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Review article

Synthesis and Antibacterial Evaluation of Some New Pyrimidine, Pyridine and Thiophene Derivatives

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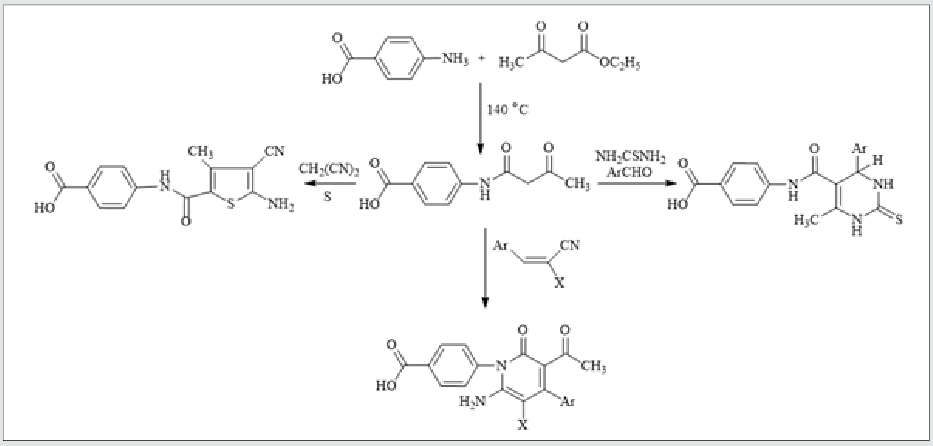
Abstract

New series of pyrimidine, pyridine and thiophene derivatives were prepared by reaction of appropriate 3-oxobutanamides with urea, thiourea, active methylene compounds, arylidines, salicyaldehyde, chalcones, benzyl isothiocyanate and aminopyrazoles. Compounds 2a, 3a, 3c and 9 show activity against some bacterial species, whereas, no activity was observed for compounds 3b, 4, 5, 7e, 7f, 10 and 11 against all bacterial species (Graphical Abstract).



Graphical Abstract.

Keywords: p-Aminobenzoic acid; 3-oxobutanamides; pyrimidines; pyridines; Thiophenes; antimicrobial activity

Introduction

Derivatives of p-Aminobenzoic Acid (PABA) have shown interesting pharmacological properties [1,2]. treatment of the Alzheimer's disease [3]. it has also been used against typhus [4,5]. antimicrobial and anticancer property [2,6]. Also, many of PABA derivatives were reported for their potential inhibitory property against novel antibacterial targets –MDR-associated proteins [7,8]. antiviral targets (neuraminidase) and antifungal targets [9,10]. 3-Oxobutanamide are valuable intermediates in synthetic organic chemistry. Recently we reported a variety of synthesis of heteroaromatics that have been developed utilizing 3-oxobutanamides as readily obtainable compounds [11,12].

Results and Discussion

It has been found that reactions of 3-oxobutanamide [13]. 1 with some electrophilic and nucleophilic reagents to produce some new substituted azines and azoles moiety. So, treatment of

3-oxobutanamide 1 with urea or thiourea in EtOH/TEA afforded the pyrimidine derivatives 2a,b. Establishing of compounds 2a,b based on its elemental analysis and spectral data (IR, ^{1}H NMR, ^{13}C NMR). 1H NMR of compound 2a as example revealed a singlet signal at δ 2.00 ppm assigned to CH_3, a singlet signal at δ 6.03 ppm assigned to pyrimidine-H, a multiplet signal at δ 7.59-8.00 ppm assigned to aromatic protons, 2NH appeared at δ = 9.4, 9.9 ppm and noted signal at δ = 12.83 assigned to OH. ^{13}C NMR showed a singlet signal at δ = 18.99 assigned to CH_3, a singlet signals at δ 56.51 assigned to pyrimidine-H and signals at δ 164.16, 167.33 assigned to two carbonyl group, in addition to carbon signals of aromatic structure (Figure 1). The pyrimidinediones [14,15]. 3a-c were synthesized by reaction of 3-oxobutanamide 1 with a mixture of aromatic aldehydes and thiourea. 1H NMR spectrum of 3a as example revealed the signal at δ = 2.10 ppm assigned to CH_3, a singlet signal at δ 6.57 ppm assigned to pyrimidine- H, a multiplet signals at δ 7.26-8.19 ppm assigned to aromatic protons and NH group, a singlet signal at δ 9.44, 10.01 ppm assigned to two NH group, and hump at δ 11.89 ppm assigned to OH of carboxylic group. 13C showed a singlet signal at δ 17.01 assigned to CH_3, a singlet signal at δ 60.91 assigned to pyrimidine-H, a signals at δ 160.08, 185.47 assigned to two carbonyl group, in addition to carbon signals in structure (Figure 1). The reaction of 3-oxobutanamide 1 with active methylene reagents was studied. So, the reaction of 1 with malononitrile, ethyl cyanoacetate in ethanolic piperidine afforded the pyridone derivatives 4a, b in good yield. ^{1}H NMR of 4a as example revealed a singlet signal at δ 2.19 ppm assigned to CH_3, a singlet signal at δ 5.68 ppm assigned to pyridine-H, a singlet signal at δ = 6. 83 ppm assigned to NH2 group and OH group noted at δ 12.90 ppm. 13C NMR of compound 4a appeared a singlet signal at δ 18.69 ppm assigned to CH_3, a singlet signal at δ 69.79 ppm assigned to CH- pyridine, cyano group was detected at δ 114. 11 ppm and a singlet signals at δ 160.91, 167.54 ppm assigned to (2C=O) in addition to carbon signals in structure. Similarly, the reaction of 1 with cyanothioacetamide in ethanolic piperidine solution yield the expected pyridinethione derivative 5 under the same reaction conditions, (Figure 2). Treatment of 3-oxobutanamide 1 with malononitrile and elemental sulfur as an application of the well-known Gewald's thiophene synthesis yield the polyfunctionally substituted thiophenebutanamide 6, (Figure 3).Treatment of compound 1 with electrophilic reagents under alkaline condition was investigated. So, the reaction of 3-oxobutanamide 1 with arylidinemalononitrile or arylidine cyanoacetate in ethanolic piperidine gave the pyridine derivatives 7. Structure 7 was confirmed as the reaction product on the basis of its elemental analysis and spectroscopic data, ^{1}H NMR spectrum of 7c as example showed a triplet signal at δ 1.21 ppm assigned for CH_3 ester, a singlet signal at δ 1.25 ppm assigned to (CH_3), quartet signal at δ 4.29 ppm for CH_2 ester, multiple signals at δ 7.33-8.43 ppm corresponding to aromatic protons, NH_2 and hump at δ 12.92 ppm assigned to OH group. 13C NMR of compound 7c appeared a singlet signal at δ 14.16, 14.41 ppm assigned to (2CH_3), singlet signal δ 62.92 ppm assigned to CH_2 group, and signals at δ 154.12, 158.16, 162.09, 167.21 ppm assigned to (4C=O) in addition to aromatic carbons, (Figure 4).The quinoline derivative 9 was obtained in good yield by reaction of 3-oxobutanamide 1 with salicylaldehyde in refluxing pyridine solution through the intermediate 8 which transformed by Dimroth rearrangement [16]. To 4-(3-Acetyl-2-oxoquinolin-1(2H)-yl) benzoic acid (9). Establishing compound 9 based on the spectroscopic data. 13C NMR showed signal at δ 18.95 ppm (CH_3), signals at δ 167.92, 172.05, 187.31 ppm (3C=O), in addition to carbon signals in structure, (Figure 5).

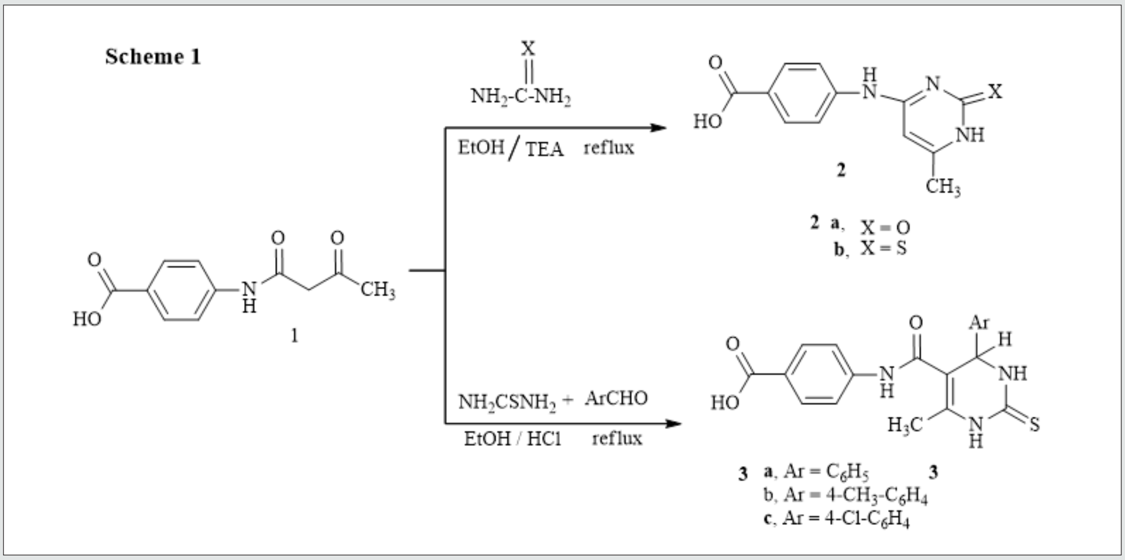
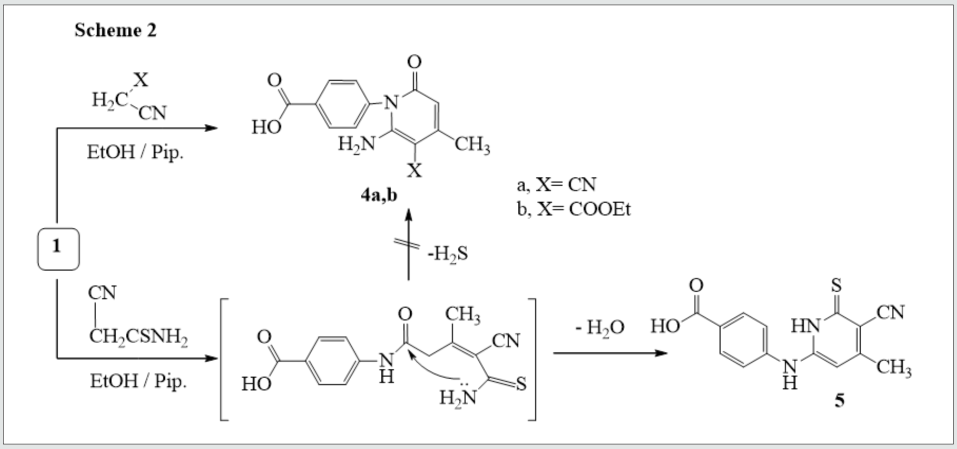


Figure: 1



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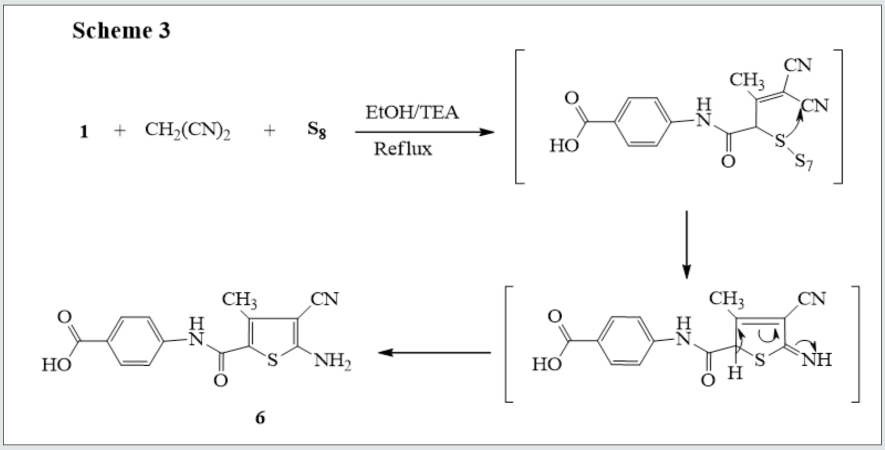

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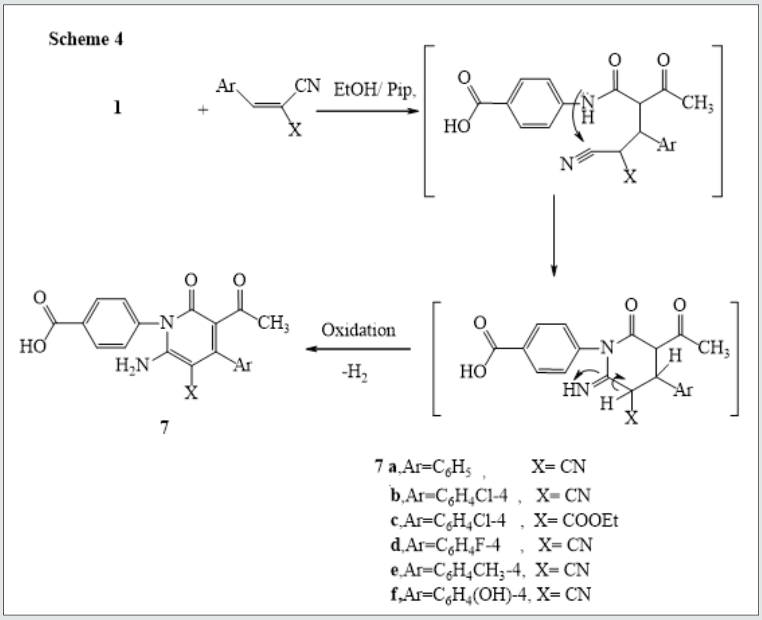

Figure: 4

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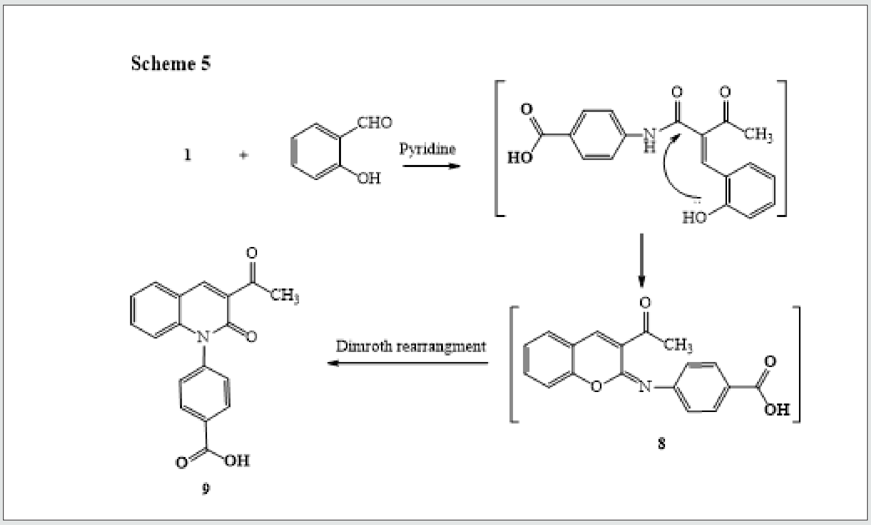

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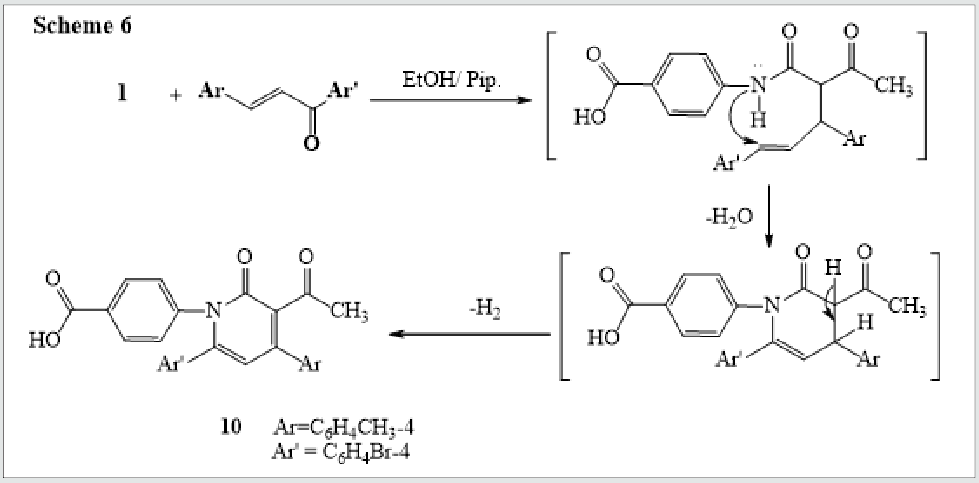

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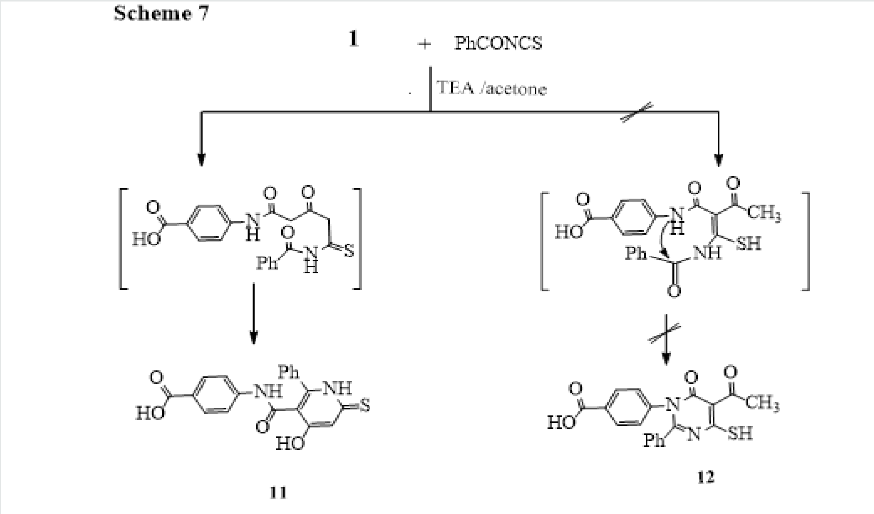

Figure: 7

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Also, reactions of 3-oxobutanamide 1 with chalcone derivative in ethanolic piperidine yield the pyridine derivative 10 [17]. via elimination of water. The ^{1}H NMR of compound 10 revealed the presence of a singlet signals at δ 2.21, 2.36 ppm assigned to ($2CH_3$), a multiplet signals at δ 6.62-8.11 ppm assigned to aromatic protons, and hump at δ 12.76 ppm for OH group. (Figure 6). Treatment of 3-oxobutanamide 1 with benzoyl isothiocyanate in refluxing acetone afforded the unexpected pyridine 11 rather than the expected pyrimidine 12. Structure 11 was assigned for the reaction product based on spectroscopic data (IR, 1H NMR and 13C NMR) (Figure 7). On the other hand, condensation of compound 1 with amino pyrazole derivative [18]. gave the condensation product 13 with loss of two water molecules (Figure 8).

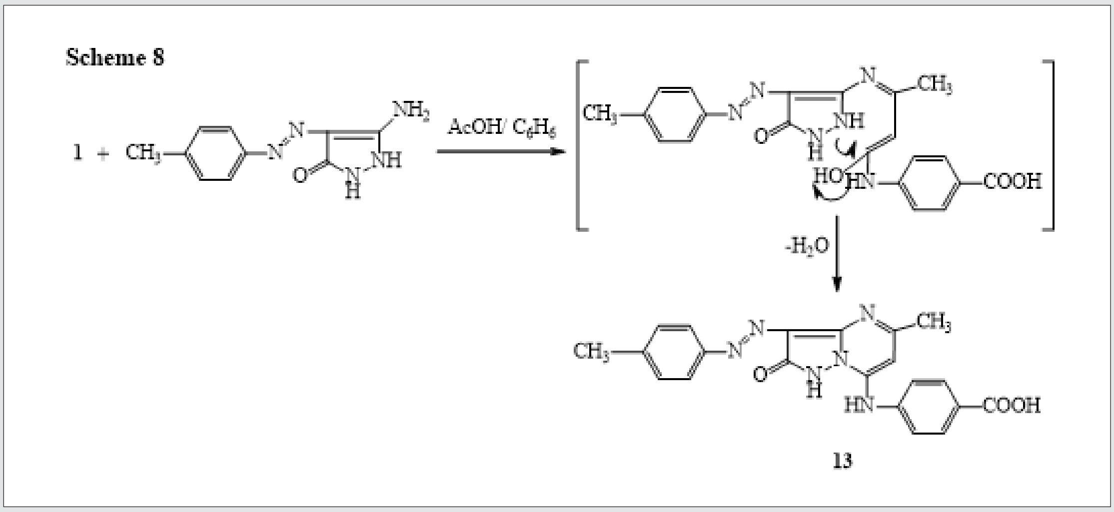

Figure: 8

Antibacterial activity

Evaluation of in vitro antibacterial activity of synthesized compounds was carried out using agar disc diffusion method [19]. against the growth of six pathogenic bacterial isolates; three Gram-positive bacteria (Bacillus cereus, Micrococcus luteus and Staphylococcus aureus) and three Gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa and Serratia marcescens). Nutrient agar plates previously inoculated with 24 h old broth cultures of the bacterial strains were used for the antibacterial activity. Pre sterilized filter paper discs (What man No. 3, 6 mm in diameter) were loaded with 15 µl of the tested compounds (conc.10%) and allowed to dry in a laminar flow biological safety cabinet. The discs were placed aseptically on the surface of the inoculated solidified plates at equal distances. All plates inoculated with bacteria were kept in the refrigerator at 4°C for 1 h to allow for diffusion of extracts and to minimize the effects of variation in time between the applications of different solutions. The plates were incubated for 24 h at 37°C for bacteria, and then observed for the presence of inhibition of bacterial growth that was indicated by a clear zone around the discs. The diameter of the zones of inhibition (with paper discs) was measured in millimeters. Control assay discs impregnated with the antibiotic's chloramphenicol (250 µg/ml) served as the positive controls. The antibacterial activities of the tested compounds were estimated on the growth of six pathogenic bacteria representing three Gram-positive bacteria (*B. cereus*, *M. luteus*, and *S. aureus*) and three Gram-negative bacteria (*E. coli, P. aeruginosa* and *S. marcescens*) by disc diffusion method. According to the results, compounds (2a, 3a, 3c and 9) showed antibacterial activity against all tested bacteria and compound 3c had the highest activity with inhibition zones ranged 13-16 mm (Table 1). Compound 7c showed a weak activity against *B. cereus*, *E. coli* and *P. aeruginosa*, while compounds 6 and 7b were active against P. aeruginosa and compound 7d against *E. coli*. On the other hand, compounds 3b, 4, 5, 7e, 7f, 10 and 11 did not exhibit any effect on the tested bacteria.

Table1: Antibacterial activities of the investigated compounds against pathogenic bacterial isolates by disc diffusion assay.

Compounds	**Zone of inhibition (mm)**					
	G +ve			**G -ve**		
	B. cereus	*M. luteus*	*S. aureus*	*E. coli*	*P. aeruginosa*	*S. marcescens*
2a	10	12	10	14	12	10
3a	12	12	12	15	14	12

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3b	ND	ND	ND	ND	ND	ND
3c	16	13	15	16	16	15
4	ND	ND	ND	ND	ND	ND
5	ND	ND	ND	ND	ND	ND
6	ND	ND	ND	ND	7	ND
7b	ND	ND	ND	ND	7	ND
7c	8	ND	ND	8	7	ND
7d	ND	ND	ND	8	ND	ND
7e	ND	ND	ND	ND	ND	ND
7f	ND	ND	ND	ND	ND	ND
9	10	10	10	14	10	14
10	ND	ND	ND	ND	ND	ND
11	ND	ND	ND	ND	ND	ND
Chloramphenicol (250 µg/ml)	18	24	34	26	42	28

ND=Not detected

Conclusion

we have developed a simple, efficient procedure for the synthesis of some substituted pyrimidine, pyridine and thiophene derivatives was carried out using 3-oxobutanamides with some electrophilic and nucleophilic reagents, Spectroscopic data were introduced as well as reactivity indices, some of newly synthesized compounds have antibacterial activities.

Experimental

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (δ, cm-^{1}). The ^{1}H NMR spectra were recorded in DMSO-d$_{6}$ at 500 MHz on a Broker NMR spectrometer (δ, ppm) using TMS as an internal standard. Elemental analysis was carried out by the Micro analytical Research Center, Faculty of Pharmacy at Buni Swef University and Sohag University. Micro analytical Research Center, Assiut University δ δ.

General procedure for preparation of compounds (2a, b)

A mixture of 1 (0.01 mol), urea (0.01 mol) or thiourea (0.01 mol) in ethanol (30 mL) containing catalytic amount of piperidine was heated under reflux for 6 h. The separated solid product was filtrated off, washed with water and recrystallized by the proper solvent to give 2a,b.

4-((6-Methyl-2-oxo-1,2-dihydropyrimidin-4-yl) amino) benzoic acid (2a, C12H11N3O3)

Brown crystals from ethanol, Yield (62%), m.p = 220 °C, IR (KBr) ν = 3410 (OH), 3230, 3160 (2NH), 1698,1646 (2C=O) cm-^{1}. ^{1}H NMR (DMSO-d$_{6}$) δ = 2.00 (s, 3H, CH$_{3}$), 6.03 (s, 1H, CH-pyrimidine), 7.59-8.00 (m, 4H, Ar-H), 9.4,9.9 (s, 2H, 2NH) and 12.83(s, 1H, OH) ppm.^{13}C NMR δ = 18.99 (CH3), 56.51, 117.89, 119.02, 119.46, 121.37, 126.46, 130.87, 143.20, 143.34, 164.16 (CO), 167.33 (CO). Anal. Calcd. For $C_{12}H_{11}N_{3}O_{3}$ (245.23): C, 58.77; H, 4.52; N, 17.13. Found: C, 58.80; H, 4.63; N, 17.25%.

4-((6-Methyl-2-thioxo-1,2-dihydropyrimidin-4-yl) amino)benzoic acid (2b, C12H11N3O2S).

Compound 2b was obtained as brown crystals from ethanol, Yield (65%), m.p = 198°C,IR (KBr) ν = 3430 (OH),3305,3260 (2NH), 1691 (C=O) cm-^{1}.^{1}H NMR (DMSO-d6) δ = 2.22 (s,3H,CH3), 6.53(s, 1H, CH-pyrimidine), 7.61-8.06(m, 5H, Ar-H+NH),10.56 (s, 1H, NH) and12.90 (hump, 1H,OH) ppm. Anal. Calcd. For $C_{12}H_{11}N_{3}O_{2}S$ (261.30): C, 55.16; H, 4.24; N, 16.08; S, 12.27.Found: C, 55.27; H, 4.30; N, 16.18; S, 12.35%.

General procedure for preparation of compounds (3a-c)

To a solution of 1(0.01 mol) in ethanol (30 mL) containing hydrochloric acid (5 mL), thiourea (0.01 mol), benzaldehyde or p-methyl- benzaldehyde or p-chloro benzaldehyde (0.01 mol) were added respectively. The reaction mixture was heated under reflux for 12h, the separated solid was filtrated washed with water and recrystallized from the proper solvent to give 3a-c.

4-(6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carbox-amido) benzoicacid (3a, C19H-17N3O3S)

Compound 3a was obtained as dark red from ethanol Yield, (67%), m.p = 118 °C. IR (KBr) ν = 3470 (OH), 3324, 3309, 3245 (3NH), 1705, 1673 (2C=O) cm-^{1}. ^{1}H NMR (DMSO-d6) δ = 2.10 (s, 3H,CH$_{3}$), 6.57(s, 1H, CH-pyrimidine) 7.26-8.19 (m, 10H, Ar-H+NH), 9.44 (s, 1H, NH), 10.01 (s, 1H, NH) and 11.89 (s, 1H, OH) ppm.^{13}C NMR δ = 17.01, 60.91, 113.14, 119.42, 126.83, 127.28, 127.65, 128.83, 129.09, 129.44, 129.61, 130.49, 130.73, 158.11, 160.08, 185.47, 186.53. Anal. Calcd. For $C_{19}H_{17}N_3O_3S$ (367.10) C, 62.11; H, 4.66; N, 11.44; S, 8.73. Found: C, 62.22; H, 4.76; N, 11.56; S, 8.82%.

4-(6-Methyl-2-thioxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carbox- amido) benzoic acid (3b, C20H19N3O3S).

Compound 3b was obtained as brown crystals from ethanol, Yield, (71%), m.p = 152 °C. IR (KBr) ν = 3491 (OH), 3320, 3203, 3165 (3NH), 1701, 1639 (2C=O) cm^{-1} .^{1}H NMR (DMSO-d_6) δ = 2.20 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 5.94 (s, 1H, CH-pyrimidine), 6.58-7.24 (m, 10H, Ar-H+2NH), 9.24 (s, 1H, 1NH) and 11.99 (hump, 1H, OH) ppm.^{13}C NMR δ = 18.93, 21.06, 56.52, 89.77, 104.56, 127.81, 130.18, 131.46, 138.36, 141.76, 143.40, 161.1, 171.45, 189.54. Anal. Calcd. For $C_{20}H_{19}N_3O_3S$ (381.11): C, 62.97; H, 5.02; N, 11.02; S, 8.41. Found: C, 63.10; H, 5.10; N, 11.16; S, 8.53%.

4-(4-(4-Chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamido) benzoic acid (3c, C19H16ClN3O3S)

Compound 3c was obtained as brown crystals from ethanol, Yield (70%), m. p = 148-150 °C. IR (KBr) ν = 3423 (OH), 3364, 3292, 3167 (3NH), 1716, 1639 (2C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ = 2.34 (s, 3H, CH_3), 6.19 (s, 1H, CH), 6.60-7.91 (m, 10H, Ar-H+2NH), 10.00 (s,1H, NH) and 11.30 (hump, 1H, OH) ppm. Anal. Calcd. For $C_{19}H_{16}ClN_3O_3S$ (401.06): C, 56.79; H, 4.01; Cl, 8.82; N, 10.46; S, 7.98. Found: C, 56.87; H, 4.13; Cl, 8.91; N, 10.59; S, 7.90%.

General procedure for preparation of compounds (4a,b)

A solution of 1 (0.01 mol), malononitrile or ethyl cyanoacetate (0.01 mol) in ethanol (30 mL), a few drops of piperdine was added and refluxed for 7 h. The solid product which produced on hot was collected by filtration and recrystallized from ethanol to give 4a, b.

4-(6-Amino-5-cyano-4-methyl-2-oxopyridin-1(2H)-yl) benzoic acid (4a, C14H11N3O3)

Compound 4a was obtained as brown crystals from ethanol yield, (70%), m. p = 250°C; IR(KBr) ν = 3420 (OH, NH2), 2206 (C≡N), 1693, 1642 (2C=O) cm^{-1}.^{1}H NMR (DMSO-d_6) δ = 2.19 (s, 3H, CH_3), 5.68(s, 1H, CH-pyridine), 6.83 (s, 2H, NH2),7.37-8.09 (m, 4H, Ar-H) and 12.90 (hump, 1H, OH) ppm.13C NMR δ = 18.69, 69.79, 114.11, 120.00, 129.77, 130.23, 130.53, 140.01, 143.20, 160.91, 167.54, 182.15. Anal. Calcd. For $C_{14}H_{11}N_3O_3$ (269.26) C, 62.45; H, 4.12; N, 15.61. Found: C, 62.54; H, 4.23; N, 15.73 %.

4-(6-Amino-5-(ethoxycarbonyl)-4-methyl-2-oxopyridin-1(2H)-yl)benzoicacid(4b, C16H16N2O5)

Compound 4b was obtained as brown crystals from ethanol. Yield, (77%), m. p = 264°C; IR (KBr) δ = 3423 (OH); 3317, 3296 (NH_2), 1684, 1633 (2C=O) cm-1.1H NMR (DMSO-d_6) δ = 1.20 (t, 3H, CH_3), 2.22 (s, 3H, CH_3), 4.21 (q, 2H, CH2), 6.58-7.71 (m, 6H, Ar-H+NH2) and 12.59 (hump, 1H, OH) ppm.^{13}C NMR δ =14.74, 16.16, 59.90, 78.00, 119.64, 130.64, 130.86, 131.65, 141.83, 147.88, 162.52, 165.80, 167.38, Anal. Calcd. For $C_{16}H_{16}N_2O_5$ (316.11) C, 60.75; H, 5.10; N, 8.86. Found: C, 60.84; H, 5.19; N, 8.93%.

4-((5-cyano-4-methyl-6-thioxo-1,6-dihydropyridin-2-yl)amino)benzoic acid (5, C14H11N3O2S)

A mixture of 1 (0.01 mol), cyanothiocetamide (0.01 mol) in ethanol (30 mL), a few drops of piperdinewere added and refluxed for 8h. The solid product which produced on hot was collected by filtration and recrystallized from ethanol to give 5 as brown crystals, yield (73%), m.p = 264°C, IR (KBr) ν = 3498 (OH), 3214, 3189 (2NH), 2207 (C≡N), 1682(C=O) cm^{-1}. ^{1}H NMR (DMSO-d6) δ = 2.38 (s, 3H, CH3), 6.55 (s, 1H, CH-pyridinethione), 7.73-7.95(m, 5H, Ar-H +NH), 9.83 (s, 1H, NH) and 10.90 (hump, 1H, OH) ppm. ^{13}C NMR δ = 15.50, 69.55, 119.51, 119.89, 120.43, 120.63, 130.62, 130.97, 131.65, 167.27, 182.36. Anal. Calcd. For $C_{14}H_{11}N_3O_2S$ (285.06) C, 58.93, H; 3.89, N; 14.73; S, 11.24. Found: C, 58.02; H, 3.96; N, 14.85; S, 11.33%.

4-(5-Amino-4-cyano-3-methylthiophene-2-carboxamido) benzoic acid (6, C14H11N3O3S)

To a solution of 1 (0.01 mol), elemental sulfur, malononitrile and few drops of triethylamine 4 drops in absolute ethanol (30 mL) was refluxed for 8 h. The reaction mixture left to cool, the solid which formed collected by filtration, washed with ethanol, dried and recrystallized from ethanol to give 6 as brown crystals, yield (85%), m.p = 310°C. IR (KBr) δ = 3499(OH), 3379, 3327 (NH2), 3217 (NH), 2204 (C≡N), 1680,1639 (2C=O) cm 1.1H NMR (DMSO-d6) δ = 2.39 (s, 3H, CH3), 7.72-7.91 (m, 6H, Ar-H+NH_2), 9.83 (s, 1H, NH) and 12.61 (s, 1H, OH) ppm.^{13}C NMR δ = 15.41, 88.77, 113.17, 115.75, 119.91,125.76, 130.62, 141.82,143.53, 161.14, 165.92, 167.41. Anal. Calcd. For $C_{14}H_{11}N_3O_3S$ (301.05): C, 55.80; H, 3.68; N, 13.95; S, 10.64%. Found: C, 55.91; H, 3.77; N, 14.13; S, 10.72%.

Preparation of compounds (7a-f): General procedure

A mixture of 1 (0.01 mol) with arylidine derivatives (0.01 mol) in ethanol (30 ml) was treated with few drops of piperdine and heated under reflux for 6 h. The solid product which produced on hot was collected by filtration and recrystallized from the proper solvent to give (7a-f).

4-(3-Acetyl-6-amino-5-cyano-2-oxo-4-phenylpyridin-1(2H)-yl) benzoic acid (7a, C21H15N3O4)

Compound 7a was obtained as yellow crystals from ethanol, Yield (85%), m.p = 132-134 °C; IR (KBr) ν = 3500 (OH), 3395, 3334 (NH2), 2187 (C≡N), 1690,1634 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ = 2.35 (s, 3H, CH_3), 6.94-8.08 (m, 11H, Ar-H +NH2), and 10.65 (s, 1H, OH) ppm.13C NMR δ = 24.60, 56.50,113.31,114.38,119.22, 128.72, 129.11, 129.40, 130.77, 131.73, 151.15, 154.52, 159.66, 166.08, 167.18, 168.50. Anal. Calcd. For $C_{21}H_{15}N_3O_4$(373.11) C, 67.56; H, 4.05; N, 11.25%. Found: C, 67.65; H, 4.17; N, 11.30%.

4-(3-Acetyl-6-amino-4-(4-chlorophenyl)-5-cyano-2-oxopyridin-1(2H)-yl) benzoicacid (7b, C21H14ClN3O4)

Compound 7b was obtained as yellow crystals from ethanol, Yield (85%), m. p =144-146°C; IR (KBr) ν = 3500 (OH), 3338, 3320 (NH2); 2204 (C≡N); 1698,1634 (C=O) cm-1. 1H NMR(DMSO-d6) δ = 2.25 (s, 1H, CH3), 6.91-8.06 (m,10H, Ar-H+NH_2) and 12.80 (OH) ppm.^{13}C NMR δ =14.42, 63.83, 117.93, 128.51, 128.83, 129.03, 129.11, 129.19, 129.40, 130.98, 132.78, 156.34, 165.66, 167.42, 203.85. Anal. Calcd. For $C_{21}H_{14}ClN_3O_4$(407.07): C, 61.85; H, 3.46; Cl, 8.69; N, 10.30%. Found: C, 61.94; H, 3.55; Cl, 8.69; N, 10.43%.

4-(3-Acetyl-6-amino-4-(4-chlorophenyl)-5-(ethoxycarbonyl)-2-oxopyridin-1(2H)-yl) benzoic acid (7c, C23H19ClN2O6)

Compound 7c was obtained as brown crystals from ethanol, yield (79%), m.p = 102-104°C; IR (KBr) ν = 3516(OH), 3356, 3310 (NH_2); 1713, 1700, 1692, 1636 (4C=O) cm-^{1}. ^{1}H NMR (DMSO-d6) δ = 1.21 (t, 3H, CH_3), 1.25(s, 3H, CH_3), 4.29(q, 2H, CH_2), 7.33-8.07 (m, 10H, Ar-H +NH2) and 12.92 (hump, 1H, OH) ppm.^{13}C NMR δ = 14.16, 14.41, 62.92, 86.21, 103.83, 113.07, 115.82, 119.30, 128.89, 129.18, 129.93, 130.72, 131.64, 132.87, 138.47, 154.12, 158.16, 162.09, 167.21. Anal. Calcd. For $C_{23}H_{19}ClN_2O_6$ (454.09) C, 60.73; H, 4.21; Cl, 7.79; N, 6.16. Found: C, 60.82; H, 4.33; Cl, 7.88; N, 6.29%.

4-(3-Acetyl-6-amino-5-cyano-4-(4-fluorophenyl)-2-oxopyridin-1(2H)-yl) benzoic (7d, C21H14FN3O4)

Compound 7d was obtained as yellow crystals from ethanol, Yield (85%), m.p = 180°C; IR (KBr) ν = 3510 (OH), 3338, 3320 (NH_2); 2206 (C≡N); 1698,1634 (C=O) cm-^{1}. ^{1}H NMR (DMSO-d_6) δ = 2.27 (s, 1H, CH_3), 6.56-7.64 (m, 10H, Ar-H +NH2) and 12.54 (s, 1H, OH) ppm.^{13}C NMR δ = 22.60, 113.06, 116.04, 119.28, 129.35, 130.44, 130.61, 130.72, 130.97, 131.15, 131.24, 131.24, 131.42, 131.65, 153.57, 153.87, 167.22, 182.60. Anal. Calcd. For $C_{21}H_{14}FN_3O_4$ (391.10) C, 64.45; H, 3.61; F, 4.85; N, 10.74. Found: C, 64.54; H, 3.70; F, 4.96; N, 10.84%.

4-(3-Acetyl-6-amino-5-cyano-2-oxo-4-(p-tolyl) pyridin-1(2H)-yl)benzoic acid (7e, C22H17N3O4)

Compound 7e was obtained as yellow crystals from ethanol, Yield (85%), m.p = 158-160°C; IR (KBr) ν = 3510 (OH), 3338, 3320 (NH_2); 3250 (NH), 2206 (C≡N); 1698, 1634 (3C=O) cm-1. ^{1}H NMR (DMSO-d_6) δ = 2.27, 2.33(2s, 6H, $2CH_3$), 6.66 (s, 2H, NH_2), 7.26-8.17 (m, 8H, Ar-H) and 12.73 (s, 1H, OH) ppm. 13C NMR δ = 18.94, 21.13, 113.09, 119.31, 128.70, 129.22, 130.80, 131.65, 133.96, 139.90, 142.00, 167.21, 174.37,174.96, 177.17. Anal. Calcd. For $C_{22}H_{17}N_3O_4$ (387.12): C, 68.21; H, 4.42; N, 10.85 %. Found: C, 68.29; H, 4.51; N, 10.93%.

4-(3-Acetyl-6-amino-5-cyano-4-(4-hydroxyphenyl)-2-oxopyridin-1(2H)-yl) benzoic acid (7f, C21H15N3O5)

Compound 7f was obtained as yellow crystals from ethanol, Yield (85%), m.p = 160 °C; IR (KBr) ν = 3486 (OH), 3327, 3305 (NH_2); 2204 (C≡N); 1712, 1693, 1634 (3C=O) cm-^{1}. ^{1}H NMR (DMSO-d_6) δ = 2.19 (s, 3H, CH3), 5.62 (s, 2H, NH2), 6.65-8.09 (m, 10H, Ar-H +NH2) and 11.85 (s, 1H, OH) ppm. 13C NMR δ = 18.29, 62.42, 115.68, 116.29, 128.05, 128.40, 129.15, 129.92, 130.00, 131.57, 132.21, 135.19, 158.93, 166.01, 167.35, 170.47, 172.10. Anal. Calcd. For $C_{21}H_{15}N_3O_5$ (389.10) C, 64.78; H, 3.88; N, 10.79. Found: C, 64.86; H, 3.97; N, 10.87%.

4-(3-Acetyl-2-oxoquinolin-1(2H)-yl) benzoic acid (9, C18H13NO4)

A mixture of 1 (0.01 mol) with salicylaldehyde (0.01 mol), Pyridine (10 ml) heated under reflux for 13 h. The solid product which produced on hot was collected by filtration and recrystallized from the proper solvent to give 9 as brown crystals. Yield (65%), m.p = 164-166 °C; IR (KBr) ν = 3482 (OH), 1709, 1680, 1635 (3C=O) cm-1.1H NMR (DMSO-d6) δ = 2.59 (s, 3H, CH_3), 6.58-7.38 (m, 9H,Ar-H) and 12.50 (hump, 1H, OH) ppm.^{13}C NMR δ = 18.95, 113.44, 116.57, 125.41, 126.83, 130.68, 131.21, 131.65, 131.84, 134.94, 144.00, 144.51, 147.46, 153.03, 154.68, 167.92, 172.05, 187.31. Anal. Calcd. For $C_{18}H_{13}NO_4$ (307.30) C, 70.35; H, 4.26; N, 4.56. Found: C, 70.46; H, 4.37; N, 4.63%.

4-(3-Acetyl-6-(4-bromophenyl)-2-oxo-4-(p-tolyl) pyridin-1(2H)-yl)benzoic acid (10, C27H20BrNO4)

To a solution of 1 (0.01 mol) in ethanol (40 mL) containing catalytic amount of piperidine 4 drops, 1-(4-bromophenyl)-3-(*p*-tolyl)prop-2-en-1-one (0.01 mol) was added. The reaction mixture was heated under reflux for 5 h. The solid product formed on heating was collected by filtration, recrystallized from the proper solvent to give 10 as orange crystals. yield (83%),; m.p = 140-142 °C. IR (KBr) ν = 3490 (OH), 1703,1654, 1636 (3C=O) cm-1.1H NMR (DMSO-d6) δ = 2.21 (s, 3H, CH3), 2.36 (s, 3H, CH3), 7.12-7.91 (m, 13H, Ar-H) and 12.76 (s, 1H, OH) ppm.13C NMR δ = 21.56, 121.21, 127.61, 129.45, 130.01, 130.94, 132.26, 132.35, 137.16, 141.33, 145.05, 167.26, 175.21, 188.76. Anal. Calcd. for C27H20BrNO4 (501.06) C, 64.55; H, 4.01; Br, 15.91; N, 2.79. Found: C, 64.64; H, 4.13; Br, 15.98; N, 2.87%.

4-(4-Hydroxy-2-phenyl-6-thioxo-1,6-dihydropyridine-3-carboxamido)-benzoic acid (11, C19H14N2O4S)

To a solution of 1 (0.01 mol), in dry acetone (30 ml) and Phenyl isothiocyanate (0.01 mol), was refluxed for 8 h. The solvent is left to evaporation, the solid which formed collected to give 11 as yellow crystals. yield (85%), m.p = 206-208 °C. IR. (KBr) ν = 3499(OH), 217(NH), 1680,1639 (2C=O) cm$^{-1.1}$H NMR (DMSO-d_6) δ = 7.19-8.01 (m,12H, Ar-H+CH +2NH) and 11.56, 12.77 (s,2H, OH) ppm.^{13}C NMR δ =118.88, 123.92, 128.61, 128.92, 129.16, 130.39, 132.57, 133.56, 142.41, 167.14, 168.67, 179.51. Anal. Calcd. For $C_{19}H_{14}N_2O_4S$ (366.07): C, 62.28; H, 3.85; N, 7.65; S, 8.75. Found: C, 62.37; H, 3.91; N, 7.71; S, 8.84%.

4-((5-Methyl-2-oxo-3-(p-tolyldiazenyl)-1,2-dihydropyrazolo[1,5-a] pyrimidin-7-yl) amino) benzoic acid (13, C21H18N6O3)

In a round-bottomed flask attached to a Dean and Stark constant water separator which is connected to a reflux condenser are placed a mixture of 1 (0.05 mol), 5-amino-4-(p-tolyldiazenyl)-1H-pyrazol-3(2H)-one (0.05 mol), 100 ml of benzene, and 1 ml of glacial acetic acid. The flask is heated in an oil bath at about 125 °C, and the water which distils out of the mixture is removed at intervals. Refluxing is continued until no more water separates and then for an additional

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30 minutes. The benzene is then distilled under reduced pressure, The solid product formed was filtered off and recrystallized from the proper solvent to give 13 as red crystals. Yield (63%), m.p = 230 °C. IR. (KBr) ν= 3500 (OH) 3250, 3176 (2NH), 1670, 1632 (2C=O) cm ^{1}. 1H NMR (DMSO-d_6) δ = 1.23, (s, 1H, CH_3), 2.29 (s, 1H, CH_3), 6.54-7.93 (m, 10H, Ar-H+NH+CH), 10.56 (s, 1H, NH) and 12.96 (s, 1H, OH) ppm. ^{13}C NMR δ = 20.89, 21.17, 115.60, 117.49, 119.18, 130.28, 130.79, 131.66, 134.04, 137.58, 140.00, 150.34, 153.57, 154.45, 156.14, 160.55,167.39, 167.94. Anal. Calcd. For $C_{21}H_{18}N_6O_3$ (402.14): C, 62.68; H, 4.51; N, 20.88 %. Found: C, 62.78; H, 4.61; N, 20.68 %.

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