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RESEARCH ARTICLE

Synthesis, Characterization of Some Novel 1, 4- Benzoxazine- 3-One Derivatives Starting From *O*-Amino Phenol and Study Their Biological Activity

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Abstract

In this work: Benzoxazinone derivatives were used as a precursor to synthesize of many heterocyclic systems. The aim of current study was to use the easily available *o*-amino phenol for the synthesize of 1,4-benzoxazine-3-one. The benzoxazinone compound of interest was synthesized by reacting the *o*-amino phenol with chloroacetyl chloride, The treatment of *o*-chloro acetamidophenol (FH) and anhydrous potassium carbonate in refluxing DMF afforded the corresponding 1,4-benzoxazine -3-one (1) in excellent yield. The treatment of ethyl chloroacetate with compound (1) gave compound (2), while compound (3) was produced by reacting of hydrazine hydrate with compound (2). Compound (3) was used as precursor to synthesize (5a-d),(ST),(6),(7a,7b),(8,9) by its reaction with different chemical reagents, while on treatment of the compound (1) with 4-nitrobenzaldehyde in acetic anhydride: triethylamine (2:1) as a solvent gave chalcone (10). The structures the synthesized compounds have been confirmed by FT-IR, ^{1}H-NMR, and Mass spectroscopy. The synthesized derivatives have been screened in vitro for antimicrobial properties. The results of this investigation revealed that the newly synthesized compounds are potent antimicrobial agents.

Keywords: *2-Aminophenol, Benzoxazinone, Schiff's base, 1, 2, 4-triazole, Antimicrobial.*

Introduction

Heterocyclic is the largest and most varied family of organic compounds and are of immense importance [1] biologically and industrially. The heterocyclic compounds containing nitrogen received a great amount of attention [2], because these compounds play an important role in medical chemistry by assisting in various biological processes [3].

In recent years benzoxazine derivatives containing nitrogen have attracted increased attention due to the broad spectrum of their biological activities [4] like antibacterial [5, 6], antifungal [7], anti-plasmodial [8], anti-cancer [9], antidepressant [10], anti-tumour [11], anti-oxidant [12] and anti-tuberculosis [13]. Schiff base derivatives have been attracted researchers interest in bioorganic and medicinal chemistry fields to their significance for antibacterial, antifungal activities and insecticidal properties. The 1, 2, 4-trazole (five-membered hetero cyclics) have the most significant range of research in medicinal chemistry field and were considered as a substantial contribution of science to humanity. On the other hand chalcone are still promising to conduct new drug analyzes. For this, new ways of synthesizing the alkalo derivatives which exhibited a range of pharmacological and biological effects. From this points compounds (FH,1-3,5a-d,6,7a-b,8-10) were prepared with different moieties and screened against several bacterial species (gram positive and gram negative) and also against Candida albicans.

Material and Methods

All starting materials and solvents were purchased from Aldrich and Fluka and used without further purification. Melting points were determined on an electro thermal capillary apparatus and are uncorrected; FT-IR measurements were recorded on a Shimadzu model FTIR-8400S. Mass spectra were recorded on a Shimadzu GC MS-QP2010 Ultra apparatus. ^{1}HNMR spectra were obtained with a Bruker spectrophotometer model ultra-shield at 300 MHz in DMSO-d6 solution with the TMS as internal standard.

Synthesis

Synthesis of 2- Chloro- N- (2-hydroxyphenyl) Acetamide (FH) [14]

A mixture of *o*-amino phenol (2.18 g, 0.02 mol) and anhydrous K_2CO_3 (0.5g) in dry acetone (25ml), chloroacetyl chloride (2.26ml, 0.02 mol) was added drop-wise at (0-5 ^oC). The reaction mixture was allowed to stirr at room temp. For 1h and heated under reflux for 6h after cooling, the solution was poured into ice-cold water. The precipitate formed was filtered off, dried and recrystallized from ethanol. Dark brown powder; yield 92%, m.p. 130-132 °C, IR (v/cm^{-1}): 3367(NH), 3010 (aromatic C-H), 2875, 2991 (aliphatic C-H), 3190 (OH Broad), 1654(C=O) amide. ^{1}HNMR (300MHz, DMSO-*d*$_6$) δ (ppm): 4.39 (s, 2H, CH_2), 6.77- 7.90 (m, 4H, Ar-H), 9.45 (s, 1H, NH), 9.97(s, 1H, OH). MS, *m/z* $[M]^+$: 185(185.5) found (calcu.) for $C_8H_8O_2NCl$.

Synthesis of 1, 4- Benzoxazine- 3- One (1)

A mixture of 2-chloro-N-(2-hydroxyphenyl) acetamide (0.01 mol) and anhydrous K_2CO_3 (0.01 mol) was dissolved in DMF (25ml), then refluxed for 10 h. The solvent was evaporated under reduced pressure and poured into ice-cold water. The precipitate was separated by filtration, washed with water, dried and recrystallized from ethanol.

Pale red powder; yield 85 %, m.p. 170-171 °C, IR (v/cm^{-1}): 3182(NH), 3059 (aromatic C-H), 2856, 2982 (aliphatic C-H), 1699(C=O) amide. ^{1}HNMR (300MHz, DMSO-*d*$_6$) δ (ppm): 4.55(s, 2H, CH_2), 6.87-6.96 (m, 4H, Ar-H), 10.71(s, 1H, NH), MS, *m/z* $[M]^+$: 149 (149.14) found (calcu.) for $C_8H_7NO_2$.

Synthesis of ethyl 2-(3-oxo-2, 3-dihydro-4H-benzo[b] [1, 4] oxazin-4-yl) acetate (2) [15]

A mixture of compound (1) (0.01 mol), ethyl chloroacetate(0.01 mol) and anhydrous K_2CO_3 (2g) in dry acetone (30ml) was refluxed for 15 h. The mixture was cooled, then poured into ice-cold water. The formed precipitate was separated by filtration, washed with water, dried and recrystallized from ethanol.

Pale orange powder; yield 85%, m.p. 68-70 ^oC, IR (v/cm^{-1}): 3072 (aromatic C-H), 2854, 2983 (aliphatic C-H), 1735(C=O) ester, 1676(C=O) amide, 1213(C-O). ^{1}HNMR (300MHz, DMSO-*d*$_6$) δ (ppm):1.19(t, 3H, CH_3), 4.15(q, 2H, CH_2), 4.47(s, 2H, CH_2), 4.71(s, 2H, CH_2) (oxazine ring), 6.92-7.03 (m, 4H, Ar-H).

Synthesis of 2H-1, 4-Benzoxazine- 3- one-4- Yl- acetic acid hydrazide (3) [16]

A solution of compound (2) (0.001mol) in absolute ethanol (25ml), hydrazine hydrate 80% (0.002mol) was added, and then refluxed for10h. The mixture was concentrated, cooled and poured into ice-cold water. The solid was filtered, dried and recrystallized from ethanol.

White powder; yield 60%, m.p. 163-165 °C, IR (v/cm^{-1}): 3331(NH), 3255, 3213(NH_2), 3055 (aromatic C-H), 2850, 2970 (aliphatic C-H), 1683, 1668 (C=O) amide. ^{1}HNMR (300MHz, DMSO-*d*$_6$) δ (ppm): 4.27 (s,2H,CH_2), 4.47 (s,2H,NH_2), 4.69(s,2H,CH_2)(oxazine ring), 6.85-7.03(m,4H, Ar-H), 9.33 (s,1H, NH).MS, *m/z* $[M]^+$: 221 (221.21) found (calcu.) for $C_{10}H_{11}N_3O_3$.

General Procedure for the Synthesis of 5-(substituted phenyl) furan- 2-carboxaldehyde (4a–d) [17]

4-Substituted aniline (0.136 mol) was dissolved in a mixture of concentrated HCl (33.7 ml) and H_2O (22.5 ml), then cooled to 0 ^oC and diazotized at (0–5) ^oC with sodium nitrite (9.5 g, 0.138 mol) dissolved in H_2O (25 ml). The solution was stirred for another 10 min, filtered and then furan-2-carboxaldehyde (15.4 g, 0.16 mol) in H_2O (50 ml) was added along with a solution of $CuCl_2.2H_2O$ (5 g, 0.04mol) in H_2O (25 ml) at a temperature of (10–15) ^oC. The reaction mixture was slowly warmed up to 40 ^oC and stirred at this temperature for 4 h. The formed precipitate was filtered off, washed with water and an aqueous solution of sodium hydrogen carbonate (5%) and water. The products were dried at room temperature and recrystallized from ethanol.

5-(4- Bromophenyl) furan- 2-carboxaldehyde (4a)

Dark brown powder; yield 59%, m.p. 154-156 ^oC, IR (v/cm^{-1}): 3117 (aromatic C-H), 2850 (aldehyde C-H), 1676 (C=O), 1597, 1521 (C=C).

5- (4- Chlorophenyl) furan- 2-carboxaldehyde (4b)

Dark brown powder; yield 67%, m.p. 130-132 ^oC, IR (v/cm^{-1}): 3115 (aromatic C-H), 2856 (aldehyde C-H), 1678 (C=O), 1600, 1519 (C=C).

5-(4- Nitrophenyl) furan- 2-carboxaldehyde (4c)

Dark orange powder; yield 62%, m.p. 202-205 ^{o}C, IR (v/cm^{-1}): 3119 (aromatic C-H), 2845 (aldehyde C-H), 1681 (C=O), 1599, 1514 (C=C).

5-(2, 4- diChlorophenyl) furan- 2-carboxaldehyde (4d)

Yellow powder; yield 79%, m.p. 121-123 ^{o}C, IR (v/cm^{-1}): 3107 (aromatic C-H), 2843 (aldehyde C-H), 1680 (C=O), 1585, 1508 (C=C).

Synthesis of Schiff bases (5a-d) [18]

To a solution of compounds (4a-d) (0.01 mol) in absolute ethanol (30 ml) with few drops of glacial acetic acid, acid hydrazide compound (3) (0.01 mol) was added . The mixture was refluxed for 10-12 h , then cooled and filtered. The obtained products were recrystallized from ethanol.

N'-((5-(4-bromophenyl) furan- 2- yl) methylene)-2-(3-oxo-2, 3- dihydro- 4H-benzo[b] [1, 4] oxazin-4-yl)acetohydrazide (5a)

Pale brown powder; yield 75%, m.p. 284-286 °C, IR (v/cm^{-1}): 3155 (NH), 3043 (aromatic C-H), 2897, 2949 (aliphatic C-H), 1699, 1664 (C=O) amide, 1608(C=N). ^{1}HNMR (300MHz, DMSO-*d$_6$*) δ (ppm): 4.67 (s, 2H, CH_2), 5.06 (s, 2H, CH_2) (oxazine ring), 7.02-7.94 (m, 10H, Ar-H), 8.13(s, 1H, CH=N), 11.78 (s, 1H, NH). MS, *m/z* [M] $^{+}$: 453 (454.27) found (calcu.) for $C_{21}H_{16}BrN_3O_4$.

N'-((5- (4-chlorophenyl) furan- 2-yl) methylene)-2- (3-oxo-2, 3- dihydro-4H-benzo[b] [1, 4] oxazin- 4-yl) acetohydrazide (5b):

Pale yellow powder; yield 77%, m.p. 290-292 °C, IR (v/cm^{-1}): 3171(NH), 3051 (aromatic C-H), 2891, 2949 (aliphatic C-H), 1697, 1664(C=O) amide, 1608(C=N). ^{1}HNMR (300MHz, DMSO-*d$_6$*) δ (ppm):4.71 (s, 2H, CH_2), 5.08(s, 2H, CH_2) (oxazine ring), 7.07-7.95 (m, 10H, Ar-H), 8.15(s, 1H, CH=N), 11.75 (s, 1H, NH).

N'-((5- (4-nitrophenyl) furan- 2-yl) methylene)-2-(3- oxo- 2, 3 - dihydro-4H-benzo [b] [1, 4] oxazin- 4-yl) acetohydrazide (5C):

Orange powder; yield 81%, m.p. 313-315 °C, IR (v/cm^{-1}): 3163(NH), 3091 (aromatic C-H), 2897, 2983 (aliphatic C-H), 1701, 1668 (C=O) amide, 1637(C=N), 1521, 1359 (NO_2). ^{1}HNMR (300MHz, DMSO-*d$_6$*) δ (ppm):4.69 (s, 2H, CH_2), 5.08(s, 2H, CH_2) (oxazine ring), 7.03-8.29 (m, 10H, Ar-H), 8.31(s, 1H, CH=N), 11.85 (s, 1H, NH). MS, *m/z* [M]$^{+}$: 420(420.37) found (calcu.) for $C_{21}H_{16}N_4O_6$.

N'-((5- (2, 4- dichlorophenyl) furan-2-yl) methylene)-2-(3-oxo-2, 3-dihydro-4H-benzo[b] [1, 4] oxazin-4-yl) acetohydrazide (5d):

Grey powder; yield 70%, m.p. 280-282 °C, IR (v/cm^{-1}): 3167(NH), 3051 (aromatic C-H), 2899, 2945 (aliphatic C-H), 1699, 1662(C=O) amide, 1608(C=N). ^{1}HNMR (300MHz, DMSO-*d$_6$*) δ (ppm): 4.67 (s, 2H, CH_2), 5.05(s, 2H, CH_2) (oxazine ring), 7.02-8.09 (m, 9H,Ar-H), 8.17(s ,1H , CH=N), 11.83 (s, 1H, NH). MS, *m/z* [M]$^{+}$: 443 (444.26) found (calcu.) for $C_{21}H_{15}Cl_2N_3O_4$.

Synthesis of potassium 2-(2-(3-oxo-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)acetyl) hydrazine -1-carbodithioate (ST) [19]

Potassium hydroxide (1.68 g, 0.03 mol) was dissolved in absolute ethanol (25 ml), then cooled in ice bath, acid hydrazide compound (3) (2.21g, 0.01 mol) was added with stirring. To above mixture carbon disulfide (0.05 mol, 4 ml) was added drop wise with continuous stirring. The reaction mixture was agitated continuously for 18 h at room temperature, then cold ethanol (20ml) was added to this solution. The solid product (ST) was filtered, washed with dry ether and dried. The potassium salt thus obtained was used in the next step without further purification.

White powder; yield 90%, m.p. 229-231^{o}C, IR (v/cm^{-1}): 3217, 3115(NH), 3080 (aromatic C-H), 2895, 2982 (aliphatic C-H), 1683, 1658(C=O) amide, 1232(C=S).

Synthesis of 4-((4-amino-5-mercapto-4H-1, 2, 4-triazol-3-yl) methyl)-2H- benzo[b] [1, 4] oxazin-3(4H)-one (6)

A mixture of compound (ST) (1g, 0.003mol) and hydrazine hydrate (80%, 10 ml) was heated under reflux for 18– 20 h.

The color of the reaction mixture changed to green with the evolution of hydrogen sulfide gas. A homogeneous reaction mixture was obtained during the reaction process. The reaction mixture was cooled at room temperature and diluted with cold water (20 ml) and acidified with conc. HCl .The formed precipitate was filtered, washed with cold water several times, dried and recrystallized from ethanol.

White powder; yield 67%, m.p. 246-248 °C, IR(v/cm^{-1}), 3294,3115(NH_2), 3064 (aromatic C-H), 2802,2937 (aliphatic C-H), 1668(C=O) amide. ^{1}HNMR (300MHz, DMSO-*d*$_6$) δ (ppm):4.72 (s,2H,CH_2), 5.17(s,2H,CH_2)(oxazine ring), 5.65 (s,2H,NH_2) ,7.02-7.06(m,4H, Ar-H), 13.59 (s, 1H, SH).MS, m/z [M]$^+$: 277 (277.30) found (calcu.) for $C_{11}H_{11}N_5O_2S$.

Synthesis of Schiff bases (7a, 7b)

To a solution of different aromatic aldehyde (3,4-dimethoxy benzaldehyde, 5-(2,4-dichlorophenyl) furan-2-carboxaldehyde) (0.01 mol), in absolute ethanol (20 ml) with few drops of glacial acetic acid. The compound (6) (0.01 mol) was added and refluxed for 10-12 h, then cooled and filtered. The obtained products were recrystallized from ethanol.

4-((4-((3, 4-dimethoxybenzylidene) amino)-5-mercapto-4H-1, 2, 4-triazol-3-yl) methyl)-2H-benzo[b] [1, 4] oxazin-3(4H)-one (7a)

Yellow powder; yield 83%, m.p. 193-195 °C, IR (v/cm^{-1}): 3159(NH), 1242 (C=S), 3074 (aromatic C-H), 2839, 2951 (aliphatic C-H), 1695 (C=O) amide, 1634(C=N). ^{1}HNMR (300MHz, DMSO-*d*$_6$) δ (ppm):3.83(s,3H,OCH_3), 3.86(s,3H,OCH_3), 4.68 (s, 2H,CH_2), 5.29(s, 2H,CH_2) (oxazine ring), 7.01-7.88 (m, 7H,Ar-H), 8.63(s ,1H , CH=N), 13.89 (s, 1H, SH).

4-((4-(((5-(2,4-dichlorophenyl)furan-2-yl)methylene)amino)-5-mercapto-4H-1,2,4-triazol-3-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (7b)

Orange powder; yield 87%, m.p. 208-210 °C. IR (v/cm^{-1}): 3124(NH), 1249 (C=S), 3061 (aromatic C-H), 2858, 2941 (aliphatic C-H), 1681 (C=O) amide, 1654 (C=N). ^{1}HNMR (300MHz, DMSO-*d*$_6$) δ (ppm):4.69 (s, 2H, CH_2), 5.31(s, 2H, CH_2) (oxazine ring), 7.01-8.01 (m, 9H, Ar-H), 8.62(s, 1H, CH=N), 13.90 (s, 1H, SH).

Synthesis of 4-(2-(3-methyl-5-oxo-4, 5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl)-2H-benzo[b] [1, 4] oxazin-3(4H)-one (8) [20]

A mixture of compound (3) (0.002 mol) and ethyl acetoacetate (0.002 mol) in absolute ethanol (20ml) was refluxed for 16h. The reaction mixture was cooled and then poured into ice-cold water. The precipitate was separated by filtration, dried and recrystallized from ethanol: water (7:3) ml.

White powder; yield 55%, m.p. 117-118 °C, IR (v/cm^{-1}): 3039 (aromatic C-H), 2850, 2982 (aliphatic C-H), 1732(C=O) pyrazole ring, 1697, 1676 (C=O) amide, 1365(CH_3). ^{1}HNMR (300MHz, DMSO-*d*$_6$) δ (ppm):1.97(s, 3H, CH_3), 4.08(s, 2H ,CH_2)cyclic, 4.70(s, 2H ,CH_2), 4.92(s, 2H ,CH_2) (oxazine ring), 6.90-7.01 (m, 4H,Ar-H) ,10.77(s,1H,OH).

Synthesis of N-(naphthalen-2-yl)-2-(2-(3-oxo-2, 3-dihydro-4H- benzo[b] [1, 4] oxazin-4-yl) acetyl) hydrazine-1-carboxamide (9) [21]

To a solution of compound (3) (0.01 mol) in dioxane (20ml), 1-Naphthyl isocyanate (0.01 mole) was added. The reaction mixture was heated under reflux for 10 h. The reaction mixture was left to stand at room temperature overnight. The solid product which separated was filtered off, dried, and recrystallized from dioxane.

Pale green powder; yield 78%, m.p. 251-253 °C, IR (v/cm^{-1}): 3294, 3209 (NH), 3057 (aromatic C-H), 2852, 2958 (aliphatic C-H), 1695, 1691 (C=O) amide. ^{1}HNMR (300MHz, DMSO- *d*$_6$) δ (ppm): 4.67(s,2H,CH_2), 4.78(s,2H,CH_2) (oxazine ring), 7.01-8.09 (m,11H,Ar-H), 8.45(s,1H,CONH- Naphthyl), 8.79(s,1H,CONH), 10.21 (s,1H,NHCO).

Synthesis of 2-(4-nitrobenzylidene)-2H-benzo[b] [1, 4] oxazin-3(4H)-one (10) [22]

4-Nitrobenzaldehyde (2.26g, 0.015mol) was added to a mixture of 1, 4-benzoxazine-3-one (1) (1.49g, 0.01mol), acetic anhydride (8 ml) and triethylamine (4 ml). The reaction mixture was refluxed for 7 h, left overnight at room temperature, then poured into ice-cold water. The obtained solid was collected by filtration and washed with acetonitrile. The crude product was purified by recrystallization from ethanol.Yellow powder; yield 59%, m.p. 283-285 °C, IR (v/cm^{-1}): 3111 (NH), 3051 (aromatic C-H), 2839, 2937 (aliphatic C-H), 1685(C=O) amide, 1629 (-C=CH-), 1519, 1340 (NO_2). ^{1}HNMR (300MHz, DMSO-*d*$_6$) δ (ppm):6.74 (s, 1H, CH=C), 7.68-8.25 (m, 8H, Ar-H), 12.70 (s, 1H, NH). MS, *m/z* [M]$^+$: 282 (282.25) found (calcu.) for $C_{15}H_{10}N_2O_4$.

Biological Activities [23]

In vitro the agar well-diffusion method was used to estimate the antimicrobial activity for the 1, 4-benzoxazine-3-one derivatives against *Gram-positive* bacteria, namely

Staphylococcus aureus, Staphylococcus epidermidis, and against *gram-negative* bacteria, namely, *Klebsiella spp., Escherichia coli* as well as *Candida albicans* and measuring the inhibition zone in mm. The derivatives were screened for both antibacterial and antifungal in nutrient agar medium. This sterilized agar media was poured in to petri-dishes and allowed to solidify.

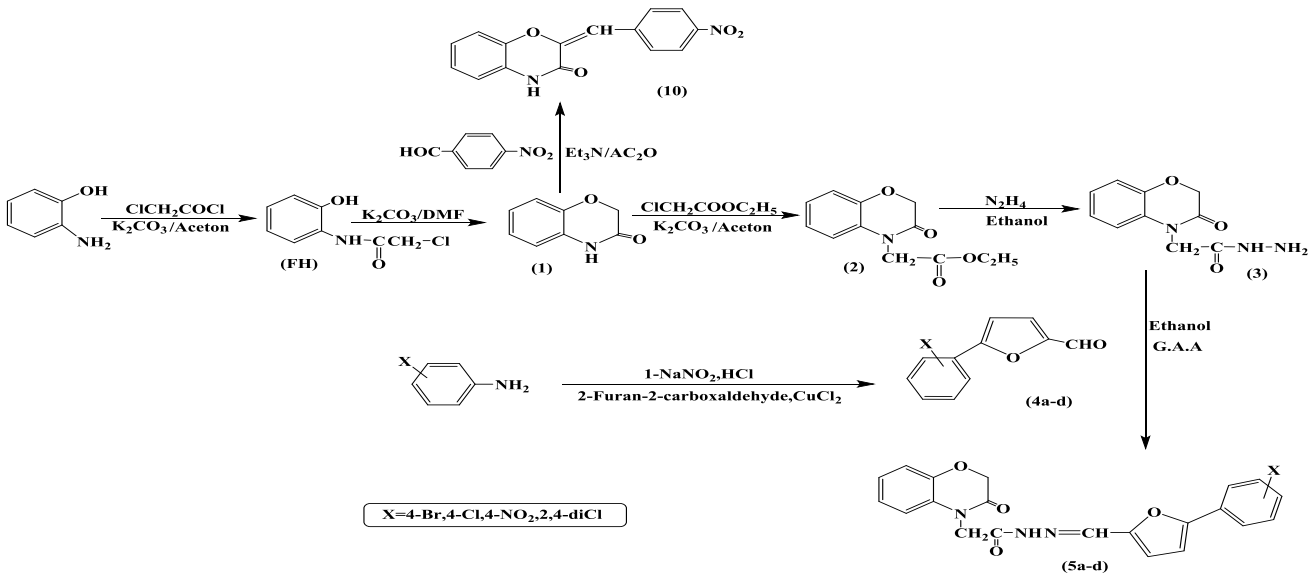
On the surface of the media microbial suspensions were spread with the help of sterilized triangular loop (diameter 6mm). DMSO was used as control and as solvent for all compounds. All The synthesized derivatives (10mg/ml) were placed in the cavities with the help of micropipette and allowed to diffuse for 1 h. The plates were incubated at 37 °C and checking after 24 h. Zones of inhibition were measured and recorded in millimeter diameter.

Results and Discussion

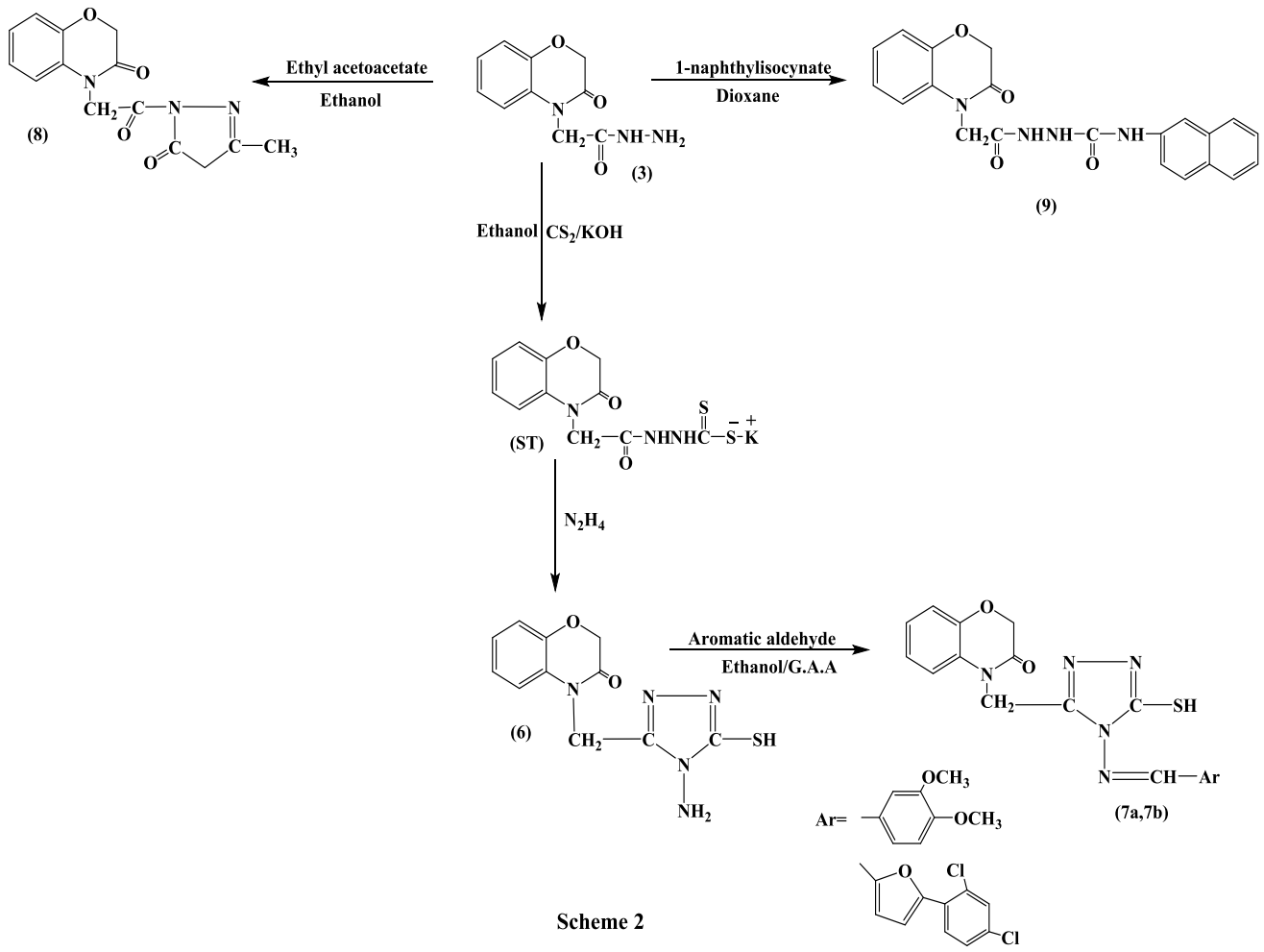
Chemistry

Our study was based on the use of easily available *o*-chloro acetamidophenol (FH) which is synthesized from *o*-amino phenol. So a cyclization of *o*-chloro acetamido phenol (FH) and anhydrous K_2CO_3 in refluxing DMF gives compound (1),where the alkylation of 1,4-benzoxazine-3-one (1) occurs at the ring nitrogen using ethyl chloroacetate and anhydrous K_2CO_3 as base to give compound (2) . Compound (2) was converted to hydrazide compound on its treatment of with hydrazine hydrate. 5-(Substituted phenyl) furan-2-carboxaldehyde [4a–d] were obtained by the reactions of diazonium salts $RPhN_2^+Cl^-$ and furan-2-carboxaldehyde in the presence of cuprous chloride. Novel Schiff bases (5a-d) were synthesized in excellent yields by the refluxing Compound (3) with compounds (4a-d) in ethanol and glacial acetic acid. The hydrazide was converted to the compound (ST) using CS_2/KOH in ethanol, the above compound was also used to synthesize compound (6) by the treatment of this compound with hydrazine hydrate. Compound (6) was next converted to Schiff bases (7a, 7b) using different aromatic aldehydes in acidic ethanolic solution. On the other hand hydrazide converted to compounds (8, 9) by reacting it with different chemical reagents.

Finally compound (10) was obtained by refluxing the 1, 4-benzoxazine-3-one with 4-nitrobenzaldehyde in the presence of acetic anhydride: triethylamine (2:1), as summarized in Schemes 1 and 2. The reaction was monitored throughout by thin layer chromatography (TLC) using n-hexane-ethylacetate (different ratios) as mobile phase. The synthesized derivatives were characterized after recrystallization from an appropriate solvent by recording their IR, ^{1}HNMR and Mass spectroscopy. In general the IR spectra afforded absorption 1608-1654 cm^{-1} band due to C=N and 1668-1701 cm^{-1} due to (C=O) oxazine ring. In ^{1}HNMR the signals of the respective protons of the synthesized title compounds were verified on the basis of their chemical shifts and multiplicities in DMSO *d6*. The spectra showed a singlet at δ 4.08-5.17 ppm corresponding to CH_2, multiplet at δ 6.77-8.29 ppm corresponding to aromatic protons.



Scheme1



Scheme 2

Antimicrobial Activities

The *in vitro* assay of the synthesized compounds (FH, 1-3, 5a-d, 6, 7a-b, 8-10) against different pathogenic bacteria and yeast were achieved using 10mg/ml concentration as illustrated by Table 1. The activity of compounds (FH, 1-3, 5a-d, 6, 7a-b, 8-10) was evaluated against *Staphylococcus aureus, Staphylococcus epidermidis* (gram positive bacteria), *Klebsiella spp., Escherichia coli* (gram negative bacteria) and *Candida albicans* (yeast). Some the prepared compounds revealed promising activity against the different species, while compound (10) exhibited excellent and highest activity against all kinds of bacteria as well as *Candida albicans*. This may be due to the presence of NO_2 group in the phenyl ring.

Table 1: In Vitro antimicrobial inhibition zone (mm) of the synthesized compounds

Comp.	Inhibition zone (mm) at 10 mg/ml against				
	Gram positive		Gram negative		Fungi
	S.aureus	S.epidermidis	E.coli	Klebsiellaspp	C.albicans
FH	13	16	14	12	11
1	12	14	12	12	13
2	11	-	11	-	10
3	12	11	-	-	-
5a	6	3	10	-	-
5b	10	-	11	12	-
5c	13	-	15	14	-
5d	-	12	-	11	-
6	12	14	-	10	16
7a	13	12	-	-	-
7b	15	16	-	-	-
8	13	15	-	-	-
9	13	11	-	12	14
10	15	13	16	17	11
DMSO	-	-	-	-	-

Conclusion

In this study, the novel 1, 4-benzoxazine-3-one derivatives were synthesized via different routes in good yield. The structures of these compounds were supported by FTIR, ^{1}HNMR, and Mass spectroscopy. The antimicrobial study of these derivatives against some *Gram positive* and *Gram negative* species as well as against *Candida albicans* was studied using the well diffusion method. The results reveal that some of the compounds of the series exhibited promising antibacterial and antifungal activity.

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