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Synthesis, Characterization and Evaluation the Biological Activity of New Heterocycle Compounds Derived from 4-Aminoacetophenone

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Abstract
This research included the synthesis of new heterocycle compounds from 4-Aminoacetophenone as starting material via three deferent routs; the first one included the synthesis of N-Aacetophenone-1,2,3-triazole derivatives. At the second rout we prepared chalcones, which cyclized by reacting with thiourea and hydroxyl amine hydrochloride. The third rout included the reaction of starting material with 2-mercaptobenimidazole and 2-mercaptobenzthiozole. The structures of newly synthesized heterocyclic compounds established on the basis of their m.p, TLC, IR, UV-Vis, C.H.N. and ^{1}H-NMR data. The results of antimicrobial activity of newly synthesized heterocyclic compounds showed that some of it have good antimicrobial activity when compared with standard antibiotic.
Keywords: triazole, Chalcone, pyrimidine, oxazole, Antimicrobial activity.

Introduction

1,2,3-Tiazole have been widely used in synthetic intermediates and industrial applications; such as dyes, anticorrosive agents, photo stabilizers, photographic materials and agrochemicals[1].

Chalcones, precursors of open chain flavonoids and isoflavonoids present in edible plants[2,3], and their derivatives have attracted increasing attention due to numerous potential pharmacological applications[4,5,6].

Pyrimidine derivatives are known to be biologically active compounds and substituted pyrimidine have shown wide range of biological activities such as antitubercular[7], antibacterial[8-10], antioxidant[11] and anti-infalmmatory activity[12].

Experimental

Materials and physical measurements

All reagents and solvents used in this study were reagent grade and it available from Sigma-Aldrich and Fluka companies. Melting points were determined on Electro-Thermal capillary apparatus and were uncorrected. Purity of the prepared compounds was checked on silica coated Merck-TLC plates using water, chloroform, benzene and ethyl acetate as mobile phase. FTIR mesuerments were recorded on schimadzu model FT-IR 8400S. The UV-Visible spectra were recoded in ethanol using Shimadzu UV-Vis. 160 a spectrophotometer. Proton NMR spectra were obtained with a Bruker spectrophotometer model Ultra Shield at 300 MHz in DMSO-d_6 solution with the TMS as internal standard. Elemental analyses (C.H.N), were measured by using EUROEA instrument.

Synthesis of Diazonium Salt (I)

A solution of 4-aminoacetophenone (0.01 mol) in concentration HCl (3 ml) was cooled to (0-5) C^0. A coold solution of sodium nitrate (0.01 mol) in (10 ml) of water was added dropwise during (10 min.), and then the reaction mixture was stirred for (30 min.).

Synthesis of 1-(4-azidophenyl)ethanone (II)

(2.5 ml) of aqueous solution of sodium azide (0.012 mol) was added dropwise to an aqueous solution of diazonium salt (I). The mixture was stirred for (20 min.) to give compound (II). Yield:85%, m.p. 178-180 C^0. UV.(λ max nm) 216, 293. FTIR (KBr, υ,cm^{-1}) 2129 (N=N-N).

Synthesis of [1-(4-Acetyl phenyl)-5-methyl-7H-1,2,3-triazole-4-carboxylic acid] (1).

A mixture of compound (II) (0.01 mol) and ethylacetoacetate (0.01 mol) in methanol (30 ml) was cooled to $0c^0$. Sodium methoxide (0.01 mol) in (20 ml) was added gradualy to the mixture and heated under reflux on a water bath for (6 hrs.). The crude product was recrystallized from ethanol. Yield 90%, m.p 156-168 C^0 , UV.(λ max nm) 224, 303; FTIR (KBr, υ,cm-1): 3348 (-OH) acid, 1726 (C=O) acid, 1685 (C=O) keton, 981 (N=N); ^{1}H-NMR (300MHz, DMSO-d_6,ppm): 8.02 (d, 2H, Ar-H), 7.61 (d, 2H, Ar-H), 2.65 (S, 3H, $COCH_3$), 2.31 (S, 3H, CH_3 of triazole), 11.5 (S, 7H, COOH); Anal. Calc. for c $C_{12}H_{11}N_3O_3$: C=58.7%, H=4.48%, N=17.1% ; found: C=58.89%, H=4.67%, N=17.03%.

Synthesis of [1-(4-Acetyl phenyl)-4-acetyl-5-methyl-7H-1,2,3-triazole] (2).

To cold solution of sodium ethoxide (7 ml) and acetyl acetone (0.01 mol), compound (II) (0.01 mol) was added and the mixture heated under reflux on a water bath for (3 hrs.) The crude product was recrystallized from

ethanol. Yield 75%, m.p 128-129 C^0 , UV.(λ max nm) 215, 267; FTIR (KBr, υ,cm-1): 1687(C=O) , 956 (N=N); ^{1}H-NMR (300MHz, DMSO-d_6,ppm): 8.04 (d, 2H, Ar-H), 7.55 (d, 2H, Ar-H), 2.67 (S, 3H, $COCH_3$), 2.31 (S, 3H, CH_3 of triazole), 2.12 (S, 7H, $COCH_3$ triazol); Anal. Calc. for c $C_{13}H_{13}N_3O_2$: C= 64.1%, H= 5.34%, N=17.2% ; found: C= 64.25%, H= 5.56%, N=17.13%.

Synthesis of compounds (3), (4).

A mixtures of (4-aminoaetophenone) (0.01 mol) with an aldehydes (0.01 mol), were stirred in (40 ml) of ethanol and (1 ml) NaOH (40%) wasd to it. The mixtures were acetified with HCl. The separated solids were filtered and recrystallized from ethanol.

(E)-1-(4-aminophenyl)-3-(furan-3-yl)prop-2-ene-1-one (3). Yield 66%, m.p 79-80 C^0 , UV.(λ max nm) 202, 312; FTIR (KBr, υ,cm-1): 3433, 3352(-NH_2), 1637(C=O)α,β , 1602 (C=C), 1176 (C-O-C); ^{1}H-NMR (300MHz, DMSO-d_6,ppm): 6.82-8.31 (m, 5H, CH=CH, furan), 7.5 (d, 2H, Ar-H), 6.45 (d, 2H, Ar-H), 5.6 (S, 2H, NH_2). Anal. Calc. for c $C_{13}H_{11}NO_2$: C= 73.23%, H= 5.16%, N=6.57% ; found: C= 73.11%, H= 5.37%, N= 6.75%.

(E)-1-(4-aminophenyl)-3-(4-chlorophenyl-3-yl)prop-2-ene-1-one (4). Yield 69%, m.p 138-140 C^0 , UV.(λ max nm) 235, 347; FTIR (KBr, υ,cm-1): 3466, 3350(-NH_2), 1666(C=O)α,β , 1589 (C=C), 750 (C-Cl); ^{1}H-NMR (300MHz, DMSO-d_6,ppm): 7.53 (d, 2H, Ar-H), 6.42 (d, 2H, Ar-H), 6.73-8.41 (m, 6H, CH=CH, furan), 5.8 (S, 2H, NH_2). Anal. Calc. for c $C_{15}H_{12}NOCl$: C= 59.90%, H= 4.66%, N= 4.43% ; found: C= 59.67%, H= 4.84%, N= 5.21%.

Synthesis of [4-(4-aminophenyl)-6-(furan-3-yl)6,5-dihydropyrimidine-2-(1H)-thione] (5) and [4-(4-aminophenyl)-6-(4-chlorophenyl)6,5-dihydropyrimidine-2-(1H)-thione] (6).

Clalcones (3), (4), (0,01 mol) were added to amixture of thiourea (0.01 mol) in ethanol (20 ml) and concentrated HCl (0.5 ml), then refluxed for (6 hrs.). The mixture was concentrated to half its volume, cooled and neutralized with ammonium hydroxide. The solid precipitates were filtered off , washed with water, dried and recrystallized from ethylacetate. ***Compound (5)*** Yield 70%, m.p 136-138 C^0 , UV.(λ max nm) 215, 327; FTIR (KBr, υ,cm^{-1}): 3429,3352 (-NH_2), 3207 (N-H), 2660 (S-H), 1240 (C=S), 1176 (C-O-C); ^{1}H-NMR (300MHz, DMSO-d_6,ppm): 13.1 (s, 1H, SH), 7.63 (d, 2H, Ar-H), 6.98 (d, 2H, Ar-H), 6.13-7.25 (m, 3H, furan), 5.83 (s, 2H, NH_2), 4.0 (t, 1H, CH of pyrmidine), 2.1 (d, 2H, CH_2 of pyrmidine). Anal. Calc. for c $C_{14}H_{13}N_3OS$: C= 61.99%, H= 4.79%, N= 15.49% ; found: C= 62.11%, H= 4.92%, N= 15.25%. ***Compound (6)*** Yield 66%, m.p 185-187 C^0 , UV.(λ max nm) 235, 342; FTIR (KBr, υ,cm-1): 3420,3340 (-NH_2), 3281 (N-H), 2670 (S-H), 1250 (C=S), 767 (C-Cl); ^{1}H-NMR (300MHz, DMSO-d_6,ppm): 13.2 (s, 1H, SH), 6.53-7.44 (m, 8H, Ar-H), 5.79 (s, 2H, NH_2), 4.2 (t, 1H, CH of pyrmidine), 2.19 (d, 2H, CH_2 of pyrmidine). Anal. Calc. for c $C_{16}H_{14}N_3SCl$: C= 62.12%, H= 4.43%, N= 10.14% ; found: C= 62.01%, H= 4.15%, N= 10.23%.

Synthesis of [4-(5-(Furan-3-yl)isoxazole-3-yl)aniline] (7) and [4-(5-(4-Chlorophenyl)isoxazole-3-yl)aniline] (8).

A mixture of copounds (3) , (4) (0.01 mol), hydroxylamine hydrochloride (0.01 mol) and sodium acetate (0.01 mol) in (25 ml) ethanol were refluxed for (6 hrs.). The reaction mixture was concentrated and poured into ice water. The obtained precipitate was filtter off, washed and recrystallized from ethanol.

Compound (7):Yield 63%, m.p 115-117 C^0 , UV.(λ max nm) 211, 375; FTIR (KBr, υ,cm^{-1})1616 (C=N), 1564 (C=C), 1211 (C-O) of isoxazole ring ; ^{1}H-NMR (300MHz, DMSO-d_6,ppm): 6.14-7.25 (m, 3H, furan), 7.5 (d, 2H, Ar-H), 6.41 (d, 2H, Ar-H), 6.8 (s, 1H, isoxazole), 5.9 (S, 2H, NH_2). Anal. Calc. for c $C_{13}H_{10}N_2O_2$: C= 69.02%, H= 4.42%, N=12.38% ; found: C= 69.15%, H= 4.61%, N= 12.17%.

Compound (8):Yield 67%, m.p 155-157 C^0 , UV.(λ max nm) 247, 367; FTIR (KBr, υ,cm^{-1}); 3420,3340 (NH_2)1620 (C=N), 1570 (C=C), 1219 (C-O) of isoxazole ring, 765 (C-Cl); ^{1}H-NMR (300MHz, DMSO-d_6,ppm): 8.21 (d, 2H, Cl-Ph-H), 7.68 (d, 2H, Cl-Ph-H), 7.51 (d, 2H, Ar-H), 6.41 (d, 2H, Ar-H), 6.8 (s, 1H, isoxazole), 5.9 (S, 2H, NH_2). Anal. Calc. for c $C_{15}H_{11}N_2OCl$: C= 66.54%, H= 4.06%, N=10.35% ; found: C= 66.41%, H= 4.15%, N= 10.23%.

Synthesis of compounds (9), (10).

4-Aminoacetophenone (0.01 mol) react with 2-Mercaptobenzimidazole and 2-mercaptobenzthiazole (0.01 mol), respectively in (30 ml) ethanol was refluxed for (7-12 hrs.). The sold precipitate was collected and recrystallized from ethanol.

Compound (9):Yield 70%, m.p 207-209 C^0 , UV.(λ max nm) 220, 336; FTIR (KBr, υ,cm^{-1}); 3113 (N-H)1647 (C=O), 1564 (C=N); ^{1}H-NMR (300MHz, DMSO-d_6,ppm): 8.20 (d, 2H, Ar-H), 7.60 (d, 2H, Ar-H), 7.52-7.12 (m, 4H, benzimidazole), 5.3 (s, 1H, N-H of imidazole), 4.2 (S, 1H, N-H), 2.32 (s,3H, $COCH_3$). Anal. Calc. for c $C_{15}H_{13}N_3O$: C= 71.71%, H= 5.17%, N=16.73% ; found: C= 71.82%, H= 5.29%, N= 16.70%.

Compound (10):Yield 68%, m.p 198-200 C^0 , UV.(λ max nm) 215, 320; FTIR (KBr, υ,cm^{-1}); 3120 (N-H)1650 (C=O), 1593 (C=N), 665 (C-S-C); ^{1}H-NMR (300MHz, DMSO-d_6,ppm): 8.30 (d, 2H, Ar-H), 7.60 (d, 2H, Ar-H), 7.52-7.15 (m, 4H, benzothaizole), 4.1 (s, 1H, N-H), 2.40 (s,3H, $COCH_3$). Anal. Calc. for c $C_{15}H_{12}N_2OS$: C= 67.16%, H= 4.47%, N=10.44% ; found: C= 67.21%, H= 4.51%, N= 10.39%.

Results and discussion

Synthesis

The new derivatives were prepared folloing the reaction sequences depicted in scheme (1). The first route include synthesis of N-acetophenone-1,2,3-triazole derivatives (1), (2) by prepared diazotation of 4-aminoacetophenone to obtain diazonium chloride (I). The reaction must be carried out at low tempature (0-5) C^0, since the diazonium salt dissociated at temperature higher than (5) C^0, the obtained diazonium salt (I) was treated with calculated amount of sodium azide to affored 1-(4-azidophenyl)ethanone (II). FTIR spectrum of compound (II) shows absorption at υ cm^{-1} (2129 for N=N-N group). The azide (II) was converted to 1-(4-acetylphenyl)-5-methyl-1H-1,2,3-triazole (2), by the reaction with ethylacetoacetate and acetylacetone respectively (scheme 1). FTIR spectra showed the disappearance of characterstic band of azide group (N_3), which observed in the starting metrial (II) at (2129 cm^{-1}). FTIR spectrum of compound (1) showed new absorption bands at 1726 cm^{-1} for υ (C=O) acid , 981 cm-1 for υ (N=N) and band at 3348-3464 cm^{-1} for υ(C=O-OH). While the ^{1}H-NMR spectrum showed signals at 8.02 (d, 2H, Ar-H), 7.61 (d, 2H, Ar-H), 2.65 (S, 3H, $COCH_3$), 2.31 (S, 3H, CH_3 of triazole), 11.5 (S, 7H, COOH).

FTIR spectrum of compounds **(2)** showed absorption bands at 1687cm^{-1} for υ(C=O) of ketone, 956 cm-1for υ(N=N), whie ^{1}H-NMR spectrum revealed the following signals; 8.04 (d, 2H, Ar-H), 7.55 (d, 2H, Ar-H), 2.67 (S, 3H, $COCH_3$), 2.31 (S, 3H, CH_3 of triazole), 2.12 (S, 7H, $COCH_3$ triazol).

Chalcones **(3), (4)**, were prepared by reacting a-aminaceophenone with furfryl and 4-chloro benzaldehyde respectively. FTIR spectrum of **(3)** shows a band at (1637, 1602) cm^{-1} assigned to (C=O) and (C=C) of α,β-unsaturated compound, respectively; while ^{1}H-NMR spectrum revealed the following signals; 6.82-8.31 (m, 5H, CH=CH, furan), 7.5 (d, 2H, Ar-H), 6.45 (d, 2H, Ar-H), 5.6 (S, 2H, NH_2).

FTIR spectrum of **(4)** showed a new bands at (1666, 1589) cm^{-1} assigned to (C=O) and (C=C) of α,β-unsaturated compound, respectively; while ^{1}H-NMR spectrum revealed the following signals; 7.53 (d, 2H, Ar-H), 6.42 (d, 2H, Ar-H), 6.73-8.41 (m, 6H, CH=CH, furan), 5.8 (S, 2H, NH_2).

FTIR spectrum of **(5)** showed (NH) streching a bsorption bands in 3207 cm^{-1} and (C=S) at 1240 cm^{-1} with a weak band near 2660 cm^{-1} due to (SH) stretch because of thiol-thion tautomersim. while ^{1}H-NMR spectrum revealed the following signals; 13.1 (s, 1H, SH), 7.63 (d, 2H, Ar-H), 6.98 (d, 2H, Ar-H), 6.13-7.25 (m, 3H, furan), 5.83 (s, 2H, NH_2), 4.0 (t, 1H, CH of pyrmidine), 2.1 (d, 2H, CH_2 of pyrmidine).

FTIR spectrum of **(6)** showed (NH) streching a bsorption bands in 3281 cm^{-1} and (C=S) at 1250 cm^{-1} with a weak band near 2670 cm^{-1} due to (SH) stretch vibration. The ^{1}H-NMR spectrum shwed the following signals; 13.2 (s, 1H, SH-NH tautomeric state), 6.53-7.44 (m, 8H, Ar-H), 5.79 (s, 2H, NH_2), 4.2 (t, 1H, CH of pyrmidine), 2.19 (d, 2H, CH_2 of pyrmidine).

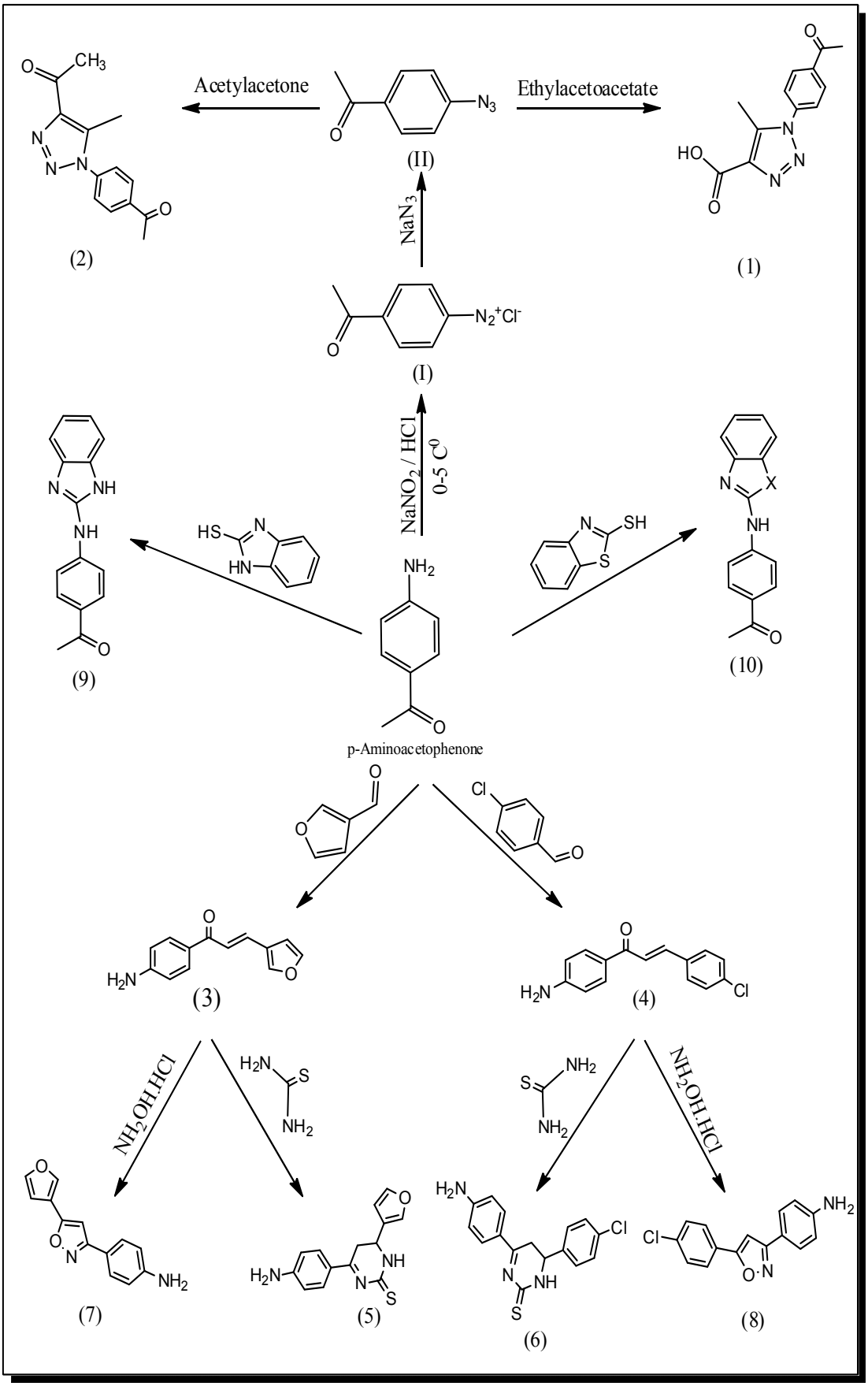
Cyclization of chalcones **(3)** and **(4)** with hydroxyl amine hydrochloride afforded compounds **(7)** and **(8).** FTIR spectrum of **(7)** showed a bsorption bands at 1616 cm^{-1} , 1564 cm^{-1} and 1211 cm^{-1} , assigned to (C=N), (C=C) and (C-O) of izoxazole ring, respectively. The ^{1}H-NMR spectrum of compound **(7)** shwed the following signals; 6.14-7.25 (m, 3H, furan), 7.5 (d, 2H, Ar-H), 6.41 (d, 2H, Ar-H), 6.8 (s, 1H, isoxazole), 5.9 (S, 2H, NH_2).

FTIR spectrum of **(8)** showed a bsorption bands at 1620 cm^{-1} , 1570 cm^{-1} and 1219 cm^{-1} , assigned to (C=N), (C=C) and (C-O) of izoxazole ring, respectively. While the ^{1}H-NMR spectrum of compound **(8)** shwed the following signals; 8.21 (d, 2H, Cl-Ph-H), 7.68 (d, 2H, Cl-Ph-H), 7.51 (d, 2H, Ar-H), 6.41 (d, 2H, Ar-H), 6.8 (s, 1H, isoxazole), 5.9 (S, 2H, NH_2).

Compounds **(9)** and **(10)** were prepared by reacting 4-aminoacetophenone with 2-Mercaptobenzimidazole and 2-mercaptobenzthiazole, respectively. The reaction was followed by using lead paper till the end of libration of H_2S. The FTIR spectra showed disappearance the streching vibration band of (S-H) and appearance the streching vibration band of of (NH) at (3113) cm^{-1}.

The ^{1}H-NMR spectrum of compound **(9)** revealed the following signals; 8.20 (d, 2H, Ar-H), 7.60 (d, 2H, Ar-H), 7.52-7.12 (m, 4H, benzimidazole), 5.3 (s, 1H, N-H of imidazole), 4.2 (S, 1H, N-H), 2.32 (s,3H, $COCH_3$).

The ^{1}H-NMR spectrum of compound **(10)** revealed the following signals; 8.30 (d, 2H, Ar-H), 7.60 (d, 2H, Ar-H), 7.52-7.15 (m, 4H, benzothaizole), 4.1 (s, 1H, N-H), 2.40 (s,3H, $COCH_3$).



Scheme 1: Synthesis routes of compounds (I), (II), and (1-10)

Antimicrobial activity

Standard antimicrobial drug (Ampicilin) and antifungal drug (Fluconazole), were used for comparision. The experiments were performed in triplicate in order to minimize errors.

The results of antimicrobial studied were given in Table (1). Compounds (1-10) are potential antimicrobial .

4-Aminoacetophenone carring triazole, chalcone, pyrimidine, isoxazole, benzothiazole, benzimidazole, which are responsible for antimicrobial activity. It seems that the compound **(6)** is very eignificant for activity against both bacterial and fungal species due to the prescence of pyrimidine ring. The increasing in activity of the new derivatives can be explained that act as more powerfull and potent bacterial agents, thus killing most of bacteria. The delocalization π-electrones over the new derivatives increases the lipophilic character and favers its permeation through the lipoid layer of the bacterial memberane.

Table (1): Antimicrobial and Antifungal evaluation of compounds (1-10)

Compound	Antimicrobial activity				Antifungal Activity	
	Zone of inhibition (mm)					
	Gram Negative		Gram positive		Fungi	
	E-Coli	P.aeragines	S.aureas	S.pyogenes	C.albicans	A.niger
1	80	50	10	50	70	50
2	50	0	0	30	60	50
3	70	60	0	20	70	50
4	80	50	0	30	70	50
5	100	80	10	60	80	60
6	120	110	10	80	70	80
7	80	60	0	50	70	50
8	70	50	0	50	70	55
9	---	---	---	---	---	---
10	---	---	---	---	---	---
Ampicilin	100	100	100	100	---	---
Fluconozol	---	---	---	---	100	100

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