From the Research Laboratories
В изследователските лаборатории

SYNTHESIS AND CHARACTERIZATION OF NOVEL HETEROCYCLES WITH ANTICIPATED ANTIMICROBIAL ACTIVITIES FROM PYRANOPYRAZOLE DERIVATIVE

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Abstract. The previously reported 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano [2, 3-c] pyrazole-5-carbonitrile **1** was prepared and utilized as a precursor for novel heterocycles such as Benzoxazinone 4, Pyrazolopyranopyrimidines 8, 9, 12, 13 and 20 tetrazolopyrimidine 15 and triazolopyrimidine 16 with anticipated antimicrobial activity. The structural features of these novel heterocycles were characterized and confirmed by their spectral analysis as well as elemental analyses.

Keywords: pyrazolopyranooxazinones; pyranopyrimidines; triazolopyrimidines tetrazolopyrimidines and pyrazolopyranopyrimidinthion

Introduction

In recent years, the pyrazole fused heterocycles such as pyrano[2,3-c] pyrazole derivatives are known to possess diverse biological activities as anticancer (Han et al., 2015),antibacrerial and anti-infalmatoryactivites (Santhosh et al., 2012). The literature survey reveals that numerous condensed pyrazole derivatives have been synthesized and advanced to clinic studies with various biological activities (Duan et al., 2014). Pyrrolo[3,4-c] pyrazol-4(1H)-one derivatives have been reported to exhibitanti BVDV activity (Fargualy et al., 2013). Many substituted pyranopyrazoles are known to possess diverse biological activities as new neuropeptide S receptor antagonists (Batran et al., 2017), antitubercular and antimicrobial (Kamdar et al., 2010), antioxidant (Saundane et al., 2013). The fused pyrimidine derivatives have been constructed and evaluated their antimicrobial activity (Mahmoud et al., 2012; 2013). Bezoxazinones are one of the important ring systems that have drawn the attention for their different biological activities (Gao et al., 2017; Piecyk et al., 2017; Martinand-Lurin et al., 2014).Some pyranotriazolopyrimidine derivatives were synthesized and their antigenotoxic activity were tested in *Escherichia coli* PQ37 by using the SOS chromotest (Chabcloub, 2007).Based on these find-

ings, it was of interest to synthesis newheterocyclic compounds such as Benzoxazinone 4, Pyrazolopyranopyrimidines 8, 9, 12, 13 and 20 tetrazolopyrimidine 15 and triazolopyrimidine 16 with anticipated antimicrobial activity..

Experimental

All the chemicals that we used in this paper are of high purity and have been purchased from Al-Gomhouria Company - Cairo – Egypt. All melting points were measured on a Gallenkamp electric melting point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide disks on a PyeUnicam SP-3-300 and Shimdazu FT IR 8101 PC Infrared spectrophotometers. The ^{1}HNMR was recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}HNMR spectra were run at 300 MHz and on a Varian Gemini 200 MHz, Brucker AC-200 MHz using TMS as internal standard in deuterated chloroform ($CDC1_3$) or deuterated-dimethylsulphoxide (DMSO-d6). Chemical shifts are quoted in δ and were related to that of the solvents. The mass spectra were recorded on a Shimadzu GCMS-QP-1OOOEX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. All the reactions and the purity of the new compounds were followed and cheeked by TLC.

2-((4-(4-chlorophenyl)-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-yl)amino)-2-oxoacetylchloride (2)

A mixture of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*] pyrazole-5-carbonitrile **(1)** (1.43gm, 0.005 mole) in dry toluene (50 mL) and oxalyl chloride (1 gm, 0.0075 mole) was refluxed on a hot plate for 2 hours, excess toluene and oxalyl chloride was removed under reduced pressure, the formed semisolid was washed three times with dry toluene and evaporated under reduced pressure. The semisolid remains after evaporation was allowed to react directly with the appropriate alcohol or amine in some coming reactions.

2-(2-((4-(4-chlorophenyl)-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-yl)amino)-2-oxoacetamido) benzoic acid(3)

A mixture of 2-((4-(4-chlorophenyl)-5-cyano-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-yl)amino)-2-oxoacetyl chloride **(2)** (1.9 gm, 0.005 mole) and anthranilic acid (1.4 gm, 0.01 mole) was added to dry pyridine (25 mL) and refluxed for 2 hours, the solvent then removed under reduced pressure, the formed solid collected and crystallized from ethanol / acetic acid (drops), to give **(3)**, as yellow crystals, M.p.: 288-290ºC, yield 60%. Anal. Calcd. for $C_{23}H_{16}N_5ClO_5$ (477.9) C, 57.81; H,3.37; N, 14.66; Cl, 7.42. Found: C, 57.73; H, 3.44; N, 14.59; Cl, 7.33. IR (υ/cm^{-1}): 3379, 3266 and 3119 (NH amide and NH pyrazole), 2217 (C≡N), 1681 and 1632 (C=O). MS m/z (%):478 (70.2%), 432 (50%), 353 (62.9%), 254 (52.4%), 239 (100%), 190 (53.2%) and 147 (76.6%). ^{1}HNMR (DMSO-d_6) δ

(ppm): 12.77 (s, 2H, NH amide exchangeable with D_2O), 10.59 (s, 1H, NH pyrazole exchangeable with D_2O), 8.71 (s, 1H, OH carboxylic exchangeable with D_2O) 8.10-7.25 (m, 8H, ArH), 4.80 (s, 1H, benzylic H) and 1.87 (1s, 3H, CH_3).

4-(4-chlorophenyl)-3-methyl-7-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)-1H-pyrazolo[4',3':5,6] pyrano[2,3-d][1,3] oxazin-5(4H)-one(4)

A mixture of 2-(2-((4-(4-chlorophenyl)-5-cyano-3-methyl1,4-dihydropyrano[2,3-*c*]pyrazol-6-yl)amino)-2-oxoacetamido)benzoic acid **(3)** and acetic anhydride (25 mL) are refluxed for 8 hours, the excess anhydride then removed under reduced pressure, the formed solid collected and crystallized from ethanol / acetic acid (drops), to give **(4)**, as yellow crystals, M.p.:>300ºC, yield 40%. Anal. Calcd. for $C_{23}H_{13}N_4ClO_5$ (460.8) C, 59.95; H,2.84; N, 12.16; Cl, 7.69. Found: C, 60.07; H, 2.77; N, 12.26; Cl, 7.60. IR (υ/cm^{-1}): 3268 (NH pyrazole), 1765 (C=O),1628 (C=N). MS m/z (%):461 (61.2%), 322 (92.2%), 246 (100%), 177 (2.91%), 174 (13.6%) and 136 (7.8%) .^{1}HNMR (DMSO-d_6) δ (ppm): 12.69 (s, 1H, NH pyrazole exchangeable with D_2O), 8.25-7.32 (m, 8H, ArH), 5.11 (s, 1H, benzylic H) and 1.90 (s, 3H, CH_3).

Methyl 2-((4-(4-chlorophenyl)-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c] pyrazol-6-yl)amino) -2-oxoacetate(5) and Ethyl 2-((4-(4-chlorophenyl)-5-cyano-3-methyl-1,4-dihydropyrano [2,3-c]pyrazol-6-yl) amino)-2-oxoacetate(6)

2-((4-(4-chlorophenyl)-5-cyano-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6 yl)amino)-2- oxoacetyl chloride **(2)** (1.9 gm, 0.005 mole) was added to dry methanol and/or dry ethanol (50 mL) and refluxed for 30 minutes , the solvent then removed under reduced pressure, the formed solid collected and crystallized from ethanol / acetic acid (drops), to give **(5)**, as yellow crystals, M.p.:>300 ºC, yield 75%. Anal. Calcd. for $C_{17}H_{13}N_4ClO_4$ (372.8) C, 54.78; H, 3.52; N, 15.03; Cl, 9.51. Found: C, 54.71; H, 3.50; N, 14.92; Cl, 9.45. IR (υ/cm^{-1}(ν/cm^{-1}) at: 3373 and 3207 (NH amide and NH pyrazole), 2217 (C≡N), 1723 and 1649 (C=O)MS m/z (%):$M^{\cdot+}$ at m/e 372.8 (not observed), 357 (69.5%), 264 (74.7%), 261 (100%), 218 (63.2%) and 96 (25.3%) ^{1}HNMR (DMSO-d_6) δ (ppm): 12.21 (s, 1H, NH pyrazole exchangeable with D_2O), 10.25 (s, 1H, NH amide exchangeable with D_2O), 7.43-7.17 (m, 4H, ArH), 5.01 (s, 1H, benzylic H), 1.91 and 1.84 (2s, 6H, $2CH_3$)and **(6)**, as yellow crystals, M.p.:>300 ºC, yield 70%. Anal. Calcd. for $C_{18}H_{15}N_4ClO_4$ (386.8) C, 55.89; H,3.91; N, 14.49; Cl, 9.17. Found: C, 55.94; H, 3.82; N, 14.40; Cl, 9.24.IR (υ/cm^{-1}): 3196 and 3121 (NH amid and NH pyrazole), 2217 (C≡N), 1725 and 1647 (C=O)MS m/z (%):386.8 (not observed), 372 (56.9% relative abundance), 312 (55.9%), 235

(100%), 189 (69.6%) and 120 (26.5%) ^{1}HNMR (DMSO-d_6) δ (ppm): 12.24 (s, 1H, NH pyrazole exchangeable with D_2O), 11.0 (s, 1H, NH amide exchangeable with D_2O), 7.46-7.20 (m, 4H, ArH), 4.85 (s, 1H, benzylic H), 1.96 (q, 2H, CH_2), 1.85 (s, 3H, CH_3pyrazole) and 1.30 (t, 3H, CH_3).

4-(4-chlorophenyl)-5-hydroxy-3-methyl-4,8-dihydropyra-zolo[4',3':5,6] pyrano[2,3-d] pyrimidin-7(1H)-one (8) and *4-(4-chlorophenyl)-5-hydroxy-3-methyl-4,8- dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-7(1H)-thione (9)*

A mixture of 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*] pyrazole-5-carboxamide **(7)** (1.5 gm, 0.005 mole) , urea (0.3gm, 0.005 mole) and / or thiourea (0.4 gm, 0.005 mole) in dry toluene (50 mL)was refluxed on a hot plate for 24 hours. The excess solvent was removed under vacuum; the solid remained was crystallized from ethanol / acetic acid (drops) to give **(8)** as yellow crystals, M.p.:>300 ºC, yield 70%. Anal. Calcd. for $C_{15}H_{11}N_4ClO_3$ (330.7) C, 54.47; H,3.35; N, 16.94; Cl, 10.72. Found: C,54.53; H,3.42; N, 16.87; Cl, 10.79. IR (υ/cm^{-1}): 3308, 3157 (OH & NH), 1729 (C=O), 1655 (C=N) MS m/z (%):331 (1.14%), 246 (2.83) 221 (30.6%) and 111 (1.03%). ^{1}HNMR (DMSO-d_6) δ (ppm): 12.15 (s, 1H, NH pyrazole exchangeable with D_2O), 7.63-7.18 (m, 4H, ArH), 6.94 (s, 2H, 2OH exchangeable with D_2O), 4.63 (s, 1H, benzylic H), 1.79 (s, 3H, CH_3). and **(9)** as yellow crystals, M.p: 224-226 ºC, yield 70%. Anal. Calcd. $C_{15}H_{11}N_4SClO_2$ (346.8) C, 51.95; H,3.20; N, 16.16; Cl, 10.22; S,9.25 Found: C,51.87; H, 3.29; N, 16.10; Cl, 10. 30; S,9.17. IR (υ/cm^{-1}): 3340 and 3166 (OH and NH), 1089 (C=S). MS m/z (%):345 (1.26% relative abundance), 268 (34.9) 236 (9.75%), 143 (5.03%).^{1}HNMR (DMSO-d_6) δ (ppm): 11.0 (s, 1H, NH pyrazole exchangeable with D_2O), 7.38-7.05 (m, 4H, ArH), 6.92 (s, 2H, SH, OH exchangeable with D_2O), 5.06 (s, 1H, benzylic H) and 1.90 (s, 3H, CH_3).

4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidin-5-ol (10)

A mixture of 4-(4-chlorophenyl)-3-methyl-4,6-dihydropyrazolo[4',3':5,6] pyrano[2,3-*d*] pyramidin5(1*H*)-one **(7)** (1.5 gm, 0.005 mole) and formamide (20mL) was refluxed with stirring on a hot plate with magnetic stirrer at 120 ºC for 2 hours. The reaction mixture was poured after cooling into water and crushed ice; the solid formed was filtered off, washed with cold water and crystallized from dilute ethanol to give **(10)** as white crystals, M.p.: 236-238 ºC, yield 84%. The structure of **10** has been confirmed by comparison with the previously prepared from the reaction of **7** with formic acid (El-Ziaty et al., 2014).

5-chloro-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrazolo[4',3':5,6] pyrano[2,3-d]pyrimidine (11)

A mixture of well-dried 4-(4-chlorophenyl)-3-methyl-4,6-dihydropyrazolon [4',3':5,6] pyrano[2,3-*d*]pyrimidin-5(1*H*)-one **(10)** (1.6 gm, 0.005 mole) and phosphorous oxychloride (20 mL) was refluxed on boiling water bath for 2 hours, after completion the excess phosphorous oxychloride was almost evaporated under reduced pressure, the remained mixture was dded gradually with vigorous stirring to crushed ice, the solid formed was filtered off immediately and washed with cold water, then crystallized from ethanol to give **(11)** as yellow crystals, M.p: 261-264 ºC, yield 40%. Anal. Calcd. $C_{15}H_{10}N_4Cl_2O$ (333.2) C,54.07; H,3.03; N, 16.82; Cl, 21.28. Found: C,53.95; H,3.10 N, 16.89; Cl, 21.20. IR (υ/cm^{-1}): 3303 (NH), 1650 (C=N) MS m/z (%):332 (7.9%), 293 (7.9%), 261 (8.29%), 166 (1.46%), 165 (0.77%). ^{1}HNMR (DMSO-d_6) δ (ppm): 11.0 (s, 1H, NH pyrazole exchangeable with D_2O), 7.15-7.06 (m, 5H, 4ArH and pyrimidine H), 4.26 (s, 1H, benzylic H), 1.98 (s, 3H, CH_3).

4-(4-chlorophenyl)-5-hydrazinyl-3-methyl-1,4-dihydropyrazolo[4',3':5,6] pyrano[2,3-d] pyramidne (12)

A mixture 5-chloro-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrazolo[4',3':5,6]pyrano [2,3-*d*] pyrimidine **(11)** (1.7gm, 0.005 mole) in ethanol (50 mL) and hydrazine hydrate (0.3 gm, 0.006 mole) was refluxed on hot plate for 4 hours. After reaction completion the excess ethanol was removed under vacuum to dryness. The solid remained was dissolved in minimum amount of ethanol, then poured into crushed ice, the solid formed was filtered off, washed with cold water and crystallized from ethanol to give **(12)** as white crystals, M.p.: 222-224 ºC, yield 60%. Anal. Calcd. $C_{15}H_{13}N_6ClO$ (328.8) C,54.80; H,3.99; N, 25.56; Cl, 10.78. Found: C,54.71; H,4.07 N, 25.48; Cl, 10.75. IR (υ/cm^{-1}): 3411 and 3257 (NH & NH_2), 1666 (NH_2 bending). MS m/z (%):329 (13.6%), 206 (1.1) 188 (4.3%), 174 (2.7%) and 126 (13.1%). ^{1}HNMR (DMSO-d_6) δ (ppm): 10.2 (s, 1H, NH pyrazole exchangeable with D_2O), 7.23-7.21 (m, 4H, ArH), 7.20 (m, 2H, NHN$\underline{H}_2$ exchangeable with D_2O), 7.03 (s, 1H, pyrimidine -H), 6.85 (s, 1H, N$\underline{H}$NH_2 exchangeable with D_2O), 4.27 (s, 1H, benzylic H), 2.11 (s, 3H, CH_3).

4-(4-chlorophenyl)-5-ethoxy-3-methyl-1,4-dihydropyra zolo[4',3':5,6]pyrano [2,3-d] pyrimidine (13)

A mixture of 5-chloro-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrazolo[4',3':5,6]pyrano [2,3-*d*]pyrimidine **(11)** (1.7gm, 0.005 mole) and sodium ethoxide solution (0.5 gm sodium metal dissolved in 30 mL of dry ethanol) was refluxed

for 4 hours, the mixture then cooled and neutralized with dilute acetic acid then poured to crushed ice, the formed solid is filtered off and washed with cold water, crystallized from ethanol to give **(13)** as white crystals, M.p: 239-241 ºC, yield 50%. Anal. Calcd. $C_{17}H_{15}N_4ClO_2$ (342.8) C, 59.57; H,4.41; N, 16.34; Cl, 10.34. Found: C,59.66; H,4.50;N,16.30; Cl, 10.26. IR (υ/cm^{-1}): 3306 (NH),1628 (C=N). MS m/z (%):343 (0.13%), 221 (100%) 222 (15.2%), 206 (0.3%), 140 (3.1%), 139 (3.0%) and 124 (1.0%). ^{1}HNMR (DMSO-d_6) δ (ppm): 11.8 (s, 1H, NH pyrazole exchangeable with D_2O), 7.3-7.22 (m, 4H, ArH), 7.06 (s, 1H, pyrimidine -H), 4.39 (m, 3H, -C$\underline{H}_2$CH$_3$ and benzylic H), 2.05 (m, 3H, -CH$_2$C$\underline{H}_3$), 1.09 (m, 3H, CH$_3$pyrazole).

11-(4-chlorophenyl)-5,10-dimethyl-8,11-dihydropyrazolo[4',3':5,6] pyrano[3,2-e]tetrazolo[1,5-c]pyrimidine (15)

(0.68gm, 0.002 mole) of 4-(4-chlorophenyl)-5-hydrazino-3,7-dimethyl-1,4-dihydropy- razolo[4',3':5,6]pyrano[2,3-*d*] pyrimidine **(14)** was dissolved in 10 mL concentrated hydrochloric acid and 5 mL acetic acid at 0 ºC, the mixture was stirred in ice bath and 10 mL of 5% sodium nitrite was added gradually on 30 minutes interval. After addition completion the mixture was stirred further for another 1 hour at room temperature, and then the mixture was diluted with water and crushed ice. The solid formed was filtered off, washed with cold water and crystallized from dilute ethanol to give **(15)** as yellow crystals, M.p.: 240-243ºC, yield 65%. Anal. Calcd. $C_{16}H_{12}N_7ClO$ (353.8) C, 54.32; H,3.42; N, 27.72; Cl, 10.02. Found: C,54.40; H,3.33 N, 27.61; Cl, 10.16. IR (υ/cm^{-1}): 3202 (NH) and 1638 (C=N). MS m/z (%):354 (4.2%), 275 (6%), 235 (15.8%), 83 (100%), 110 (14%), 245 (12.4%), 136 (19.6%), 111 (27%), 298 (9%), 256 (23.4%) and 190 (9.4%). ^{1}HNMR (DMSO-d_6) δ (ppm): 10.21 (s, 1H, NH pyrazole exchangeable with D_2O), 7.43-7.38 (m, 4H, ArH), 4.61 (s, 1H, benzylic H), 2.0 (s, 6H, 2CH$_3$).

11-(4-chlorophenyl)-5,10-dimethyl-3-phenyl-8,11 dihydropyrazolo[4',3':5,6] pyrano[3,2-e][1,2,4]triazolo[4,3-c] pyrimidine (16)

A mixture of 4-(4-chlorophenyl)-5-hydrazino-3,7-dimethyl-1,4-dihydropyrazolo [4',3':5,6]pyrano[2,3-*d*] pyrimidine **(14)** (0.68gm, 0.002 mole) and benzoyl chloride (0.28 gm, 0.002 mole) in toluene (10 mL) was refluxed on hot plate for 24 hours. After reaction completion the excess toluene was removed under vacuum to dryness. The solid remained was dissolved in minimum amount of ethanol, then poured into water with crushed ice, the solid formed was filtered off, washed with cold water and crystallized from dilute

ethanol to give **(16)** as yellow crystals, M.p.: 179-182ºC, yield 50%. Anal. Calcd. $C_{23}H_{17}N_6ClO$ (428.9)C, 64.41; H,4.00; N, 19.60; Cl, 8.27. Found: C,64.30; H,3.95 N, 19.71; Cl, 8.35. IR (υ/cm^{-1}): 3427 (NH) and 1220(C=N). MS m/z (%):430 (8.7%), 318 (42.9%), 113 (100%), 338 (46.8%), 324 (30.8%), 285 (33.3%), 176 (74%), 304 (13.9%), 238 (47.8%), 203 (28.4%) and 226 (39.7%). ^{1}HNMR (DMSO-d_6) δ (ppm): 11.68 (s, 1H, NH pyrazole exchangeable with D_2O), 7.93-7.26 (m, 9H, ArH), 4.20 (s, 1H, benzylic H), 2.04 & 2.0 (2s, 6H, $2CH_3$).

1-acetyl-4-(4-chlorophenyl)-3,7-dimethyl-4,6-dihydro pyrazolo[4',3':5,6] pyrano[2,3-d]pyrimidin-5(1H)-one (18)

A mixture of 1-acetyl-4-(4-chlorophenyl)-3,7-dimethyl-1,4-dihydro-5*H*-pyrazolo[4',3':5,6] pyrano[2,3-*d*][1,3]oxazin-5-one **(17)** (1.85gm, 0.005 mole) in formamide (20 mL) was refluxed on a hot plate at 120 ºC for 2 hours, then the reaction mixture is poured into crushed ice, the solid formed then filtered, dried and crystallized from ethanol to give **(18)**, as yellow crystals, M.p.:>300 ºC, yield 45%. Anal. Calcd. $C_{18}H_{15}N_4ClO_3$ (370.8) C, 58.31; H,4.08; N, 15.11; Cl, 9.56. Found: C,58.40; H,3.93 N, 15.03; Cl, 9.16. IR (υ/cm^{-1}): 3406, 3202 (OH and NH) and 1657 (C=O) 1608 (C=N). MS m/z (%): m/e 371 (69.8%), 243 (100%), 328 (13.9%) and 264 (44.2%). ^{1}HNMR (DMSO-d_6) δ (ppm): 9.13 (s, 1H, NH pyrimidine exchangeable with D_2O), 7.30-7.18 (m, 4H, ArH), 4.98 (s, 1H, benzylic H), 2.85, 2.27 and 1.91 (3s, 9H, $3CH_3$).

N-(1-acetyl-4-(4-chlorophenyl)-5-(hydrazinecarbonyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-yl)acetamide(19)

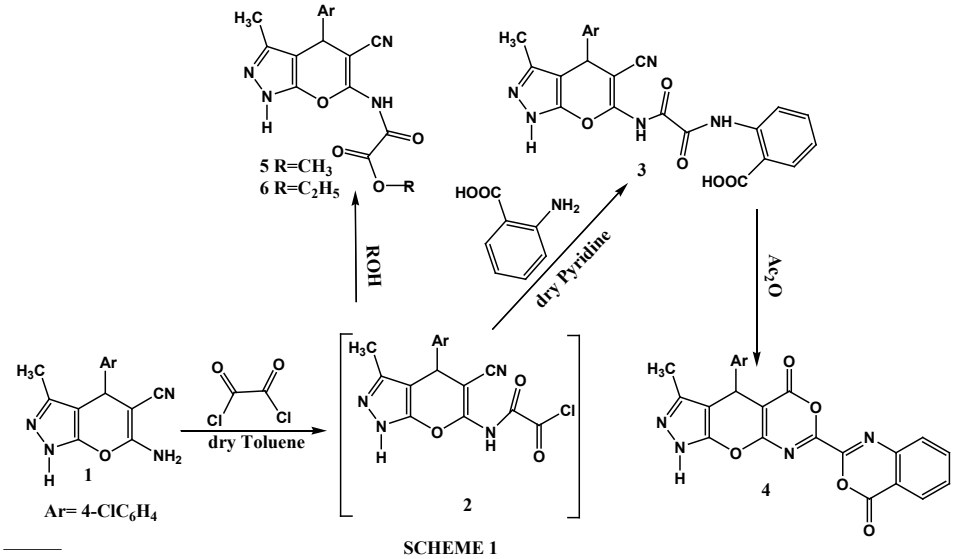
A mixture of 1-acetyl-4-(4-chlorophenyl)-3,7-dimethyl-1,4-dihydro-5*H*-pyrazolo[4',3':5,6] pyrano[2,3-*d*][1,3]oxazin-5-one **(17)** (1.85gm, 0.005 mole) in ethanol (50 mL) and hydrazine hydrate (0.3gm, 0.006 mole) was refluxed on a hot plate for 2 hours, the solid formed on hot is filtered, dried and crystallized from ethanol / acetic acid (drops) to give **(19)**, as yellow crystals, M.p.:>300 ºC, yield 60%. Anal. Calcd. $C_{18}H_{18}N_5ClO_4$ (403.8) C, 53.54; H,4.49; N, 17.34; Cl, 8.87. Found: C,53.30; H,4.83 N, 17.21; Cl, 8.78. IR (υ/cm^{-1}): 3425 and 3273 (NH_2), 3199 (NH amide), 1663 and 1610 (C=O) MS m/z (%):404 (69% relative abundance), 264 (76.3%), 153 (100%) and 143 (72.6%)^{1}HNMR (DMSO-d_6) δ (ppm): 9.4 and 9.13 (2s, 2H, 2NH amide exchangeable with D_2O), 7.33 (s, 2H, NH_2 exchangeable with D_2O), 7.31-7.17 (m, 4H, ArH), 4.98 (s, 1H, benzylic H), 2.27, 1.96 and 1.91 (3s, 9H, $3CH_3$).

Results and discussion

In our continuous interest in the synthesis and evaluation the biological and pharmaceutical activities of heterocyclic compounds (El-Ziaty et al., 2012; 2014; 2016; 2017; Shiba et al., 2008; Abou-Elmagd et al., 2015; Mahmout et al., 2013b; El-Shahawi et al., 2016; El-Shahawi & El-Ziaty, 2017).The previously reported 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c] pyrazole-5-carbonitrile **1 (**El-Zitay et al., 2014) was prepared and utilized as building block for novel heterocycles such as benzoxazinone derivative **4** which constructed by acetylation followed by dehydration and cyclization of the amide derivative **3**. The structure feature of the benzoxazinone derivative **4** was elucidated from its elemental and spectral analysis such as its I.R spectrum showed no signal corresponding to the cyano group and showed a sharp signal at 1765 cm^{-1} for the lactonic carbonyl group. The mass spectrum also elucidates the structure of **4**, it exhibited the molecular ion peak at 461(61%). The amide derivative **3** was prepared in situ from the reaction of the 2-oxoacetyl chloride derivative **2** with anthranilic acid in dry pyridine as a solvent. It is worth to be mentioned that, the 2-oxoacetyl chloride derivative **2** was prepared by treatment of the enaminonitrile**1** with oxalyl chloride and we could not separate it. The structure of **2** was confirmed chemically by esterification with anhydrous alcohol afforded the esters **5, 6,** (Scheme 1). The structure of **5,6** were confirmed from the spectral analysis. The I.R. spectrum showed signals at 1723 $cm^{-1}$and 1725$cm^{-1}$for the ester carbonyl group. also their ^{1}HNMR showed the signals at 1.96 ppm (q, 2H, CH_2) and 1.30 (t, 3H, CH_3) corresponding to the ethyl group in compound **6.**

Partial hydrolysis of the enaminonitile **1** by conc. Sulfuric acid afforded the well-known amid derivative **7**, (Ziaty et al., 2014) which allowed reacting with urea and thiourea to give the pyrazolopyranopyrimidinone **8** and pyrazolopyranopyrimidinthion **9,**respectivelly.

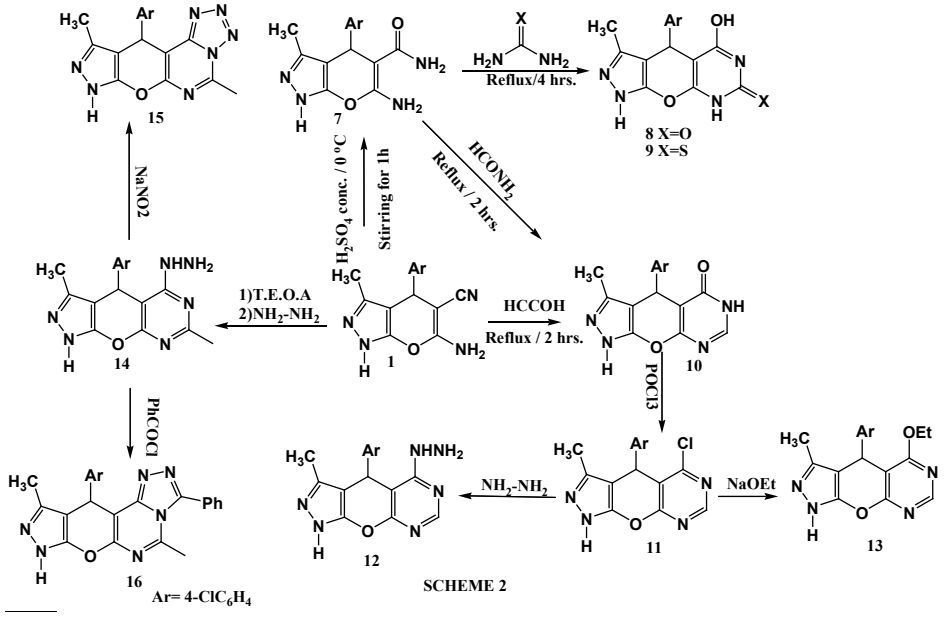
The amid derivative **7** was allowed to react with formamide to give the reported pyrazolopyranopyrimidine**10** which structure was elucidated authentically with the previously prepared from the reaction of **1** with formic acid (El-Shahawi& El-Ziaty, 2017). Chlorination of **10** with a mixture of phosphorous oxychloride and phosphorus pentachloride afforded the chloropyrimidine derivative **11**, which utilized as a precursor to the hydrazinopyrimidine**12** and the ethoxypyrimidine **13** by reaction with hydrazinhydrate and/or sodethoxide respectivlly.



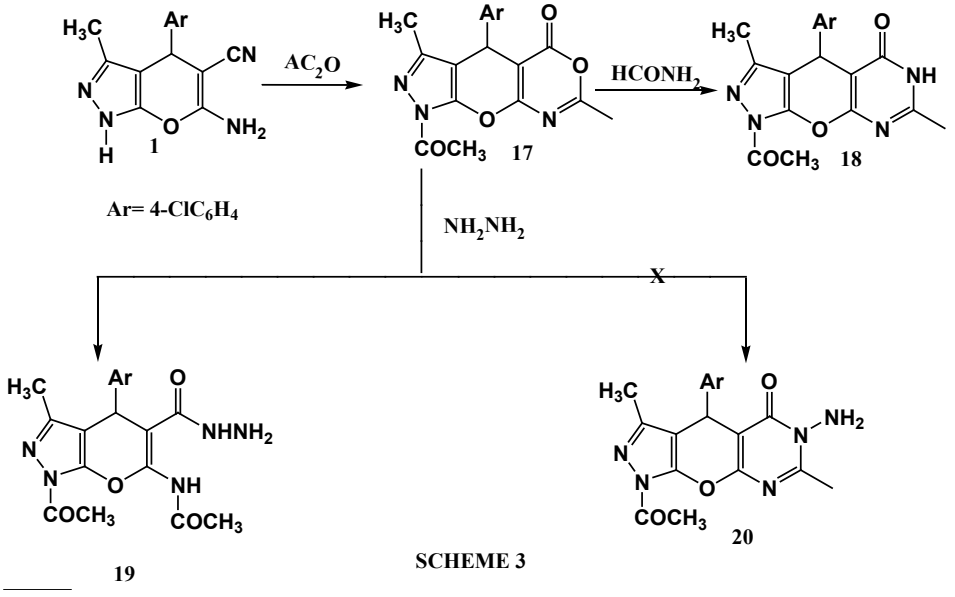
SCHEME 1

Aiming to construct novel triazolo and tetrazolopyrimidine derivatives **15** and **16**, the enaminonitile derivative **1** was allowed to react with triethylorthacetate followed by hydrazinolysis to give the well-known hydrazinopyrimidine derivative **14** [24] (El-Ziaty et al., 2017), [**Scheme 2**.] Treatment of **14** with nitrous acid afforded the tetrazolopyrimidine derivative **15** which structure was confirmed from the spectral analysis, the I.R spectrum showed no signal for the amino group also ^{1}HNMR lacks to the acidic protons of NH_2.the mass spectrum also confirms the structure of **15**, it exhibited the molecular ion peak at 354 (402%). Benzoylation of **14** by benzoyl chloride afforded the triazolopyrimidine derivative **16**which structure was elucidated from the ^{1}HNMR spectra which showed extra 5H arom. at 7.93-7.26 ppm. and the mass spectrum showed the molecular ion peak $M^{+\cdot}$ at 430(8.9%).

Acetylation of the enaminonitle derivative **1** by acetic anhydride afforded the reported pyrazolopyranooxazinone derivative **17** (El-Ziaty et al., 2014). Reaction of the benzoxazinone derivative **17** with formamide gave the corresponding pyrazolopyranopyrimidine derivative **18**. The structure feature of **18**, was confirmed from the spectral analysis, the I.R. spectrum showed no signal characteristic of the lactonic carbonyl group and shoed the new signal at 1657cm^{-1} of the cyclic amide carbonyl group. Also the ^{1}HNMR spectrum showed a strong peak at 9.13ppm for the NH of the pyrimidine moiety. hydrazinolysis of **17** yielded the hydrazide derivative **19** instead of the aminopyrazolopyranopyrimidine**19**, **Scheme 3** the structure of **20** was elucidated from the spectral and elemental analysis.



SCHEME 2



SCHEME 3

Conclusion

In conclusion, we have presented novel heterocycles with anticipated biological and pharmaceutical activates from readily available simple raw materials.

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