Egypt. J. Chem. **Vol. 67,** No. 3 pp. 475- 482 (2024)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis of Some Pyrazolo[1,5-*A*]Pyrimidine Derivatives Bearing Carbonitrile, Amidoxime, Carboxamide And Oxadiazole Substituents Using Commercially Available Reagents

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Abstract

Herein we report the synthesis of some new pyrazolo[1,5-*a*]pyrimidine derivatives. 7-(Aryl)-2-methyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile derivatives **9a-e** which were synthesized by the condensation reaction of the amino pyrazole **3** with acetylacetone **4** or with the arylpropenones (enaminones) **8a-e** in acetic acid. The reaction of the carbonitrile derivative 9e with hydroxylamine in presence of sodium acetate afforded the corresponding amidoxime derivative **10**. Additionally, cyclization of the amidoxime **10** to the corresponding methyl- and phenyl- 1,2,4-oxadiazoles, **11a** and **11b**, was accomplished by heating it with acetic-anhydride or benzoyl chloride in pyridine. On the other hand, the cyano group present in 2-methyl-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile **9e** was partially hydrolyzed with sulphuric acid to afford the carboxamide **12**. Based on their spectral information, the structures of the newly synthesized chemical derivatives were determined.

Keywords: pyrazolo[1,5-*a*]pyrimidine; 5-aminopyrazole; enaminones; thiophene; carbonitrile

1. Introduction

The development of clinically active drugs involves the use of different heterocyclic scaffolds. Many of these heterocyclic scaffolds contain nitrogen atoms at different position. Among these nitrogen containing scaffolds, the pyrazolopyrimidines standout as one of the most important bicyclic systems owing to their various pharmacological activities and their presence in different drugs as will be discussed later in this article. Pyrazolopyrimidines are a group of bicyclic ring systems with different junctions. Four of the most famous ones are pyrazolo[3,4-*d*]pyrimidines [1], pyrazolo[4,3-*d*]pyrimidines [2-5] pyrazolo[5,1-*b*]pyrimidines [6, 7], and pyrazolo[1,5-*a*]pyrimidines [8-12].

Pyrazolopyrimidines with their different junctions, particularly pyrazolo[1,5-*a*]pyrimidines, have gained the attention of many researchers in the last decades owing to their presence in the vast majority of anticancer agents and kinase inhibitors as well as in other drugs possessing other pharmacological activities [13-20]. Moreover, the market is filled with many synthetic medications that have a pyrazolo[1,5-a]pyrimidine skeleton, exemplified by indiplon (1), lorediplon (2), zaleplon (3), and ocinaplon (4) which are used for their sedative, anxiolytic and hypnotic effect. Other examples involve the anticancer drugs: dinaciclib (5) which is used in treatment of melanoma, the ALK2 kinase inhibitor dorsomorphin (6), as well as the multikinase inhibitor larotrectinib (7). Another example of drugs involving a pyrazolopyrimidine ring system is the hypoglycemic agent anagliptin (8) [15, 21-26] (Fig. 1).

Pyrazolopyrimidines comprise a pyrimidine ring fused with a pyrazole ring, each of these rings alone possesses a variety of pharmacological activities. The pyrimidine ring, or 1,3-diazine ring, is an electron rich nitrogen containing ring which is present in plenty of naturally occurring compounds like

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Receive Date: 28 August 2023 Revise Date: 10 September 2023 Accept Date: 10 September 2023
DOI: 10.21608/EJCHEM.2023.231631.8493

nucleotides, vitamins, coenzymes and uric acids.

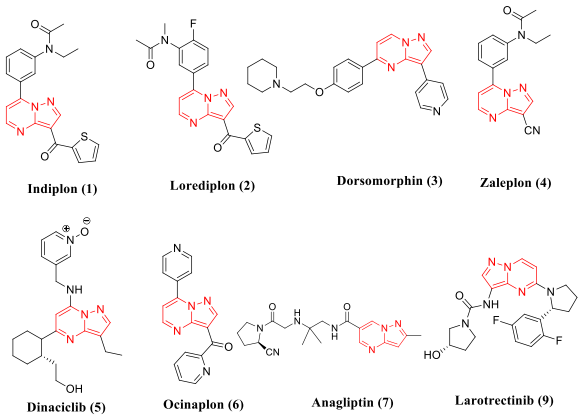


Fig.1. Synthetic drugs incorporated with a pyrazolo-pyrimidines core.

Furthermore, this heteroaromatic ring signifies a broad spectrum of pharmacological activities with limited toxicities and side effects. This is beside the presence of this ring in various available drugs as zidovudine, 5-fluorouracil, imatinib, pazopanib, uramustine, cytarabine, phenobarbital and minoxidil [27-31]. On the other hand, the pyrazole ring possesses a diverse range of pharmacologic and biological activities. These biological activities include anti-inflammatory, antibacterial, antifungal, antiproliferative, hypoglycemic and antihyperlipidemic activities [32-36]. 5-Aminopyrazole, along with its derivatives, is considered an important pyrazole as it is used as a starting material for the synthesis of various heterocyclic ring systems especially pyrazolo[1,5-*a*]pyrimidines. 5-Aminopyrazoles considered important synthon for many bicyclic ring systems through reacting them with different electrophiles as diketones including β-ketoesters [13, 14, 37]. Additionally, thiophene ring, an electron rich isostere for the phenyl ring, is present in different compounds with different pharmacological activities as antibacterial, analgesic, anti-inflammatory, antihypertensive and antitumor agents [38-41].

Many methods were reported for the synthesis Pyrazolo[1,5-*a*]pyrimidines. Most of these methods used different substituted 5-aminopyrazoles as starting materials, while different electrophilic reagents were used. In most cases the starting material amino group is typically added first by the reagent, and then the cyclization process is carried out on the NH group of the pyrazole ring, where this NH acts as a source of the N atom at the junction of the pyrazolopyrimidine ring system. One of the widely used methods involves the reaction of the aminopyrazole with different arylpropenone (β-dimethylaminovinyl, enaminones) derivatives. The reaction usually proceeds by reflux in acetic acid or ethanol [42-44]. Another used method involved treating aminopyrazoles with certain α,β-unsaturated nitriles (α-cinnamonitriles) in presence of a basic catalyst (triethylamine or piperdine) [45]. Alternatively, this bicyclic system could be obtained from the same aminopyrazoles using different chalcones in presence of the basic catalyst: KOH [46]. Also 1,3-dicarbonyl compounds ,1,3-diketones, could be used instead of the previously mentioned reagents [47]. Another method used for preparing the pyrazolo[1,5-*a*]pyrimidine from small chemical entities involved reacting hydrazine hydrate, malononitrile, benzaldehyde and oxoalkanenitriles through a one pot green synthesis [47].

As a result of these aspects, our current research plan includes the preparation of various pyrazolo[1,5-*a*]pyrimidine derivatives, some of these compounds carrying a thiophene ring, using commercially available starting materials and reagents with the goal of creating novel derivatives that are expected to have a wide range of pharmacological activities. In this work we chose to prepare our targeted compounds by reacting the corresponding substituted amino pyrazole with different enaminones due to the ease of this method, beside the advantage of obtaining our desired compounds in a high yield.

2. Experimental

2.1 Chemistry

Measurements of melting points (0C) were performed by open capillary tube using Biocote melting point apparatus (BIBBY, scientific limited stone, Staffordshire). Elemental microanalyses (C, H and N) were analysed on FLASH 2000 CHNS/O. Infrared spectra were obtained from BRUKER FT-IR spectrometers (KBr discs). ^{1}H NMR and ^{13}C NMR spectra were conducted in DMSO-*d6* as a solvent using JEOL spectrometer and chemical shifts were calculated relative to the solvent peak. Reactions were monitored by thin-layer chromatography, Silica gel Kieselgel 60 F254; (Merck, Darmstadt, Germany). The eluting system used was CH_2Cl_2 and the plates were examined under UV lamp; Vilber Lourmat 77202 (Vilber, Marne La Vallee, France) at 366, 254 nm.

The starting and intermediate compounds (2), (3) [49, 50] and (**8a-e**) [51-56] were synthesized following the procedures reported in the literature.

2.1.1. Procedure used for the synthesis of 2,5,7-trimethyl-6-substituted pyrazolo[1,5-a]pyrimidine-3-carbonitrile (5)

A blend of acetylacetone (**4**) (1.14g, 10 mmol) and 5-amino-3-methyl-1H pyrazole-4-carbonitrile (3) (1.39 g, 10 mmol) in 10 mL glacial acetic acid was refluxed for 2 h and subsequently allowed to cool.

The resulting solid product was filtered, washed using ethanol, and then dried. This product was further purified through recrystallization from ethanol to afford the product 5 as white crystals.

2.1.1.1. ***2,5,7-trimethyl-6-substituted pyrazolo[1,5-a]pyrimidine-3-carbonitrile (5)***

White crystals, 60% yield; m.p. 196-8 °C; IR (KBr, cm^{-1}): 3061 (Aromatic CH), 2998 (Aliphatic CH), 2215 (C≡N), 1621 (C=N); ^{1}H NMR (500 MHZ, DMSO-d_6) δ 2.47 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 7.09 (s, 1H, H3 pyrimidine), ^{13}C NMR (125 MHz, DMSO) δ 13.8 ($\underline{C}H_3$), 17.0 ($\underline{C}H_3$), 24.7 ($\underline{C}H_3$), 80.9 (C3 pyrazolopyrimidine), 111.6, , 114.3, 147.4, 150.7 , 157.1, 163.4; Anal. Calcd. For $C_{10}H_{10}N_4$ (186.21): C, 64.50; H, 5.41; N, 30.09. Found: C, 64.72; H, 5.68; N, 29.78.

2.1.2. ***Method used for preparing of 7-(Aryl)-2-methyl-pyrazolo[1,5-a]pyrimidine-3-carbonitriles (9a-e)***

The appropriate arylpropenone (**8a-e**) (10 mmol) and 5-amino-3-methyl-1H pyrazole-4-carbonitrile (3) (1.22 g, 10 mmol) in 15 mL glacial acetic acid was heated under reflux for a duration of 2 h, Subsequently, the reaction mixture was allowed to cool. The resulting precipitate was separated by filtration, and then washed using ethanol, dried, and subjected to recrystallization from ethanol. This process yielded the respective products (9a-e).

2.1.2.1. 7-(4-fluorophenyl)-2-methylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (9a)

White crystals, 65% yield; m.p. 218-220 °C; IR (KBr, cm^{-1}): 3073 (Aromatic CH), 2933 (Aliphatic CH), 2231 (C≡N), 1601 (C=N); ^{1}H NMR (500 MHZ, DMSO-d_6) δ 2.51 (s, 3H, $C\underline{H}_3$), 7.43-7.47 (m, 3H, H3 pyrimidine + 2H phenyl), 8.14 (br. s, 2H, phenyl H), 8.78 (br. s, 1H, H2 pyrimidine); Anal. Calcd. For $C_{14}H_9FN_4$ (252.25): C, 66.66; H, 3.60; N, 22.21. Found: C, 66.84; H, 3.71; N, 22.47.

2.1.2.2. 2-methyl-7-(4-nitrophenyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile(9b)

Pale yellow crystals, 78% yield; m.p. 290-292 °C; IR (KBr, cm^{-1}): 3071 (Aromatic CH), 2853 (Aliphatic CH), 2229 (C≡N), 1616 (C=N), (1331-1337 (NO_2);^{1}H NMR (500 MHZ, DMSO-d_6) δ 2.52 (s, 3H, $C\underline{H}_3$), 7.57 (br. S, 1H, H3 pyrimidine), 8.28 (d, *J* = 7.65 Hz, 2H, phenyl H), 8.43 (d, *J* = 7.60 Hz, 2H, phenyl H), 8.87 (br.s, 1H, H2 pyrimidine); Anal. Calcd. For $C_{14}H_9N_5O_2$ (279.25): C, 60.21; H, 3.25; N, 25.08. Found: C, 60.43; H, 3.51; N, 25.29.

2.1.2.3. 7-(3,4-dimethoxyphenyl)-2-methylpyrazolo [1,5-a]pyrimidine-3-carbonitrile (9c)

White crystals, 60% yield; m.p. 180-182°C; IR (KBr, cm^{-1}): 3074 (Aromatic CH), 2990 (Aliphatic CH), 2222 (C≡N), 1620 (C=N); ^{1}H NMR (500MHZ, DMSO-d_6) δ 2.51 (s, 3H, $C\underline{H}_3$), 3.85 (s, 3H, $OC\underline{H}_3$), 3.95 (s, 3H, $OC\underline{H}_3$), 7.15 (d, *J* = 8.10 Hz, 1H, Phenyl H),7.49 (d, *J* = 4.30 Hz, 1H, H3 pyrimidine), 7.70 (s, 1H, Phenyl H), 7.81 (d, *J* = 8.10 Hz, 1H, Phenyl H),8.72 (d, *J* = 4.30 Hz, 1H, H2 pyrimidine). ^{13}C NMR (125, MHz, DMSO) δ 13.9 ($\underline{C}H_3$), 56.3 (2C, $O\underline{C}H_3$), 81.2 (C3 pyrazolopyrimidine), 100.0, 109.9, 111.9, 113.5, 114.2, 121.9, 124.1, 147.1, 148.9, 152.3, 153.3, 157.4; Anal. Calcd. For $C_{16}H_{14}N_4O_2$ (294.31): C, 65.30; H, 4.79; N, 19.04. Found: C, 65.47; H, 4.85; N, 19.27.

2.1.2.4. 2-methyl-7-(naphthalene-2-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (9d)

White crystals, 70% yield; m.p. 200-202 °C; IR (KBr, cm^{-1}): 3150 (Aromatic CH), 2966 (Aliphatic CH), 2223 (C≡N), 1618 (C=N); ^{1}H NMR (500 MHZ, DMSO-d_6) δ 2.53 (s, 3H, CH_3), 7.57 (d, *J* = 4.25 Hz, 1H, H3 pyrimidine), 7.61-7,68 (m, 2H, Phenyl H), 8.02 (d, *J* = 8.10 Hz, 1H, Phenyl H), 8.04-8.10 (m, 3H, Phenyl H), 8.67 (s, 1H, Phenyl H), 8.83 (d, *J* = 4.30 Hz, 1H, H2 pyrimidine); ^{13}C NMR (125 MHz, DMSO) δ 14.0 ($\underline{C}H_3$), 81.6 (C3 pyrazolopyrimidine), 111.2, 114.1, 126.3, 127.6, 128.2, 128.5, 128.8, 129.5, 130.9, 132.7, 134.5, 147.5, 152.2, 153.7, 157.7; Anal. Calcd. For $C_{18}H_{12}N_4$ (284.31): C, 76.04; H, 4.25; N, 19.71. Found: 76.28; H, 4.37; N, 19.96.

2.1.2.5. ***2-methyl-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitril (9e)***

White crystals, 60% yield; m.p. 205-207 °C; IR (KBr, cm^{-1}): 3093 (Aromatic CH), 2996 (Aliphatic CH), 2221 (C≡N), 1601 (C=N); ^{1}H NMR (500 MHZ, DMSO-d_6) δ 2.58 (s, 3H, CH_3), 7.37 (t, *J* = 3.62 Hz, 1H, H4 thiophene), 7.91 (d, *J* = 5.20 Hz, 1H, H3 pyrimidine), 8.15 (d, *J* = 3.80 Hz, 1H, H3 thiophen), 8.53 (d, *J* = 3.80 Hz, 1H, H5 thiophen), 8.71 (d, *J* = 5.20 Hz, 1H, H2 pyrimidine); ^{13}C NMR (125 MHz, DMSO) δ 14.0 ($\underline{C}H_3$), 81.4 (C3 pyrazolopyrimidine), 106.9, 114.0, 128.7, 129.7, 133.9, 136.4, 141.0, 151.7, 152.8, 157.6; Anal. Calcd. For $C_{12}H_8N_4S$ (240.28): C, 59.98; H, 3.36; N, 23.32. Found: 60.21; H, 3.45; N, 23.57.

2.1.3. General method used in the synthesis of N'-hydroxy-2-methyl-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboximidamide (10)

Hydroxylamine hydrochloride (22 mmol) was added to a mixture of 2-methyl-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitril 9e (20 mmol) and sodium acetate (25 mmol), then the reaction mixture was refluxed in 50 ml ethanol for 4 h. A yellow crystalline precipitate was formed after cooling, collected by filtration; washed with ethanol, and recrystallized from ethanol.

2.1.3.1.N'-hydroxy-2-methyl-7-(thiophen-2-yl) pyrazolo[1,5-a]pyrimidine-3-carboximidamide (10)
Yellow crystals, 70% yield; m.p.236-238 °C; IR: 3460,3334 (NH2), 3217 (OH), 3090 (Aromatic CH), 2958 (Aliphatic CH), 1636 (C=N);^{1}H NMR (500 MHZ, DMSO-d_6) δ 2.61 (s, 3H, C<u>H</u>$_3$), 6.12 (br s, 2H, NH, D_2O exchangeable),7.34 (t, J = 3.80 Hz, 1H, H4 thiophene), 7.68 (br. s, 1H, H3 pyrimidine), 8.08 (br. s, 1H, H3 thiophene), 8.49-8.53 (m, 2H, H5 thiophene + H2 pyrimidine), 9.46 (s, OH, D_2O exchangeable); ^{13}C NMR (125 MHz, DMSO) δ 16.5 (<u>C</u>H$_3$), 100.7, 104.4, 128.3, 132.6, 135.3, 136.4, 139.6, 147.5, 147.9, 149.3, 152.7; Anal. Calcd. for $C_{12}H_{11}N_5OS$ (273.31): C, 52.73; H, 4.06; N, 25.62. Found: C, 53.02; H, 4.23; N, 25.84.

2.1.4. General method used for the synthesis of 5-methyl-3-[2-methyl-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-3-yl]-1,2,4-oxadiazoles (11a and 11b)

A solution of the amidoxime (10) (0.55g, 2 mmol) in 8 ml pyridine was treated with acetic anhydride (for compound 11a) or benzoyl chloride (for compound 11b) (3 mmol), the resultant solution was refluxed for 6-8 h. The solvent was then removed under vacuum, and the resulting solid was ground with water, and then collected by filtration. The collected solid was dried to remove residual moisture. For purification the solid precipitate was crystallized from a mixture of DMF and ethanol.

2.1.4.1. 5-methyl-3-[2-methyl-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-3-yl]-1,2,4-oxadiazole (11a)
Buff crystals, 70% yield: m.p. 198-200 °C; IR (KBr, cm^{-1}): 3094 (Aromatic CH), 2930 (Aliphatic CH), 1604 (C=N); ^{1}H NMR (500 MHZ DMSO-d_6) δ 2.65 (s, 3H, C<u>H</u>$_3$), 2.72 (s, 3H, C<u>H</u>$_3$ oxadiazole), 7.37 (br. s, 1H, H4 thiophene), 7.81 (br. s, 1H, H3 pyrimidine), 8.14 (br. s, 1H, H4 thiophene), 8.52 (br. s, 1H, H5 thiophene), 8.70 (br. s, 1H, H2 pyrimidine); Anal. Calcd. For $C_{14}H_{11}N_5OS$ (297.34): C, 56.55; H, 3.73; N, 23.55. Found: C, 56.71; H, 3.85; N, 23.79.

2.1.4.2. 2-[2methyl-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-3-yl]-5-phenyl-1,3,4-oxadiazole (11b)
Pale yellow crystals, 70% yield: m.p. 140-142 °C; IR (KBr, cm^{-1}): 3077 (Aromatic CH), 2968 (Aliphatic CH), 1640 (C=N); ^{1}H NMR (500 MHZ DMSO-d_6) δ 2.81 (s, 3H, C<u>H</u>$_3$), 7.37 (br. s, 1H, H4 thiophene), 7.62-7.70 (m, 3H, Phenyl H + H3 pyrimidine), 7.82 (m, 1H, Phenyl H), 8.11-8.16 (m, 3H, 2 Phenyl H + H4 thiophene), 7.32 (br. s, 1H, H5 thiophene), 8.72 (br. s, 1H, H2 pyrimidine). ^{13}C NMR (125 MHz, DMSO) δ 15.5, (<u>C</u>H$_3$), 95.9, 105.5, 106.8, 128.3, 129.9 (2C), 130.3, 133.0 (2C), 133.5, 135.5, 139.8, 148.3, 151.2, 152.7, 154.5, 164.0 (<u>C</u>=N oxadiazole), 174.7 (<u>C</u>-O oxadiazole); Anal. Calcd. For $C_{19}H_{13}N_5OS$ (359.40): C, 63.49; H, 3.65; N, 19.49. Found: C, 63.28; H, 3.76; N, 19.73.

2.1.5. General procedure for the synthesis of 2-methyl-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (12)

7-Aryl-2-methyl-pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles (9e) (1 g, 0.01 mol) was gradually added to sulfuric acid (8 ml) while stirring on ice bath. The addition period was accomplished over 1 h, and then the solution was stirred at room temperature for 24 h. Subsequently, the solution was poured onto crushed ice while stirring. The pH of the mixture was then carefully adjusted to 8 using concentrated ammonium hydroxide. The formed precipitate was then filtered and recrystallized from DMF/ethanol. *2.1.5.1. 2-methyl-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (12)*
White crystals, 70% yield; m.p. 240-242 °C; IR (KBr, cm^{-1}): 3368, 3286 (NH_2), 3095 (Aromatic CH), 2923 (Aliphatic CH), 1678 (C=O), 1625 (C=N); ^{1}H NMR (500 MHZ, DMSO-d_6) δ 2.67 (s, 3H, CH_3), 7.33-7.35 (m, 2H, ,1H, H4 thiophene + NH: D_2O exchangeable), 7.74-7.77 (m, 2H, H3 pyrimidine + NH: D_2O exchangeable), 8.10 (d, J = 4.30 Hz,1H, H3 thiophene), 8.50 (d, J = 2.85 Hz,1H, H5 thiophene), 8.64 (d, J = 5.25 Hz, 1H, H2 pyrimidine); ^{13}C NMR (125 MHz, DMSO) δ 15.1 (<u>C</u>H$_3$), 101.9, 105.3, 128.4, 130.2, 133.5, 136.9, 140.3, 148.2, 150.8, 156.8, 164.3 (<u>C</u>=O); Anal. Calcd. For $C_{12}H_{10}N_4OS$ (258.30): C, 55.80; H, 3.90; N, 21.69. Found: C, 56.03; H, 4.07; N, 21.95.

3. Results and discussion

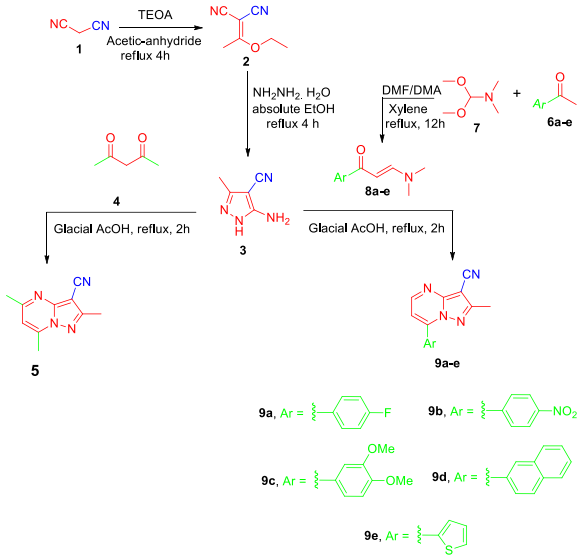
3.1. Chemistry

The synthetic pathways adopted for the preparation of the target compounds are depicted in schemes 1 and 2.

2,5,7-trimethyl-6-substituted pyrazolo[1,5-*a*] pyrimidine-3-carbonitrile (5) was obtained from the condensation reaction of acetylacetone 4 [57] and the amino pyrazole derivative (3) in acetic acid. The 5-amino pyrazole starting compound (3) was obtained as follows: first, malononitrile (1) was reacted with triethylorthoacetate and acetic anhydride yielding the malononitrile derivative (2), which was subsequently reacted with hydrazine hydrate yielding the starting compound (3) [49, 50]. The structure of compound 5 was confirmed by its NMR spectra which confirmed the presence of three methyl groups where its ^{1}H NMR spectrum displayed three singlets in the aliphatic region at 2.47, 2.53 and 2.64 ppm, while its ^{13}C NMR spectrum displayed three peaks in the aliphatic region at 13.8, 17.0 and 24.7 ppm. Also its ^{1}H NMR spectrum displayed only a single peak in the aromatic region at 7.09 ppm indicating the presence

of only one proton which is the pyrimidine H3. Additionally, the total number of peaks displayed in the ^{13}C NMR spectrum is equivalent to the total number of carbons in the compound (Scheme 1).

Scheme 1

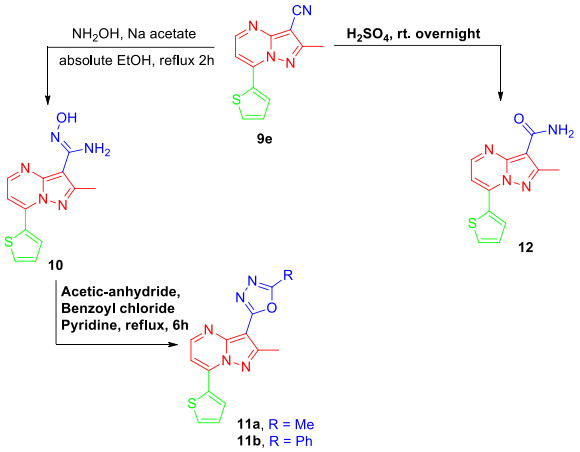


On the other hand, the 7-(Aryl)-2-methyl-pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile derivatives (9a-e) were obtained from the condensation reaction of the arylpropenones (8a-e) and amino pyrazole (3) in acetic acid. The the arylpropenones (8a-e) were synthesized by reacting the corresponding aryl methyl ketones (6a-e) with DMF-DMA (7) [54, 56]. The structures of compounds 9a-e were confirmed by their ^{1}H NMR spectra which displayed a singlet peak at 2.51-2.58 ppm, and two doublets at δ 7.43-7.91 and 8.72-8.83 ppm that could be assigned to the C$\underline{H}_3$, and H3 and H2 of the pyrimidine ring, respectively. ^{13}C NMR of compounds 9c-e displayed peaks at 13.9-14.0 and 81.2-81.6 ppm; these peaks could be assigned to the aliphatic $\underline{C}H_3$ and the aromatic carbon attached to CN (Scheme 1).

The reaction of the carbonitrile containing compound 9e with hydroxylamine in presence of sodium acetate as a catalyst furnished compound 10. ^{1}H NMR spectrum of the amidoxime 10 displayed two peaks at δ 6.12 and 9.46 ppm; both bands were exchanged by D_2O and thus could be assigned to the N$\underline{H}_2$ and OH groups, respectively. Additionally, heating of the amidoxime 10 with acetic-anhydride or benzoyl chloride led to its cyclization into the 1,2,4-oxadiazoles 11a and 11b, respectively. These compounds were confirmed by their ^{1}H NMR spectra which revealed the absence of any exchangeable signals. ^{1}H NMR spectrum of the oxadiazole derivative 11a showed the appearance of a new aliphatic signal at 2.71 ppm indicating the presence of CH_3, while ^{1}H NMR spectrum of the oxadiazole derivative 11b showed the appearance of additional aromatic signals corresponding to the aromatic protons originating from benzoyl chloride reagent. ^{13}C NMR spectrum of 11b showed two peaks at 164.0 and 174.7 ppm characteristic to C=N and C-O of the oxadiazole ring, respectively (Scheme 2).

Finally, hydrolysis of the carbonitrile group in compound 9e using sulfuric acid yielded the carboxamide 12. ^{1}H NMR spectrum of compound 12 showed two exchangeable signals, each corresponding to one proton of the NH_2 group, in the region 7.33-7.77 ppm, this is in addition to the presence of the other characteristic aliphatic and aromatic peaks. ^{13}C NMR of compound 12 showed the appearance of a peak at 164.3 ppm corresponding to the amide $\underline{C}$=O. This is beside the disappearance of the $\underline{C}$-CN peak that previously appeared at 81.4 ppm in its starting compound 9e (Scheme 2).

Scheme 2



4. Conclusion

Various pyrazolo[1,5-*a*]pyrimidine derivatives were synthesized using simple and easy working methods and commercially available starting materials and reagents with the goal of creating novel derivatives that are expected to have a wide range of biological activity. The synthesized derivatives carried different substituents as cyano, amidoxime and amide at position 3 (compounds 5, 9a-e, 10, 12) of the pyrazolo[1,5-*a*]pyrimidine. While compounds 11a and b carried an oxadiazole ring with a methyl and phenyl substituents, respectively.

Future perspective:

The anticancer activity of the newly synthesized compounds will be screened in the future.

5. Conflicts of interest

There are no conflicts to declare.

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