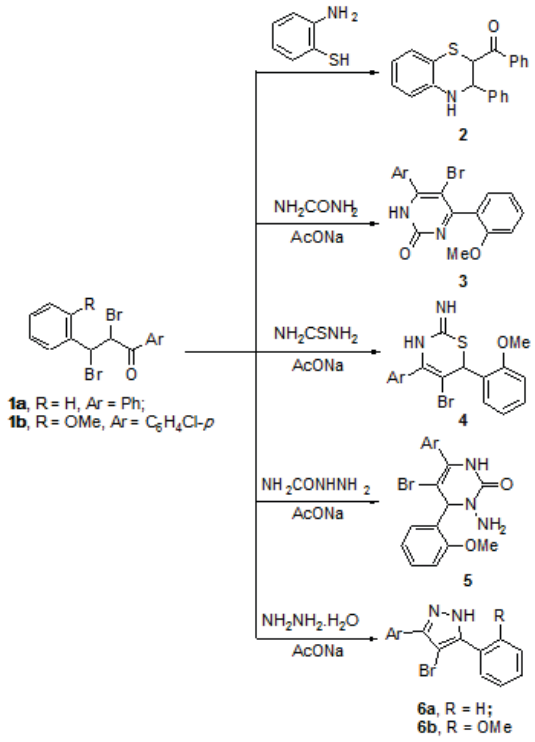
α-Glucosidase Inhibitory Assay

The α-glucosidase (Sigma-Aldrich) inhibitory activity was measured according to the method previously described[42]

with slight modifications. 1 mg of each sample or acarbose at different concentrations (500 µL) of 1.0 U mL^{-1} α-glucosidase solution in 100 mM phosphate buffer (100 mM, pH 6.8) at 37 °C for 20 minutes. The absorbance of the released *p*-nitrophenol was measured at 405 nm. The inhibition percentage was calculated using the given formula: Inhibition % = Abs control – Abs sample x 100.

RESULTS AND DISCUSSION

The heterocyclization of 2,3-dibromo-1,3-diarylpropan-1-one **1a,b** was investigated with the aim of obtaining some better antimicrobial heterocyclic derivatives in a facile route according to the process depicted in scheme 1. The synthetic strategy for the chemical transformation of dibromo ketone to heterocyclic systems depends upon the base induced dehydrobromination forming β-bromo unsaturated ketone conjugated addition of reagent nucleophilic center followed by heterocyclization through the loss of H_2O. Thus, Treatment of methanolic solution of 2,3-dibromo-1,3-diphenylpropan-1-one (**1a**) with 2-aminobenzenethiol at room temperature, then heating under reflux afforded the cyclic product **2**. The base mediated nucleophilic attack of thiolate anion to the more electrophilic carbon of dibromo ketone **1** followed by thiazine cyclization afforded benzothiazine derivative **2**. The

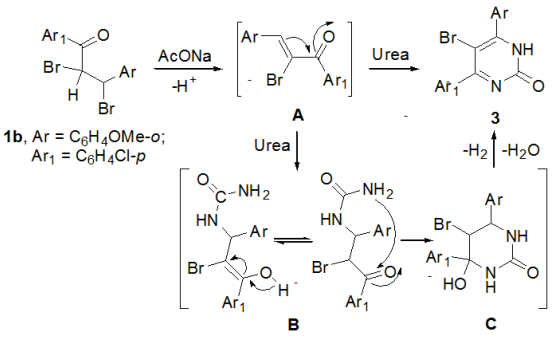


Scheme 1. Utility of α,β-dibromoketone with bidentate nucleophiles.

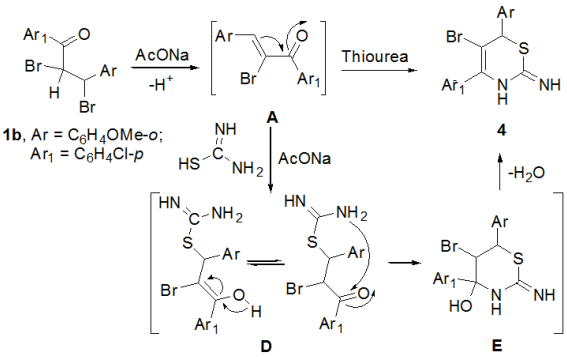
IR spectrum of compound **2** revealed the appearance of absorption bands at 3347 (NH) and 1677 (C=O) cm^{-1}. It's ^1H NMR spectrum also showed a singlet at δ 3.61 ppm assigned to NH and two deshielded doublet of doublet at δ 6.69, 5.78 ppm attributed for (SCHCO) and (Ar-CH) protons as well as mass spectrum showed ion peaks at m / z = 333 (M^+ + 2), 332 (M^+ + 1), 331 (M^+) which confirmed their chemical structure.

The [3+3] cyclocondensation of compound **1b** with urea in presence of AcONa via one-pot procedure afforded 5-bromo pyrimidin-2(1*H*)-one derivative **3** through the intermediate **A** that suffer air oxidation leading to the final product. IR spectrum of the pyrimidinone **3** showed absorption band at 1653 cm^{-1} assigned to carbonyl group and its ^1H NMR spectrum showed a singlet at δ 8.07 ppm indicated the formation of aminic (NH) and aromatic protons were observed at δ 8.06–7.06 ppm that confirmed the structure. Also, mass spectrum of **3** showed molecular ion peak at m / z 392 corresponding to its molecular formula $C_{17}H_{12}BrClN_2O_2$.

Although the detailed mechanism of above reaction remains not to be fully clarified, the formation of compound **3** could be explained by a reaction sequence presented in scheme 2. We proposed that the reaction proceeded via a reaction sequence of dehydrobromination, Michael type addition, cyclization and dehydration.



Scheme 2. Proposed mechanism of the synthesis of pyrimidine derivatives.



Scheme 3. Proposed mechanism of the synthesis of bromothiazine derivative.

Furthermore, the kinetic controlled thiazine derivative **4** was readily obtained through smooth dehydrobromination of the dibromide **1b** followed by the S-alkylation of thiourea and subsequent thiazine cyclization *via* losing H_2O (Scheme 1). The postulated mechanism of formation of the thiazine **4** was outlined in details in scheme 3.

Appearance of absorption bands of NH groups in the IR spectrum of compound **4** at 3417 cm^{-1} and its ^1H NMR spectrum revealed a singlet at δ 3.78 (Ar–CH), a multiplet δ 8.21–7.04 (Ar–H + D_2O exchangeable NH) as well as the mass spectrum showed ion peaks at *m* / *z* 411 (M^+ + 2) and 410 (M^+ + 1) confirmed its molecular formula.

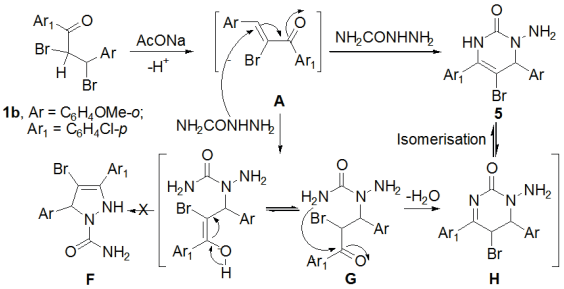
Refluxing of ethanolic solution of compound **1b** and semicarbazide in presence of AcONa afforded dihydropyrimidin-2(1*H*)-one derivative **5** (Scheme 1). This was potentiated from spectral analysis which revealed a peaks at 3450 (NH), 3287, 3221 (NH_2) 1677, (C=O) cm^{-1} and the ^1H NMR spectrum showed a singlet at δ 6.60 ppm (D_2O exchangeable NH + NH_2). ^{13}C NMR spectrum exhibited two signals at δ 55.94, 54.90 corresponding to methylenic CH and methoxy groups. MS showed a peaks at *m* / *z* 329, 328 (M^+ – Br) that confirmed its molecular formula. It seemed that semicarbazide undergo [3 + 3] cycloaddition with the conjugated intermediate formed upon basic dehydrobromination of compound **1b** followed by dehydration and isomerization resulting in the formation of dihydropyrimidine derivative **5** and none of pyrazole derivative **F** was obtained (Scheme 4).

Also, one-pot reaction of compounds **1a**,**b** with hydrazine hydrate (99 %) / AcONa in ethanol under reflux afforded 4-bromopyrazole derivatives **6a** and **6b**. Absence of absorption bands in the latter series for carbonyl group in the IR spectra as well as in the ^1H NMR spectra was characteristic for the 4-bromo-1*H*-pyrazoles. Thus, Compound **6a** were characterized with absorption band at 3445 cm^{-1} for (NH) group and absence of the carbonyl in the IR spectrum. Its ^1H NMR spectrum showed signal at δ 13.35 ppm attributed to NH (D_2O exchangeable) and the mass spectrum showed ion peaks at *m* / *z* 301, 299 and 222 corresponding to (M^+ + 2), (M^+) and (M^+ – C_6H_5), respectively which confirmed its chemical structure. IR spectrum of compound **6b** exhibited absorption band at 3280 cm^{-1} for (NH). A multiplet at δ 7.98–7.10 ppm assigned to (Ar-H + D_2O exchangeable NH) in the ^1H NMR spectrum and characteristic signals for bromopyrazole showed in ^{13}C NMR spectrum. Also the mass spectrum showed molecular ion peak at *m* / *z* 363 and (M^+ + 2) at 365 that confirmed its molecular formula $C_{16}H_{12}BrClN_2O$. The formation of compounds **6a** and **6b** could be explained by a reaction sequence presented in scheme 5.

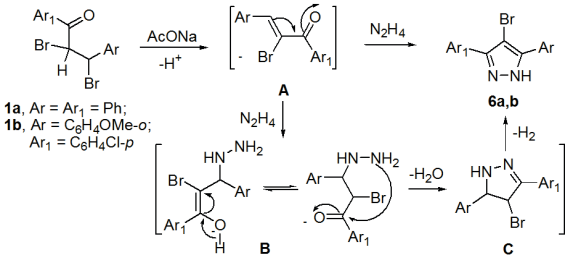
We proposed that the bromopyrazole derivatives **6a**/**6b** were obtained as the result of dehydrobromination, Michael type addition and subsequent intramolecular cyclodehydration.

Using the behavior of α,β-unsaturated carbonyl system **7** which seemed to be of suitable located functionality towards some nitrogen and/or active methylene nucleophilic reagents was investigated. The mechanistic pathway for these heterocyclization depends upon 1,4-addition followed by intramolecular cyclodehydration and air oxidation in some cases. Thus, when chalcone **7a** was allowed to react with *tert*-Butyl carbazate, cyclization occurred smoothly by heating under reflux to afford pyrazole **8** as shown in scheme 6. It presumably that the pyrazole derivative **8** was obtained via [3 + 2] intermolecular cycloaddition through the α-nitrogen of the nucleophilic reagent were added exclusively to α,β-unsaturated system with simultaneous ring closure. Hence, the structure of compound **8** was characterized with absorption bands at 3426 (NH), 1707 (C=O) cm^{-1} in IR spectrum and the presence of characteristic singlet at δ 10.81, 2.18 and 1.46 ppm in ^1H NMR spectrum for NH, methinyl CH and *tert*-butyl protons, respectively.

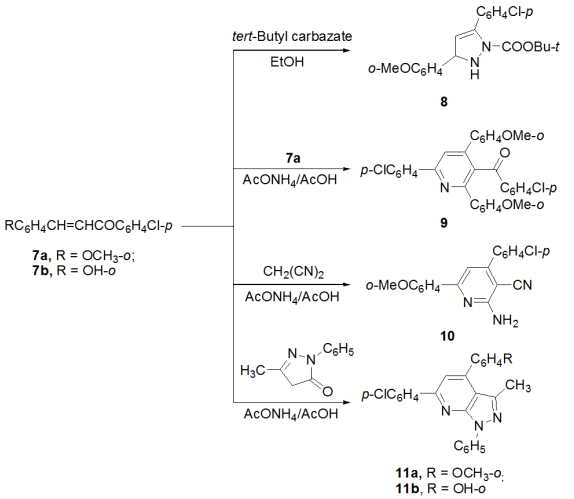
The keeping of α,β-unsaturated carbonyl derivative **7a** with ammonium acetate/AcOH under reflux resulted in pyridine cyclization via the nonisolable β-amino-ketone followed by [3 + 3] cyclodehydration to furnish the dihydropyridine derivative, which in turn underwent dehydrogenation giving the final product **9** (Scheme 6).



Scheme 4. Proposed mechanism of the synthesis of 5-bromopyrimidine derivatives.



Scheme 5. Proposed mechanism of the synthesis of bromopyrazole derivative.

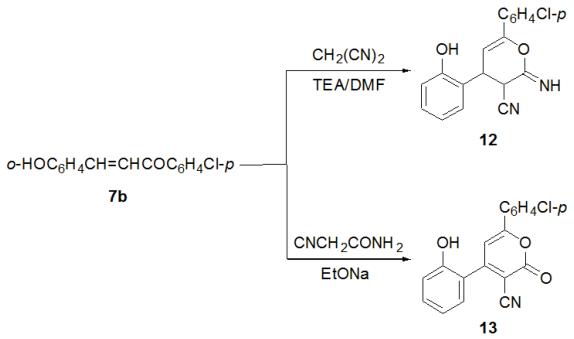


Scheme 6. Synthesis of some pyrazole, pryridine and pyrazolo[3,4-*b*]pyridine derivatives.

The analytical and spectral data were consistent with the proposed structure. Thus, the IR spectrum of **9** revealed a peak at 1658 cm^{-1} of the carbonyl group and the ^1H NMR spectrum showed a multiplet at δ 8.27-7.09 indicating the Ar-H and CH pyridine protons and a singlet at δ 3.83 ppm according to $2OCH_3$ protons.

The high yield of α,β-unsaturated system of type **7** encouraged us again to study their further reactivities towards cyano methylene reagents. Pyridine of type **10** was formed upon the addition of malononitrile to ketonic derivative **7** in the presence of ammonia source. Thus, malononitrile added its nucleophilic carbon to electrophilic carbon of **7a** producing acyclic Michael type adduct that cyclizes intramolecularly in presence of $AcONH_4$/AcOH producing pyridin-3-carbonitrile **10**. While, α,β-unsaturated system **7a,b** when allowed to react with 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one afforded pyrazolo[3,4-*b*]pyridine of type **11** (Scheme 6). The analytical and spectral data of the obtained products were in agreement with the assigned structures. Thus, the ^1H NMR spectrum of **10** showed beside the expected signals of the pyridine moiety, a singlet at δ 3.36 ppm corresponding to D_2O exchangable, NH_2 group, a multiplet at δ 8.12–6.93 ppm including the aromatic protons with CH pyridine and the IR spectrum exhibited peak at 2217 cm^{-1} of the cyano group.

Also, the ^1H NMR spectrum of product **11a** (as an example) showed beside the expected signals of the pyrazolopyridine moiety, a multiplet at δ 8.27–7.09 ppm including the aromatic protons with CH pyridine and the IR spectrum exhibited peak at 1600 (C=N) cm^{-1} and absence of carbonyl groups. The mass spectrum of product **11a** revealed molecular ion peak at *m* / *z* = 426 that confirmed the postulated structure.



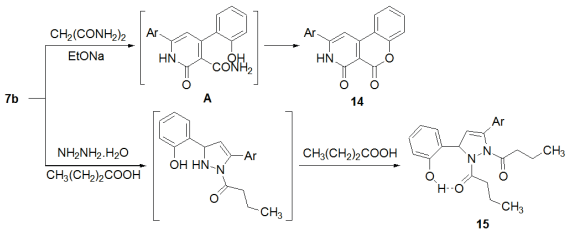
Scheme 7. Synthesis of pyrane 3-carbonitrile derivatives.

The reaction of α,β-ketonic derivative **7b** with malononitrile in DMF/TEA afforded 2-imino-3,4-dihydro-2*H*-pyran-3-carbonitrile derivative **12** (Scheme 7). This reaction presumably proceeded via Michael addition followed by intramolecular cyclization producing pyran derivative **12**. The IR spectrum of compound **12** revealed the absence of carbonyl group and showed absorption bands at 3429, 3235, 2202 and 1601 cm^{-1} for phenolic OH, iminic NH, CN groups as well as in the MS showed ion peaks at *m* / *z* 324 (M^+) and 323 ($M^+ - 1$) confirmed its molecular formula.

Cycloaddition of cyanoacetamide with the chalcone **7b** in ethanolic EtONa solution afforded an Michael type adducts intermediate which in turn underwent basic cyclization followed by dehydrogenation producing pyran-3-carbonitrile derivative **13** (Scheme 7). The analytical and spectral data was consistent with the proposed structure. Thus, the IR spectrum of compound **13** showed absorption bands at 3409, 2226, 1771, 1614 cm^{-1} for OH, CN, C=O and C=C groups, respectively. Its ^1H NMR spectrum showed signal at 10.10 ppm assigned for OH group as well as in the MS showed ion peak at *m* / *z* 324 ($M^+ + 1$), and 323 (M^+) confirmed its molecular formula.

Also, chromenopyridine **14** was prepared by nucleophilic reaction of malonamide with **7b** forming the nonisolable phenol **A** that undergo NH_3 losing by intramolecular cyclization to give pyran ring (Scheme 8). Structure of **14** assigned by IR, ^1H NMR and mass spectral data. In its IR spectrum, there are four bands assignable to NH, 2CO, C=C groups at 3433, 1777, 1638 and 1616 cm^{-1}, respectively. ^1H NMR spectrum showed deshielded singlet at 12.42 ppm attributed for NH (D_2O exchangable) and aromatic protons were observed at δ 8.50–7.36 ppm.

The synthesis of 1-[2-butyryl-5-(4-chlorophenyl)-3-(2-hydroxyphenyl)-2,3-dihydro-1*H*-pyrazol-1-yl]-1-butanone derivative **15** was achieved by intermolecular cycloaddition of hydrazine hydrate in the presence of butyric acid that form acylated pyrazole. Hence, refluxing of α,β–unsaturated derivative **7b** in presence of hydrazine hydrate 99 % in butyric acid yield the *N*–butanoyl product **15** (Scheme 8).



Scheme 8. Utility *o*-hydroxy arylidene derivatives in synthesis of condensed heterocycles.

The analytical and spectral data were consistent with the proposed structure. Thus, the IR spectrum of **15** revealed a peak at 3226 (OH) and 1638 cm^{-1} of the carbonyl groups and the ^1H NMR spectrum showed a singlet at δ 9.62 ppm assigned for OH group, double doublet at δ 5.67 according to enaminic CH group of pyrazole, double doublet at δ 3.02 indicating CH methylenic and a characteristic signals for the propyl groups. MS spectrum of **15** showed molecular ion peak at m / z = 413.

Biological Activity

The compounds bearing Pyrimidine, pyridine and/or pyrazole nucleus are well known to exhibit versatile range of biological activities such as anti-diabetic activities.[12–16] From the structure–activity relationships, it is revealed that the selected group of heterocyclic skeletons is important for anti-diabetic studies, which supports the previous results. For instance, the novel compounds **5**, **8**, **10**, **11a** and **11b** shared similar chemical features and functional groups, such as the presence of hydroxyl and methoxy groups were evaluated for their potential α-glucosidase inhibitory activity. The results are presented in Table 1. The activity comparison and the structure correlation of the tested group of the novel compounds had shown that these potencies paralleled the pyrazole moiety.

The pyrazole derivative **8** of the tested compounds were found to have less inhibitory (α-glucosidase inhibitory) activity than a commercial anti-hyperglycemic drug, acarbose (IC_{50} = 12.87 μM). The pyrazolo[3,4-*b*]pyridin-4-yl]phenol derivative **11b** was the most potent inhibitor (IC_{50} = 13.80 μM). Also, It was noted that the introduction of a 2-hydroxyphenyl group at position 4 on the condensed pyrazolopyridine moiety increased the activity (compound **11b**), while the introduction of a 2-methoxyphenyl group at position 4 on the condensed pyrazolopyridine moiety decreased the activity (compound **11a**), except for isolated pyrazole (Compound **8**). These results indicate that hydroxylation of the condensed pyrazolopyridine rings is important for α-glucosidase inhibitory activity.

Table 1. Effect of compounds **5**, **8**, **10**, **11a**, **11b** and acarbose on the anti-diabetic potential.

Compound	IC_{50} / μg L^{-1}
5	60.67
8	33.20
10	> 500
11a	185.07
11b	13.80
Acarbose	12.87

The IC_{50} value was defined as the concentration of alpha-glucosidase inhibitor to inhibit 50 % of its activity under the assayed conditions. All determinations were carried out in triplicate manner and values are expressed as the mean ± CD. Anti-diabetic activity of the tested compounds was depicted with IC_{50} value in Table 1.

CONCLUSIONS

In this work some novel condensed pyrimidine, pyrazole and pyridine derivatives were synthesized and assayed for their anti-diabetic inhibitory. The experimental work involves the synthesis of α,β-unsaturated carbonyls and α,β-dibromocarbonyls which was then heteroannelated with various 1,2; 1,3-bidentate nitrogen and carbon nucleophiles. Correlations are useful because they can indicate a predictive relationship that can be exploited in practice. Comparing of the anti-diabetic activity of the tested group of new compounds and its analogous described in the literature,[39–41] it is obvious that the highest activity might be attributed to the presence of pyrazolo[3,4-*b*]pyridine moiety bearing 2-HOC_6H_4 group.

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