Synthesis of Novel Heterocyclic Compounds with Expected Antibacterial Activities from 4-(4-Bromophenyl)-4-oxobut-2-enoic Acid

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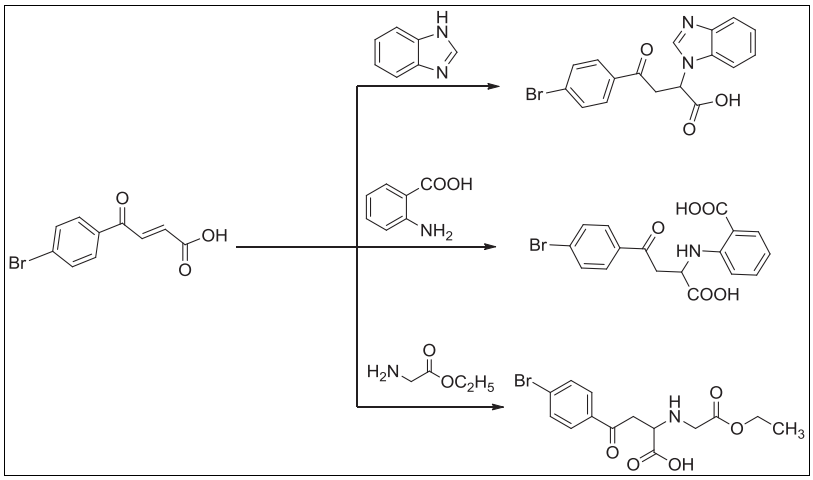


This research describes the utility of 4-(4-bromophenyl)-4-oxobut-2-enoic acid as a key starting material for preparation of a novel series of aroylacrylic acids, pyridazinones, and furanones derivatives. These heterocyclic compounds were synthesized by reaction of 4-(4-bromophenyl)-4-oxobut-2-enoic acid with benzimidazole, ethyl glycinate hydrochloride, anthranilic acid and *o*-phenylenediamine under Aza–Michael addition conditions. Every Aza–Michael adduct was allowed to react with haydrazine hydrate and acetic anhydride to form pyridazinones and furanones derivatives, respectively. In further step, some pyridazinones were allowed to react with ethyl acetoacetate, acetyl acetone, acetyl chloride, and aromatic aldehydes to form novel heterocylces. Finally, studying antibacterial activities of these compounds was performed.

INTRODUCTION

Recently, β–aroylacrylic acid derivatives showed high biological activity and exhibited a broad spectrum of physiological [1] (fungicidal, antitumor, hypotensive, hypolipedemic, and antibacterial) activities and in recovery of Alzheimer's disease. [2] Beside that, β-aroylacrylic acids were considered as inhibitors for phospholipase [3,4] and they have antiproliferative activity against human cervix carcinoma (Hela cells) [5,6]. In another side, β-aroylacrylic esters are important intermediates in field of medical science and agrochemicals [1]. Chemically, due to their electrophilicity, β-aroylacrylic acid reacts with nucleophiles including primary and secondary amines [7]. β-aroylacrylic acids also are convenient polyelectrophilic reagents in the synthesis of heterocyclic rings, for which the addition reaction of N-, S-, P-, or C-nucleophiles occurs exclusively at the α-carbonyl electrophilic position of the molecule [8–20]. In view of aforementioned facts, it seems most interesting to use 4-(4-bromophenyl)-4-oxobut-2-enoic acid to react with benzimidazole, ethyl glycinate hydrochloride, anthranilic acid, and *o*-phenylenediamine with the aim of increasing the synthetic potential of β-aroylacrylic acids and studying the antibacterial activity of synthesized compounds.

RESULTS AND DISCUSSION

The target compound 4-(4-bromophenyl)-4-oxobut-2-enoic acid **1** in the present study was readily obtained by Friedel–Crafts reaction of maleic anhydride with bromobenzene in the presence of anhydrous aluminum chloride. The interaction of 4-(4-bromophenyl)-4-oxobut-2-enoic acid (**1**) with benzimidazole in boiling ethanol and with addition of three drops of piperidine yielded the Aza–Michael adduct 2-(1*H*-benzimidazole-1-yl)-4-(4-bromophenyl)-4-oxo-butanioc acid (**2**). The structure of the product **2** agrees well with its spectroscopic parameters. Hence, the IR spectrum of compound **2** shows υ_{max} of two carbonyl groups at 1686, 1732, and broad peak for υ_{OH} centered at 3300 cm^{-1}. The ^{1}H-NMR spectrum shows two double of doublets at δ ppm 3.97, 4.02 assigned for (CH_2 group)

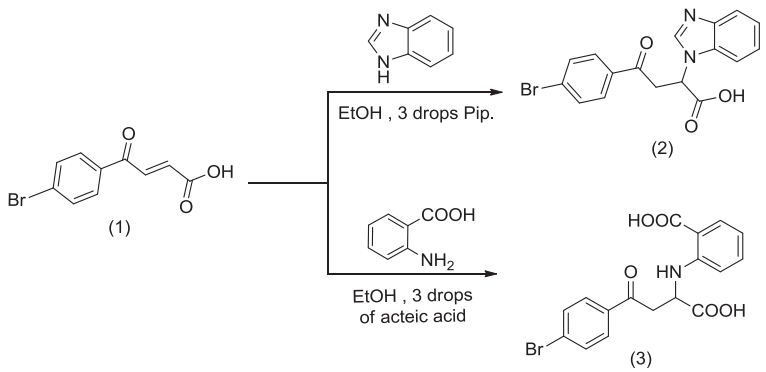
protons, double of doublet δ ppm 4.13, 4.19 assigned for (CH group) proton, 7.17–7.95 (m, 8H, ArH), 8.14 (s, 1H, CH in imidazole ring), and 8.36 (s, 1H, OH exchangeable with D_2O). The reaction takes place via nucleophilic attack of nitrogen nucleophile derived from benzimidazole on α-carbon of the acid (1,4-addition) to give the desired product. When acid **1** was allowed to react with anthranilic acid in boiling ethanol and with catalytic drops of piperidine, it yielded 2-((3-(4-bromophenyl)-1-carbox-3-oxopropyl)amino) benzoic acid (**3**) (Scheme 1). The structure of compound **3** was inferred from correct micro analytical data. Its IR spectrum revealed strong absorption bands at 1677, 3359, and 3431 cm^{-1} attributable to $\upsilon_{C=O}$ and υ_{NH} bonded and non-bonded. The bonded hydroxyl appears as a very broad band centered around 2800 cm^{-1}. The ^{1}H-NMR spectrum shows the expected number of protons. The reaction proceeds regioselectively at the 2-postion of the oxobutenoic acid moiety and yielded of non-proteinogenic unnatural amino acid **3**.

In a continuation of our investigation of the reactivity of enone systems towards nitrogen-containing binucleophiles [15–17], the reaction of acid **1** with *o*-phenylenediamine was studied. The presence of different kinds of electrophilic positions in the acid leads to suggest that six or seven membered annulated, nitrogen-containing heterocyclic compound may be formed. However, actually the only product reported is 3-(2-(4-bromophenyl)-2-oxoethyl)-3,4-dihydroquinoxalin-2-(1*H*)-one (**4**) [28] (Scheme 2). The IR spectrum of compound **4** shows two bands at 1679 and 1728 cm^{-1}, which are assigned to the vibrations of the carbonyl groups [highly value by about 25 cm^{-1} due to mutual induction between two carbonyl groups] and also a band for the stretching vibrations of secondary amide group at 3190 and 3300 cm^{-1} for secondary amino group. The ^{1}H-NMR spectrum compound **4** showed singlet signal at δ ppm 5.69 assigned to (NH) and singlet at 8.87 for (NH–CO), which were exchangeable in D_2O.

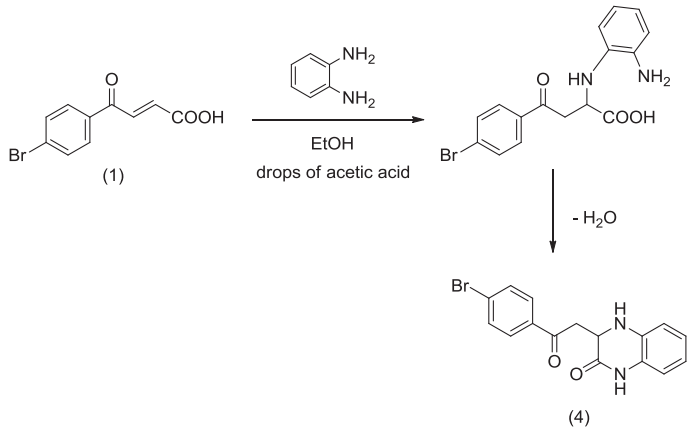
Furthermore, the reaction between ethyl glycinate hydrochloride with β-aroyl acrylic acid **1** in boiling ethanol in the presence of sodium acetate afforded ester **5** via Aza–Michael addition.

The ^{1}H-NMR spectrum of compound **5** showed δ ppm 1.18 (t, 3H, CH_3 of ester), 4.09 (q, 2H, CH_2 of ester), 8.16 (d, 1H, NH exchangeable with D_2O). The structure

Scheme 1



Scheme 2



of compound **5** also was inferred chemically via (i) Interaction of compound **5** with acetic anhydride yielded furanone derivative (**6**). The IR spectrum of compound **6** exhibits strong absorption bands at 1745, 1782, 2982. 3439 cm^{-1} (basic peak) attributable to υ_{max} of two carbonyl groups $\upsilon C{=}O$, υ_{CH}, and υ_{NH}, respectively. The ^{1}H-NMR spectrum compound **6** showed signals δ ppm 1.19 (t, 3H CH_3, of ester), 4.11 (q, 2H, CH_2 of ester) and devoid any signal for OH group.

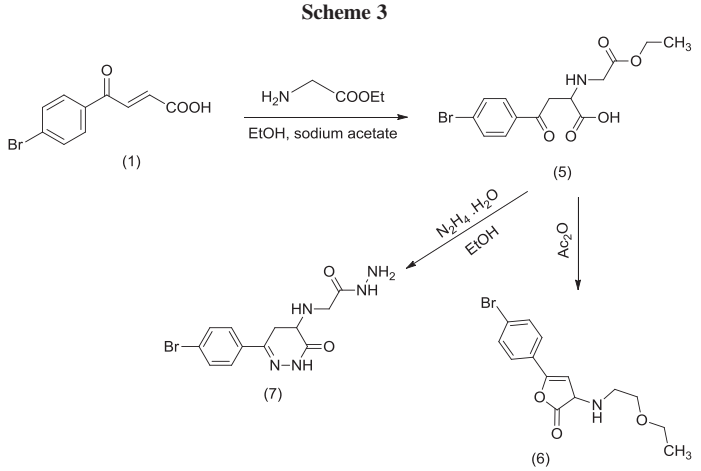
(ii) Hydrazinolysis of compound **5** by using hydrazine hydrate in boiling ethanol yielded hydrazide derivative **7** (Scheme 3). The IR spectrum of compound **7** exhibits strong absorption bands at 3224 and 3386 cm^{-1} attributable to NH and NH_2 groups. The ^{1}H-NMR spectrum of compound **7** showed signals at δ ppm 4.86 (br, s, 2H, NH_2 exchangeable with D_2O) and 8.55 (d, 2H, NH exchangeable with D_2O).

The second stage of synthesizing heterocyclic compounds is designing of the new prepared compounds based structurally on containing other biologically active heterocycles on side chains reported in the field of cancer therapy such as pyrazoles [21] and oxadiazoles [22,23]. This aim pushes authors to synthesize some interesting heterocyclic compounds, for example, pyrazole and/or oxadiazole derivatives incorporated with pyridazinone nucleus. From this point of view, compound **7** was allowed to react with ethyl acetoacetate (EAA) in boiling ethanol yielded pyrazole derivative (**8**). The ^{1}H-NMR spectrum of compound **8** showed singlet signals at δ ppm 1.92 assigned for CH_3 and 2.32 assigned for CH_2 (pyrazole moiety). Cyclization of compound **7** with acetylacetone afforded pyrazole derivative **9**. The ^{13}C-NMR spectrum of compound **9** exhibited the expected number of signals for the aromatic carbons as well as carbonyl signals and two methyl carbons at 26.3 and 16.8 ppm. Reaction of compound **7** with acetyl chloride gave the corresponding oxadiazole derivative **10**. The ^{1}H-NMR spectrum of compound **10** showed signals at δ ppm 1.92 (s, 3H, CH_3, oxadiazole ring). Interaction of the compound **7** with 4-nitrobenzaldehyde in boiling ethanol afforded 2-((6-(4-bromophenyl)-3-oxa-2,3,4,5-tetrahydropyridazin-4-yl) amino)-(4-nitrobenzalidene)acetohydrazide (**11**) (Scheme 4). The structure of compound **11** was confirmed from IR spectrum that exhibits absorption at 1648, 3313, 3424 cm^{-1} due to $\upsilon_{C=O}$ and υ_{NH} bonded and non-bonded. The ^{1}H-NMR spectrum of compound **11** showed methylidene proton at δ ppm 8.06. The ^{13}C-NMR spectrum of compound **11** exhibited the expected number of signals for the aromatic carbons as well as carbonyl signals at 163.6 and 160.2 ppm.

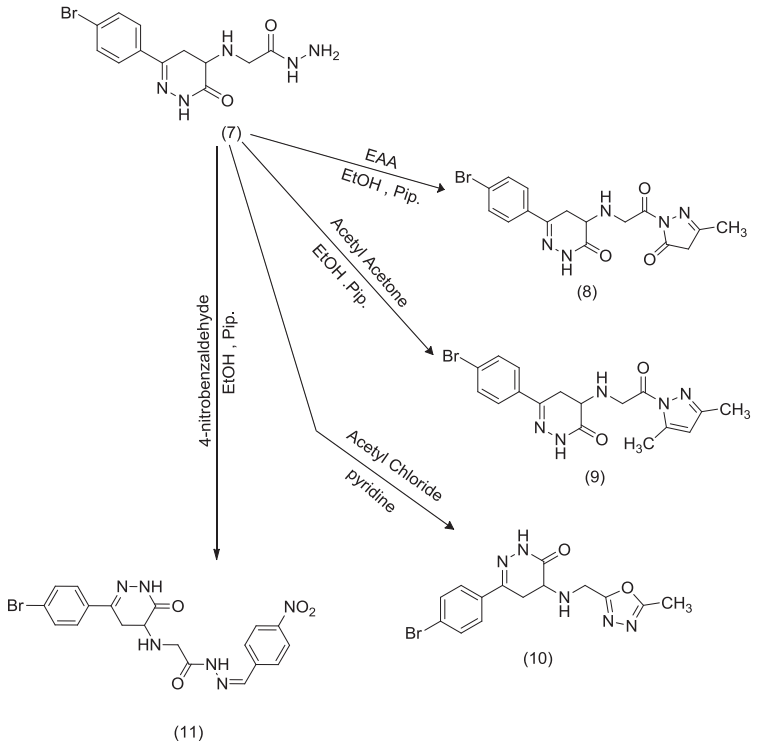
Due to their common occurrence in nature and the fact that 2-(3*H*) furanone exhibit rich photochemistry [24], oxygen-containing heterocycles are frequent and important targets for synthesis either as final products or as useful synthetic intermediates. Besides that, synthetic 3-(2*H*)-pyridazinones are important intermediates in drug discovery, with many of their analogs being in the treatment of various human pathological states. They were described as non-steroidal anti-inflammatory drugs [25]. From the previous two facts, authors planned to synthesize furanones and pyridazinones derivatives through reacting acids **2**, **3** with acetic anhydride and hydrazine hydrate, respectively. Thus, when acids **2**, **3** were allowed to react with acetic anhydride they gave furanone derivatives **12a**, **b** respectively. The IR spectrum of compounds **12a**,**b** exhibits strong absorption bands at 1782 and 1785 cm^{-1} attributable to $\upsilon_{C=O}$ of γ-lactone, respectively. The ^{1}H-NMR spectrum of compound **12b** showed signals at δ ppm 3.98 (d, 1H, CH–N), 5.23 (d, 1H, CH in furanone ring), and 6.48 (s, 1H, NH exchangeable in D_2O).

When carboxylic acid derivatives **2**, **3** were allowed to react with hydrazine hydrate in boiling ethanol, afforded pyridazinone derivatives **13a**,**b** respectively (Scheme 5). The IR spectrum of compound **13a** showed a characteristic

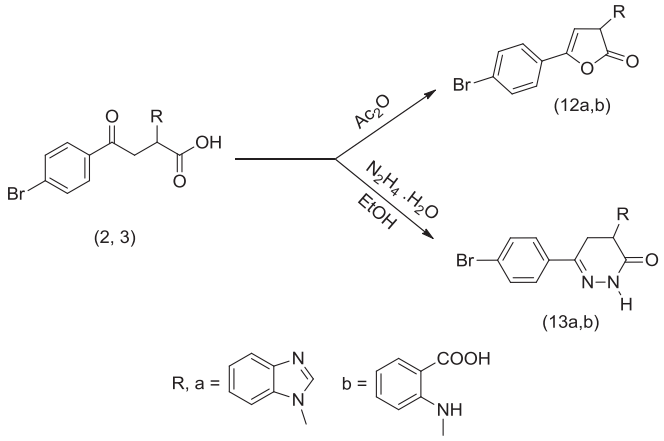
Scheme 3



Scheme 4



Scheme 5

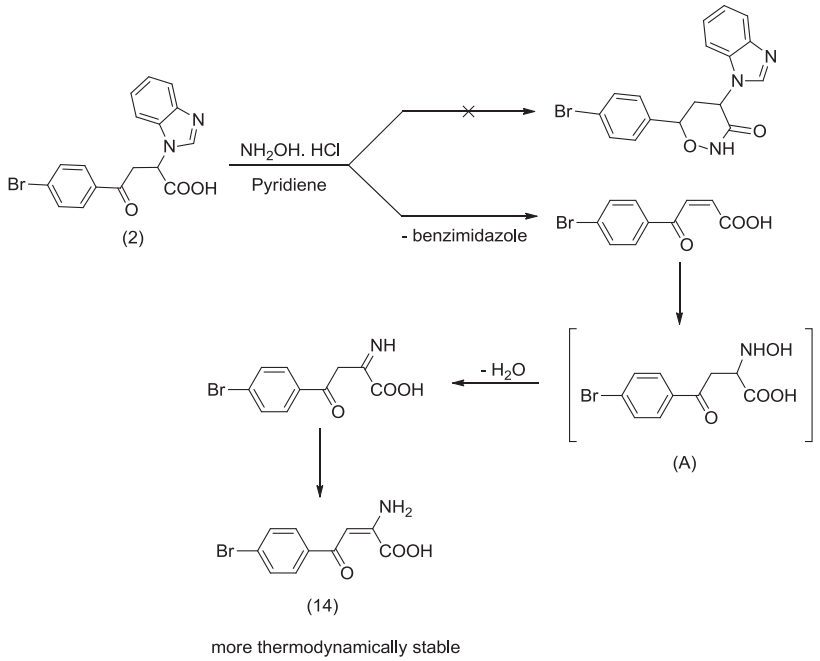


absorption bands at υ 1660 cm^{-1} corresponding to CO group. The ^{1}H-NMR spectrum of compound **13b** showed NH (pyridazinone moiety) at δ 9.21 ppm, which was exchangeable in D_2O.

When carboxylic acid derivative **2** was allowed to react with hydroxylamine hydrochloride in boiling pyridine with the aim of obtaining the oxazinone derivative, but with an unexpected manner [26], 2-amino-4-(4-bromophenyl)-4-oxobut-2-enioc acid (**14**) is obtained. The reaction occurs via addition of (NH_2OH) after loss of benzimidazole moiety to the double bond to give the fleeting intermediate **A**, dehydration, and isomerisation of the resulting imine into enamine **14** was performed (Scheme 6). The structure of enamine **14** was inferred from correct micro analytical data, its IR spectrum revealed strong absorption bands at 3387 and 1610 cm^{-1} attributable to υ_{NH} and $\upsilon_{C=C}$, respectively. The ^{1}H-NMR spectrum compound **14** showed singlet signal at δ ppm 11.74 assigned to (NH_2).

Furthermore, compound **4** reacted with acetic anhydride in boiling water bath, hydroxyl amine hydrochloride in pyridine and hydrazine hydrate in ethanol to afford 4-acetyl-3-(2-(4-bromophenyl)-2-oxoethyl)-3,4-

Scheme 6



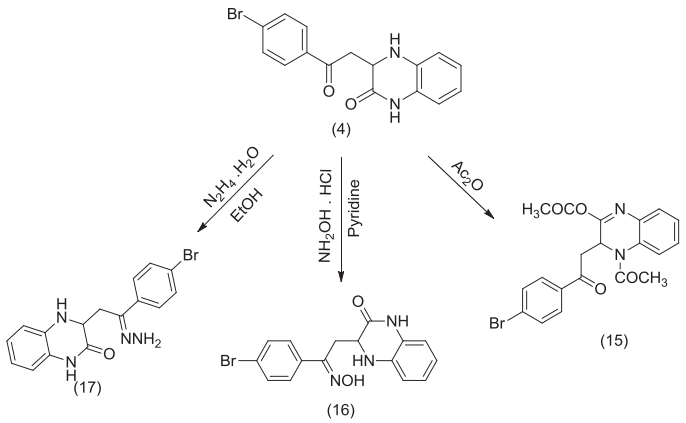
dihydroquinoxalin-2-yl acetate (**15**) and 3-(2-(4-bro mophenyl)-2-(hydroxyimino)ethyl-3,4-dihydroquino xalin-2(1*H*)-one (**16**) and 3-(2-(4-bromo phenyl)-2-hydrazonoethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (**17**), respectively (Scheme 7).

The IR spectrum of compound **15** revealed strong absorption bands at 1685 and 1778 cm^{-1} attributed to υ_{max} of two carbonyl groups and devoid any band for υ_{NH}, its ^{1}H-NMR spectrum showed two singlet signals at δ ppm 1.24, 2.08 ppm attributable to two CH_3 groups. The ^{1}H-NMR spectrum of compound **16** exhibited signals at δ ppm 3.30 (dd, 1H of methylene proton), 3.69 (dd, 1H for other methylene proton, diastereotopic proton), 4.20 (dd, 1H, methine proton, stereogenic proton), 6.65–8.51 (m, 8H, ArH), 8.87 (s, 2H for NH protons exchanged with D_2O), and 11.07 (S, 1H, OH exchanged with D_2O). The IR spectrum of compound **17** showed strong absorption bands at 1603 and 3372 attributable to $\upsilon_{C=N}$ and υ_{NH2} groups, respectively. The ^{13}C-NMR spectrum of compound **17** exhibited the expected number of signals for the aromatic carbons as well as carbonyl signal.

The behavior of the pyridazinone derivative **13a** towards carbon electrophiles was studied. Interaction of pyridazinone **13a** with 1,5-[d]-gluconic acid lactone in boiling ethanol afforded a cyclo *N*-nucleoside **18**. When pyridazinone **13a** interact with acetic anhydride, yielded 2-acetyl-4-(1*H*-benzo[d]imidazol-1-yl)-6-(4-bromophenyl)-4,5-dihydropyridazin-3-(2*H*)-one (**19**).

Furthermore, pyridazinone **13a** reacted with ethyl chloroacetate in boiling acetone and in the presence of

Scheme 7



potassium carbonate to afford ethyl ester **20** (Scheme 8). The IR spectrum of compound **18** revealed strong absorption broad band 3436 cm^{-1} attributable υ_{OH} and devoid any band for υ_{NH}.

While compound **19** was confirmed from its IR spectrum that exhibits characteristic absorption band at 1647 cm^{-1} and devoid any bands for υ_{NH}. The ^{13}C-NMR spectrum of compound **19** exhibited the expected number of signals for the aromatic carbons as well as methyl signal at 19.6 ppm. The ^{1}H-NMR spectrum of compound **20** exhibited signals at δ ppm 1.17 (t, 3H, CH_3 of ethyl ester) and 4.13 (q, 2H, CH_2 of ethyl ester). The reaction of pyridazinone derivative **13a** with ethyl chloroacetate possibly takes place via *N*-alkylation followed by elimination of benzimidazole. Compound **20** was allowed to react with hydrazine hydrate in refluxing ethanol to afford the hydrazide **21**. [27] (Scheme 8).

Compound **21** was allowed to react with acetyl acetone, acetyl chloride, and 4-nitrobenzaldehyde to give pyrazole derivative **22**, oxadiazole derivative **23** Schiff's base derivative **24** (Scheme 9).

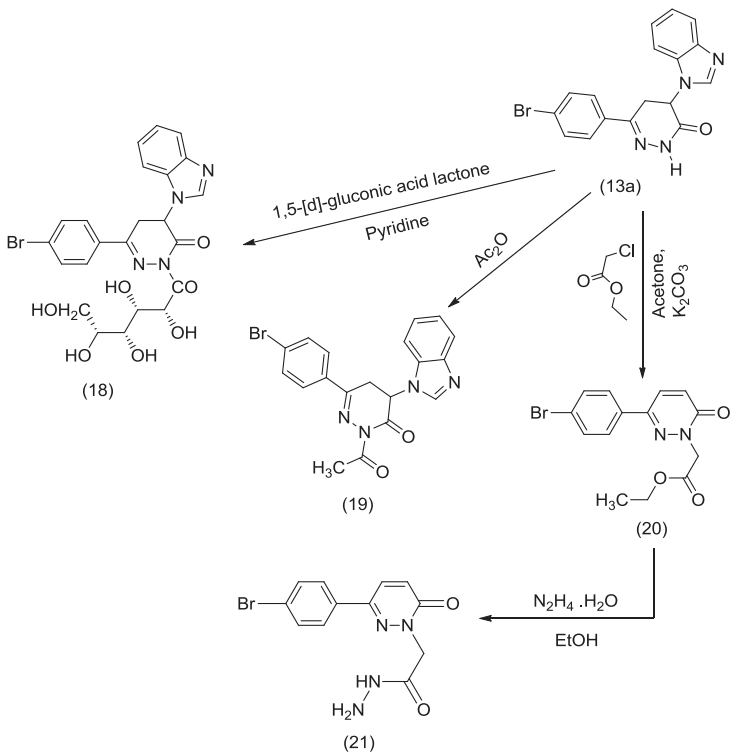
The structure of compound **22** was confirmed from its IR spectrum that exhibits strong absorption band at 1666 cm^{-1} due to $\upsilon_{C=O}$. The ^{1}H-NMR spectrum of compound **22** exhibit signals at δ ppm 2.39 (s, 3H, CH_3 in pyrazole ring) and 2.45 (s, 3H, CH_3 in pyrazole ring). IR spectrum of compound **23** showed strong absorption bands at 1666 cm^{-1} due to $\upsilon_{C=O}$. The ^{13}C-NMR spectrum of compound **23** exhibited the expected number of signals for the aromatic carbons as well as carbonyl signal at 159.4 ppm. The ^{1}H-NMR spectra of compound **24** showed the methylidene protons at δ ppm = 8.55.

When the hydrazide derivative **21** was submitted to react with EAA in boiling ethanol it yielded pyrazole derivative **26** that was reported in 2008 [27]. But in this reaction, the ester **25** was isolated. IR spectrum of compound **25** exhibits strong absorption bands at 1666, 1751, and a basin peak centered at 3424 cm^{-1} attributable to υ_{max} of two carbonyl groups and υ_{NH}, respectively while the ^{1}H-NMR spectrum exhibit signals at δ ppm 1.21 (t, 3H, CH_3 of ester), 1.87 (s, 3H, CH_3), 2.29 (s, 2H, CH_2), 4.15 (q, 2H, CH_2 of ester), and 8.46 (s, 1H, NH exchangeable in D_2O) (Scheme 10).

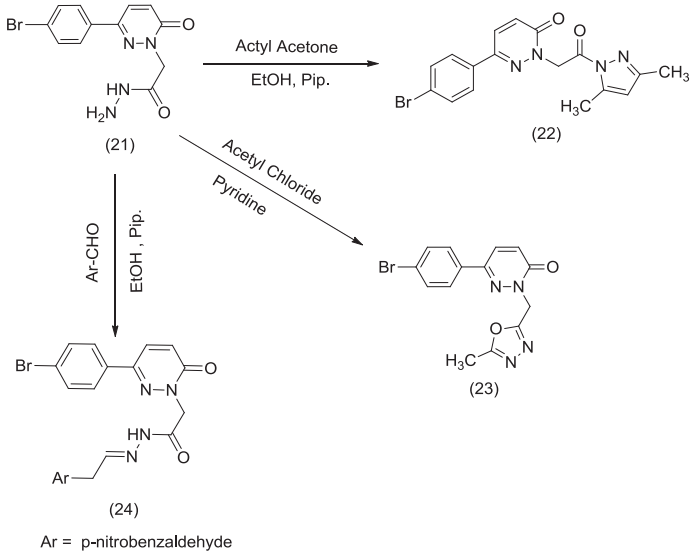
APPLICATION

β-aroyl acrylic acid and its derivatives represent one of the most active classes of compounds possess a wide spectrum of biological activity. Many of these compounds have been used for the treatment of various diseases, such as Alzheimer's disease [2] and exhibit a broad spectrum of physiological (fungicidal, antitumor, hypotensive, hypolipidemic, and antibacterial) activities [1]. In the present work, synthesis of some β-aroyl acrylic acid and their derivatives were reported. Some of the new synthesized compounds have been evaluated for their antibacterial activity. The antibacterial activity of each compound under investigation was evaluated by the disk diffusion method against Gram-positive bacteria (*Streptococci*) and Gram-

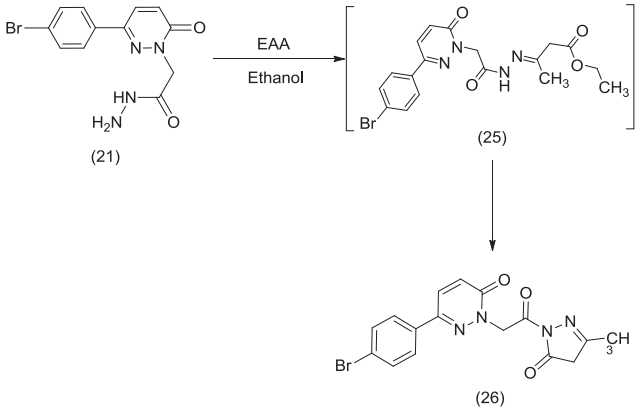
Scheme 8



Scheme 9



Scheme 10



negative bacteria (*Escherichia coli*) by using sterile whatman-No5 filter paper disks (11 mm diameter). Each compound was dissolved in ethanol. Filter paper disks (11 mm) were loaded with certain amount of the tested material (50 μL) then left with care under hot air to complete dryness. Test plates were prepared by pouring 10 mL Muller–Hinton agar medium seeded with the test organism. The disks were deposited on the surface of agar plates along with control disk, which loaded only with used solvent. The disks were incubated at 5°C for 1 h, to permit good diffusion. All the plates were then incubated for 24 h at 37°C. The zones of inhibition were measured then the following results were reported (cf. Table 1).

Table 1

Antibacterial activity of synthesized compounds.

Compound	Antibacterial activity	
	Gram-positive bacteria *Streptococci*	Gram-negative bacteria *Escherichia coli*
2	–	–
3	–	+
4	+	–
8	+	+
9	+++	–
10	+++	+
11	+++	+
12a	–	++
12b	–	–
13a	–	++
13b	++	+
14	–	–
15	+	–
16	+	–
17	+++	++
21	–	–
22	–	–
23	–	–
24	–	–
26	–	–

–, no activity; +, weak activity; ++, moderate activity; +++, strong activity.

CONCLUSION

In this research, novel heterocyclic compounds were synthesized followed by studying the antibacterial activities of these compounds. Chemically, and as an application of important and widely used reaction in organic chemistry, Aza–Michael addition was investigated with different types of amines. Furthermore, Aza–Michael adducts were used as key starting materials to generate different heterocycles that have biological potentiality. Biologically, it was

found that 3-(1*H*-benzimidazol-1-yl)-5-(4-bromophenyl) furan-2(3*H*)-one (**12a**) and 4-(1*H*-benzimidazol-1-yl)-6-(4-bromophenyl)-4,5-dihydropyridazin-3(2*H*)-one (**13a**) exhibited moderate activity against Gram-negative bacteria, which may be due to the furanone and pyridazinone moiety. While 3-(2-(4-bromophenyl)-2-hydrazonoethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (**17**) showed strong activity against Gram-positive bacteria, which may be due to hydrazone group. In another side, compound 6-(4-bromophenyl)-4-((2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-oxoethyl)amino)-4,5-dihydropyridazin-3(2*H*)-one (**9**) showed the highest activity against Gram-positive bacteria, which may be due to the pyrazole and pyridazinone moiety. Also, compounds 6-(4-bromophenyl)-4-(((5-methyl-1,2,4-oxadiazol-2-yl)methyl) amino)-4,5-dihydropyridazin-3(2*H*)-one (**10**) and 2-((6-(4-bromophenyl)-3-oxa-2,3,4,5-tetrahydropyridazin-4-yl)amino)-*N*′-(4-nitrobenzalidene)acetohydrazide (**11**) showed strong activity against Gram-positive bacteria, which may be due to pyridazinone ring that contain amino group and oxadiazole moiety or 4-nitrobenzaldehyde.

EXPERIMENTAL

Melting points were determined on STUART scientific melting point apparatus and were uncorrected. The reaction times were determined using the thin-layer chromatography (TLC) technique which was performed using plates of aluminum oxide sheets coated with silica gel (E. Merk) 60 F 254 neutral type. The IR spectra were recorded on Bruker FTIR spectrophotometer as potassium bromide disks. Mass spectra (EIMS) were performed at 70 eV with Shimadzu GCMS, QP1000 EX using the Electron Ionization Technique (EI). The proton nuclear magnetic resonance ^{1}H-NMR and ^{13}C-NMR spectra were recorded in (DMSO-d_6) on Varian Gemini spectrophotometer at 200 MHz and Varian Mercury spectrophotometer at 300 MHz, using tetra methyl silan (TMS) as an internal reference and the chemical shift values (δ) are given in part per million (ppm). Elemental analyses were carried out at the Micro Analytical Center, National Research Center, Cairo, Egypt.

Synthesis of 2-(1*H*-benzimidazol-1-yl)-4-(4-bromophenyl)-4-oxobutanoic acid (2). A mixture of 4-(4-bromophenyl)-4-oxobut-2-enoic acid (**1**) (2.55 g; 0.01 mol) and benzimidazole (1.18 g; 0.01 mol) in ethanol (50 mL) and (4 drops) of piperidine was refluxed for 2 h. The reaction mixture was allowed to cool and the separated product was filtered. Crystallization of the crude product from dioxane then drying, afforded **2** (brown powder, 2.7 g (75%) yield, mp 186°C). IR (cm^{-1}): 3300 (OH) and 1732, 1686 (2C═O).^{1}H-NMR: δ, ppm (DMSO-d_6); 3.94, 3.97, 4.00, 4.03 (dd, J = 6 Hz, 2H, CH_2); 4.12, 4.14, 4.18, 4.20 (dd, J = 4 Hz, 1H, CH); 7.17–7.95 (m, 8H, ArH), 8.14 (s, 1H, CH in imidazole ring) and 8.36 (s, 1H for one OH exchangeable with D_2O).^{13}C-NMR: δ, ppm (DMSO-d_6); 199.1 (C═O adjacent to aroyl moiety), 170.3 (C═O of acid), 143.8 (carbon of imidazole), 135.7, 132.3, 130.1, 129.4, 127.6, 128.1 (phenyl carbons), 144.9, 135.1, 125.8, 120.7, (benzimidazole carbons), 65.9 (CH–N), 39.3 (CH_2). *Anal*. Calcd (%): $C_{17}H_{13}Br\ N_2O_3$ C, 54.71; H, 3.51; N, 7.51. Found (%): C, 54.55; H, 3.32; N, 7.42.

Synthesis of 2-((3-(4-bromophenyl)-1-carboxy-3-oxopropyl) amino)benzoic acid (3). A mixture of 4-(4-bromophenyl)-4-oxobut-2-enoic acid (**1**) (3 g; 0.01 mol) and anthranilic acid (1.37 g; 0.01 mol) in ethanol (20 mL) and (4 drops) of acetic acid glacial was refluxed for 2 h. The reaction mixture was allowed to cool and the separated product was filtered. Crystallization of the crude product from toluene then drying, afforded **3** (faint yellow powder, 2.9 g (75%) yield, mp 230°C). IR (cm^{-1}): 3431, 3359 (NH bonded and non-bonded), 2800 (OH) and 1677 (C═O). ^{1}H-NMR: δ, ppm (DMSO-d_6); 3.60, 3.67 (dd, J = 6 Hz, 2H, methylene proton), 4.30, 4.27 (dd, J = 6 Hz, 1H, methine proton), 4.66 (s, 1H, NH exchangeable with D_2O), 7.17–8.36 (m, 8H, ArH), 9.13, 9.21 (s, 2H, 2 OH exchangeable with D_2O). ^{13}C-NMR: δ, ppm (DMSO-d_6); 197.7 (C═O adjacent to aroyl moiety), 175.8 (C═O of acid), 169.9 (C═O of anthranilic acid), 135.1, 130.7, 129.3, 128.5 (phenyl carbons), 150.1, 131.4, 127.6, 126.8, 120.2, 117.1 (anthranilic benzene ring), 67.9 (CH–N), 40.5 (CH_2). *Anal*. Calcd (%): $C_{17}H_{14}BrNO_5$. C, 52.06; H, 3.60; N, 3.57. Found (%): C, 52.50; H, 3.16; N, 3.68.

Synthesis of 3-(2-(4-bromophenyl)-2-oxoethyl)-3,4-dihydro quinoxalin-2-(1*H*)-one (4). A mixture of 4-(4-bromophenyl)-4-oxobut-2-enoic acid (**1**) (3 g; 0.01 mol) and *o*-phenylenediamine (1.08 g; 0.01 mol) in ethanol (20 mL) and (4 drops) of acetic acid glacial was refluxed for 2 h. The reaction mixture was allowed to cool and the separated product was filtered and dried. Crystallization of the crude product from toluene then drying, afforded **4** (dark brown powder, 2.58 g (75%) yield, mp 190°C). IR (cm^{-1}): 3300 (NH_2), 3190 (NH) and 1728, 1679 (2C═O). ^{1}H-NMR: δ, ppm (DMSO-d_6): 3.25 (dd, J = 6 Hz, 1H, methylene proton), 3.00 (dd, J = 6 Hz, 1H, other methylene proton), 4.10, 4.12 (dd, J = 6 Hz, 1H, methine proton), 5.69 (s, 1H, NH exchangeable in D_2O), 6.65–8.51 (m, 8H, aromatic protons), 8.87 (S, 1H, NH–CO exchangeable in D_2O). ^{13}C-NMR: δ, ppm (DMSO-d_6); 198.4 (C═O adjacent to aroyl moiety), 172.3 (C═O of quinoxalinone), 135.4, 132.1, 129.4, 128.6 (phenyl carbons), 140.3, 130.7, 128.2, 125.6, 119.1, 117.8 (quinoxalinone), 64.8 (CH_2–H–N), 45.3 (CH_2). *Anal*. Calcd (%): $C_{16}H_{13}BrN_2O_2$ C, 55.67; H, 3.80; N, 8.12. Found (%): C, 55.54; H, 3.74; N, 7.98.

Synthesis of 4-(4-bromophenyl)-2-((2-ethoxy-2-oxoethyl)amino)-4-oxobutanoic acid (5). A mixture of 4-(4-bromophenyl)-4-oxobut-2-enoic (**1**) (3 g; 0.01 mol) and ethyl glycinate hydrochloride (1.39 g; 0.01 mol) in ethanol (30 mL) and (4 drops) of acetic acid glacial and sodium acetate anhydrous (0.82 g; 0.01 mol) was refluxed for 2 h. The reaction mixture was allowed to cool, and the separated product was filtered. Crystallization of the crude product from acetic acid then drying, afforded **5** (white powder, 3.22 g (90%) yield, mp 160°C). IR (cm^{-1}): (OH), 3174 (NH) and 1742, 1685 (2C═O). ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.18 (t, J = 9 Hz, 3H, CH_3 of ester), 4.09 (q, J = 9 Hz, 2H, CH_2 of ester), 3.64, 3.67 (dd, 2H, methylene proton), 4.30, 4.27 (dd, J = 9 Hz 1H, methine proton) 3.64 (dd, J = 9 Hz 2H, CH_2–N), 7.72–7.94 (m, 4H, ArH), 8.16 (s, 1H, NH exchangeable with D_2O), and 9.21 (s, 1H, OH exchangeable with D_2O). ^{13}C-NMR: δ, ppm (DMSO-d_6); 195.4 (C═O adjacent to aroyl moiety), 174.8 (C═O of acid), 171.5 (C═O of ester), 135.2, 130.5, 128.7, 123.2 (phenyl carbons), 60.3 (CH–NH), 56.2 (CH_2 in acrylic system), 52.4 (CH_2 in amino system), 49.2(CH_2 of ester), 14.6 (CH_3 of ester). *Anal*. Calcd (%): $C_{14}H_{16}BrNO_5$. C, 46.92; H, 4.46; N, 3.91. Found (%): C, 46.57; H, 4.33; N, 3.73.

Synthesis of ethyl-2-((5-(4-bromophenyl)-2-oxo-2, 3-dihydrofur an-3-yl)amino) acetate (6). A mixture of acid **5** (3.58 g, 0.01 mol) and acetic anhydride (9.42 mL, 0.1 mol) was refluxed on boiling

water bath for 1 h. The reaction mixture was allowed to cool then poured into ice-water and the separated product was filtered. Crystallization of the crude product from toluene then drying, afforded **6** (dark brown powder, 2.38 g (70%) yield, mp 120°C). IR (cm^{-1}): 3439 (NH), 2982 (CH), and 1782, 1745 (2C═O, bonded and non-bonded). ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.19 (t, 3H, J = 9 Hz, CH_3 of ester), 3.51 (s, 2H, CH_2CO), 4.11 (q, J = 9 Hz, 2H, CH_2 of ester), 4,22 (d, J = 9 Hz, 1H, CH–NH in furanone ring), 5.48 (d, J = 9 Hz, 1H, CH in furanone ring) 7.71–7.79 (m, 4H, ArH), 8.54 (s, 1H, NH exchangeable with D_2O). ^{13}C-NMR: δ, ppm (DMSO-d_6); 171.7 (C═O of ester), 167.9(C═O of furanone ring), 135.3, 130.7, 128.4, 123.9 (phenyl carbons), 145.3 (C–Ar), 97.8 (CH_2 in furanone ring), 60.1 (CH–N), 46.2 (CH_2 in amino system), 49.1 (CH_2 of ester), 14.5 (CH_3 of ester) *Anal.* Calcd (%): $C_{14}H_{14}BrNO_4$ C, 49.43; H, 4.15; N, 4.12. Found (%): C, 49.33; H, 3.95; N, 4.00.

Synthesis of 2-((6-(4-bromophenyl)-3-oxo-2,3,4,5-tetrahydro pyridazin-4-yl)amino) acetohydrazide (7). A mixture of acid **5** (3.58 g; 0.01 mol) and hydrazine hydrate 98% (1.5 mL; 0.04 mol) in ethanol (50 mL) was refluxed for 2 h. The reaction mixture was allowed to cool, and the separated product was filtered. Crystallization of the crude product from ethanol then drying, afforded **7** (yellow powder, 1.87 g (55%) yield, mp 258°C). IR (cm^{-1}): 3386, 3224 (NH bonded and non-bonded), 2962, 2846 (CH), 1635 (C═O). ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.43, 1.45 (dd, J = 6 Hz 2H, CH_2 in pyridazinone moiety), 3.44 (s, 2H, CH_2CO), 4.32 (dd, J = 6 Hz 1H, CH in pyridazinone moiety), 4.86 (br, s, 2H, NH_2 exchangeable with D_2O) 7.70,7.78, 7.81, 7.83 (m, 4H, ArH), 8.55, 8.71 (s, 2H, NH exchangeable with D_2O). ^{13}C-NMR: δ, ppm (DMSO-d_6); 171.4(C═O of hydrazide), 160.3(C═O of pyridazinone), 143.7 (C═N in pyridazinone ring) 134.3, 132.5, 128.7, 123.2 (phenyl carbons), 99.4 (CH–N in pyridazinone ring) 53.8 (CH_2 in amino system), 40.3 (CH_2 in pyridazinone ring). EIMS: *m/z* (%) = (338, 0.19%), (339, 2.20%), and (340, 1.79%) (M^+). *Anal.* Calcd (%): $C_{12}H_{14}BrN_5O_2$. C, 42.37; H, 4.15; N, 20.59. Found (%): C, 42.02; H, 3.93; N, 20.21.

Synthesis of 6-(4-bromophenyl)-4-((2-(3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)-2-oxoethyl)amino)-4,5-dihydropyridazin-3-(2H)-one (8). A mixture of the hydrazide **7** (3.4 g; 0.01 mol) and EAA (1.2 mL; 0.01 mol) and few drops of piperidine in ethanol (30 mL) were refluxed for 4 h. The reaction mixture was allowed to cool, and the separated product was filtered. Crystallization of the crude product from ethanol then drying, afforded **8** (white powder, 2.31 g (57%) yield, mp 244°C). IR (cm^{-1}): 3300 (NH), 3124, 2923, 2854 (CH) and 1650 (C═O). ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.92 (s, 3H, CH_3 in pyrazole ring) 1.45 (dd, J = 6 Hz, 2H, CH_2 in pyridazinone moiety), 2.32 (s, 2H, CH_2 in pyrazole moiety), 3.44 (s, 2H, CH_2CO), 4.32 (dd, J = 6 Hz 1H, CH in pyridazinone moiety), 5.57(s, 1H, NH–CH) 7.70–7.83 (m, 4H, ArH), 8.55 (s,1H, NH–CO). ^{13}C-NMR: δ, ppm (DMSO-d_6); 163.2(C═O adjacent to pyrazole ring), 162.1 (C═O in pyrazole ring), 160.3(C═O of pyridazinone ring), 155.6 (C in pyrazole ring), 143.2 (C═N in pyridazinone ring) 134.3, 130.4,128.7, 123.2 (phenyl carbons), 91.1 (CH–NH), 73.8 (CH_2 in pyrazole ring), 54.9 (CH_2 in amino system), 40.3 (CH_2 in pyridazinone ring), 16.0 (CH_3 in pyrazole ring). *Anal.* Calcd (%): $C_{16}H_{16}BrN_5O_3$. C, 47.31; H, 3.97; N, 17.24. Found (%): C, 47.08; H, 3.65; N, 16.95.

Synthesis of 6-(4-bromophenyl)-4-((2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-oxoethyl)amino)-4,5-dihydropyridazin-3(2H)-one (9). A mixture of the hydrazide **7** (3.4 g; 0.01 mol) and acetyl acetone (1 mL; 0.01 mol) and few drops of piperidine in ethanol (20 mL) were refluxed for 4 h. The reaction mixture was allowed to cool and the separated product was filtered. Crystallization of the crude product from ethanol then drying, afforded **9** (faint yellow powder, 2.14 g (53%) yield, mp 250°C). IR (cm^{-1}): 3300, 3200 (NH), 2931, 2874 (CH) and 1658 (C═O). ^{1}H-NMR: δ, ppm (DMSO-d_6): 2.52, 2.14 (s, 6H, 2 CH_3 groups in pyrazole ring) 1.44, 1.43 (dd, J = 6 Hz, 2H, CH_2 in pyridazinone moiety), 2.32 (s, 1H, CH in pyrazole moiety), 3.41 (s, 2H, CH_2CO), 4.32, 4.28 (dd, J = 6 Hz, 1H, CH in pyridazinone moiety), 7.70–7.83 (m, 4H, ArH), 8.55 (s,1H, NH–CO exchangeable with D_2O). ^{13}C-NMR: δ, ppm (DMSO-d_6); 163.6(C═O adjacent to pyrazole ring), 159.7 (C═O of pyridazinone ring), 156.9,155.3 (2 C in pyrazole ring), 142.1 (C═N in pyridazinone ring) 133.1, 131.7, 128.9, 123.5 (phenyl carbons), 91.6 (CH–NH), 73.8 (CH in pyrazole ring), 54.2 (CH_2 in amino system), 40.6 (CH_2 in pyridazinone ring), 26.3, 16.8 (2 CH_3 in pyrazole ring). EIMS: *m/e* (%): 404(M^+) (0.43%), 405 (M^{+1}) (0.37%), 406 (M^{+2}) (0.21%). *Anal.* Calcd (%): $C_{17}H_{18}BrN_5O_2$. C, 50.51; H, 4.49; N, 17.32. Found (%): C, 50.22; H, 4.32; N, 17.11.

Synthesis of 6-(4-bromophenyl)-4-(((5-methyl-1,2,4-oxadiazol-2-yl)methyl)amino)-4,5-dihydropyridazin-3(2*H*)-one (10). A mixture of the hydrazide **7** (3.4 g; 0.01 mol) and acetyl chloride (2.1 mL; 0.03 mol) in pyridine (20 mL) was refluxed for 3 h. The reaction mixture was allowed to cool then poured into ice and HCl, and the separated product was filtered. Crystallization of the crude product from dioxane, afforded **10** (dark brown powder, 2.00 g (55%) yield, mp >360°C). IR (cm^{-1}): 3432 (NH), 2923, 2869 (CH) and 1650 (C═O). ^{1}H-NMR: δ, ppm (DMSO-d_6): 1.92 (s, 3H, CH_3 in oxadiazole ring) 1.44, 1.42 (dd, J = 6 Hz, 2H, CH_2 in pyridazinone moiety), 3.67 (s, 2H, CH_2 in amino system), 4.32, 4.28 (dd, J = 6 Hz, 1H, CH in pyridazinone moiety), 7.70–7.83 (m, 4H, ArH), 8.57 (s,1H, NH–CO). ^{13}C-NMR: δ, ppm (DMSO-d_6); 162.3(C═O of pyridazinone ring), 157.1, 154.8 (2C in oxadizole ring), 143.7 (C═N in pyridazinone ring) 132.1, 129.4, 124.2, 123.8 (phenyl carbons), 91.7 (CH–NH), 54.5 (CH_2 in amino system), 40.2 (CH_2 in pyridazinone ring), 27.1 (CH_3 in oxadiazole ring). *Anal.* Calcd (%): $C_{14}H_{14}BrN_5O_2$. C, 46.17; H, 3.87; N, 19.23. Found (%): C, 45.87; H, 3.32; N, 18.98.

Synthesis of (*Z*)-2-(6-(4-bromophenyl)-3-oxo-2,3,4, 5-tetrahydro pyridazin-4-ylamino)-*N′*-(4-nitrobenzylidene)acetohydrazide. (11). A mixture of hydrazide **7** (3.4 g; 0.01 mol) and 4-nitrobenzaldehyde (1.5 g; 0.01 mol) and few drops of piperidine in ethanol (20 mL) were refluxed for 4 h. The reaction mixture was allowed to cool and the separated product was filtered. Crystallization of the crude product from toluene then drying, afforded **11** (yellow powder, 4.48 g (95%) yield, mp 266°C). IR (cm^{-1}): 3424, 3313(NH bonded and non-bonded), 1648(C═O). ^{1}H-NMR: δ, ppm (DMSO-d_6): 1.43(dd, J = 6 Hz, 2H, CH_2 in pyridazinone moiety), 3.46 (s, 2H, CH_2CO), 4.31, 4.26 (dd, J = 6 Hz, 1H, CH in pyridazinone moiety), 7.70–7.91 (dd, 8H, ArH), 8.06 (d, J = 6 Hz, 1H, CH═N) 8.51, 8.55 (s, 2H, for 2 NH groups exchangeable in D_2O). ^{13}C-NMR: δ, ppm (DMSO-d_6); 163.6 (C═O adjacent to hydrazide), 160.2 (C═O of pyridazinone ring), 143.1, 142.3 (C═N in pyridazinone ring and C═N in hydrazide), 142.9, 135.5, 132.1, 131.6, 129.7, 128.5, 123.2, 121.9 (of 2 phenyl rings carbons), 90.3 (CH–NH), 54.1 (CH_2 in amino system), 38.9 (CH_2 in pyridazinone ring), *Anal.* Calcd (%): $C_{19}H_{17}BrN_6O_4$. C, 48.22; H, 3.62; N, 17.76. Found (%): C, 48.04; H, 3.00; N, 17.54.

General procedure for the reaction of acid (2, 3) with acetic anhydride. A mixture of the acid (0.01 mol) and acetic anhydride (9.43 mL, 0.1 mol) was refluxed on boiling water bath for 1 h. The reaction mixture was allowed to cool then poured into ice-water and the separated product was filtered.

3-(1*H*-benzimidazol-1-yl)-5-(4-bromophenyl)furan-2(3*H*)-one (12a). This compound was obtained as dark brown powder in 2.2 g (62%) yield, mp 125°C (toluene). IR (cm^{-1}): 1773 (C=O). ^{1}H-NMR: δ, ppm (DMSO-d_6): 5.19 (d, J = 6 Hz, 1H, CH–N), 5.48 (d, 1H, CH in furanone ring), 7.11–8.39 (m, 8H, 2 ArH protons), 8.16 (s, 1H, CH=N in imidazole ring). ^{13}C-NMR: δ, ppm (DMSO-d_6); 168.4 (C=O of furanone ring), 145.3 (C–Ar), 143.5 (carbon of imidazole), 135.9, 130.2, 129.8, 127.2, (phenyl carbons), 144.3, 135.2, 125.6, 123.1, 120.5, 119.8 (benzimidazole carbons), 93.3 (CH in furanone ring), 65.5 (CH–N). EIMS: *m/z* (%) = (15% 355, M^{+1}) and (5% 356, M^{+2}). *Anal*. Calcd (%): $C_{17}H_{11}BrN_2O_2$. C, 57.46; H, 3.09; N, 7.88. Found (%): C, 57.30; H, 2.94; N, 7.65.

2-((5-(4-bromophenyl)-2-oxo-2,3-dihydrofuran-3-yl)amino) benzoic acid (12b). This compound was obtained as yellow powder (toluene), 2.61 g (70%) yield, mp 210°C. IR (cm^{-1}): 3435 (OH), 3100 (NH) and 1782, 1721 (2C=O).^{1}H-NMR: δ, ppm (DMSO-d_6) 3.98 (d, 1H, CH–N), 5.23 (d, J = 6 Hz, 1H, CH in furanone ring), 6.48 (s, 1H, NH), 7.39–7.98 (m, 8H, 2 ArH protons), 13.08 (s, 1H, OH).^{13}C-NMR: δ, ppm (DMSO-d_6); 169.3 (C=O of anthranilic acid moiety), 167.8 (C=O of furanone ring), 146.7 (C–Ar), 135.2, 132.2, 129.7,127.2 (phenyl carbons), 150.5, 131.4, 127.5, 126.9, 120.3, 117.4 (anthranilic benzene ring), 93.6 (CH in furanone ring), 65.9 (CH–N). *Anal*. Calcd (%): $C_{17}H_{12}BrNO_4$. C, 54.57; H, 3.23; N, 3.74. Found (%): C, 54.66; H, 2.92; N, 3.39.

General procedure for the reaction of acid (2, 3) with hydrazine hydrate. A mixture of the acid (0.01 mol) and hydrazine hydrate 98% (1.5 mL; 0.04 mol) in ethanol (50 mL) was refluxed for 2 h. The reaction mixture was allowed to cool and the separated product was filtered.

4-(1*H*-benzimidazol-1-yl)-6-(4-bromophenyl)-4,5-dihydropy ridazin-3(2*H*)-one (13a). This compound was obtained as faint brown (ethyl acetate) in 1.84 g (50%) yield, mp 236°C. IR (cm^{-1}): 3196, 3311(NH – bonded and non-bonded) and 1660 (C=O).^{1}H-NMR: δ, ppm (DMSO-d_6): 1.94, 2.09 (dd, J = 6 Hz, 2H, CH_2 in pyridazinone ring), 4.19, 4.22 (dd, J = 6 Hz, 1H, CH in pyridazinone ring), 6.98 (singlet 1H for one NH exchangeable with D_2O), 7.67–8.06 (m, 8H, ArH), 8.14 (s, 1H, CH in imidazole ring).^{13}C-NMR: δ, ppm (DMSO-d_6); 160.1 (C=O), 144.5 (N–C=N in imidazole moiety), 143.7 (C=N in pyridazinone ring), 134.3, 131.1, 128.9, 123.2, (benzene ring carbons) 144.3, 135.2, 125.6, 123.1, 120.5, 119.8 (benzene ring carbons of benzimidazole), 70.3 (CH–N), 40.8 (CH_2 in pyridazinone). EIMS: *m/z* (%) = (369, 1.45% M^{+1}) and (371, 0.5% M^{+2}). *Anal*. Calcd (%): $C_{17}H_{13}BrN_4O$ C, 55.30; H, 3.55; N, 15.17. Found (%): C, 55.10; H, 3.50; N, 15.10.

2-(6-(4-bromophenyl)-3-oxo-2,3,4,5-tetrahydropyridazin-4-ylamino)benzoic acid. (13b). This compound was obtained as faint brown (ethyl toluene) in 2.91 g (75%) yield, mp 200°C. IR (cm^{-1}): 3241 (NH), 1669 (C=O) and 1609 (C=N).^{1}H-NMR: δ, ppm (DMSO-d_6) 2.46 (dd, J = 6 Hz, 1H, CH_2), 3.38 (dd, J = 6 Hz, 1H, CH_2), 3.31(dd, J = 6 Hz, 1H, CH), 6.48–7.80 (m, 8H, aromatic protons), 9.19, 9.21 (2 s, 2H, for 2 NH which exchanged with D_2O), 11.17 (s, 1H, OH exchangeable with D_2O). ^{13}C-NMR: δ, ppm (DMSO-d_6); 172.9 (C=O of anthranilic acid), 167.3 (C=O of pyridazinone ring), 149.3 (C=N of pyridazinone ring), 135.1, 133.4, 130.4, 131.2, 123.4, 119.5, 116.9, 115.4, 113.7, 111.2 (2 benzene ring carbons), 47.4 (CH–NH), 29.9 (CH_2 in pyridazinone ring) *Anal*. Calcd (%): $C_{17}H_{14}BrN_3O_3$. C, 52.57; H, 3.60; N, 10.82. Found (%): C, 52.30; H, 3.44; N, 10.51.

Synthesis of (*E*)-2-amino-4-(4-bromophenyl)-4-oxobut-2-enoic acid (14). A mixture of acid **2** (3.73 g; 0.01 mol) and hydroxyl amine hydrochloride (0.69 g; 0.01 mol) in pyridine (40 mL) was refluxed for 3 h. The reaction mixture was allowed to cool then poured into ice and HCl. and the separated product was filtered. Crystallization of the crude product from toluene then drying, afforded **14** (faint brown, 1.72 g (64%) yield, mp 198°C). IR (cm^{-1}): 3387 (NH) and 1704, 1670 (2C=O). ^{1}H-NMR: δ, ppm (DMSO-d_6): 6.19 (s, 1H, CH–CO), 6.98 – 8.06 (m – 4H, ArH), 11.74 (s, 2H, NH exchangeable with D_2O) and 12.32 (singlet 1H for one OH exchangeable with D_2O). ^{13}C-NMR: δ, ppm (DMSO-d_6); 167.3 (C=O adjacent to aroyl moiety), 165.8 (C=O of acid), 154.6 (C-NH2), 135.4, 132.6, 130.5, 128.9 (phenyl carbons), 99.4 (CH). *Anal*. Calcd (%): $C_{10}H_8BrNO_3$. C, 44.47; H, 2.99; N, 5.19. Found (%): C, 44.25; H, 2.45; N, 5.07.

Synthesis of 4-acetyl-3-(2-(4-bromophenyl)-2-oxoethyl)-3,4-dihydroquinoxalin-2-yl acetate (15). A mixture of compound **4** (3.45 g, 0.01 mol) and acetic anhydride (9.42 mL, 0.1 mol) was refluxed on water bath for 1 h. The reaction mixture was allowed to cool then poured into ice-water and the separated product was filtered. Crystallization of the crude product from toluene and drying, afforded **15** (brown powder, 1.71 g (40%) yield, mp 130°C). IR (cm^{-1}): 1778, 1685 (2C=O). ^{1}H-NMR: δ, ppm (DMSO-d_6): 1.24, 2.08 (s, 6H, 2 CH_3), 2.25, 2.30 (dd, J = 6 Hz, 2H, CH_2), 3.56 (t, J = 6 Hz, 1H, CH), 7.02–7.77(m, 8H, ArH). ^{13}C-NMR: δ, ppm (DMSO-d_6); 198.4 (C=O adjacent to aroyl moiety), 177.9(O–C=O), 160.9 (N–C=O), 160.2 (C=N of quinoxalinone), 142.6, 133.9, 132.4, 130.1, 129.5, 127.2, 128.7, 125.2, 122.4, 119.8, (2 benzene ring carbons), 50.3(CH–N), 39.5 (CH_2), 21.4, 19.8 (2 CH_3). *Anal*. Calcd (%): $C_{20}H_{17}BrN_2O_4$. C, 55.96; H, 3.99; N, 6.53. Found (%): C, 55.48; H, 4.02; N, 6.36.

Synthesis of 3-(2-(4-bromophenyl)-2-(hydroxyimin o)ethyl)-3,4-dihydroquinoxalin-(1*H*)-one (16). A mixture of compound **4** (3.45 g; 0.01 mol) and hydroxyl amine hydrochloride (0.69 g; 0.01 mol) in pyridine (40 mL) was refluxed for 3 h. The reaction mixture was allowed to cool then poured into ice and HCl. and the separated product was filtered. Crystallization of the crude product from toluene then drying, afforded **16** (yellow powder, 2.59 g (72%) yield, mp 210°C). IR (cm^{-1}): 3431, 3323 (OH bonded and non-bonded), 3186, 3133 (NH bonded and non-bonded), 1702 (C=O for δ-lactam) and 1612 (C=N). ^{1}H-NMR: δ, ppm (DMSO-d_6): 3.30 (dd, J = 6 Hz, 1H, methylene proton), 3.69 (dd, J = 6 Hz, 1H, other methylene proton), 4.20 (dd, J = 6 Hz, 1H, methine proton) 6.65-8.51 (m, 8H, aromatic protons), 8.87 (s, 2H, for 2 NH which exchanged with D_2O) and 11.07 (s, 1H, OH exchanged with D_2O). ^{13}C-NMR: δ, ppm (DMSO-d_6); 172.8 (C=O of quinoxalinone), 155.3 (C=N adjacent to aroyl moiety), 139.4, 135.9, 132.6, 130.2, 129.8, 128.6, 125.8, 123.7, 119.1, 117.9 (2 benzene ring carbons), 64.6 (CH_2–CH–NH), 39.5 (CH_2). *Anal*. Calcd (%): $C_{16}H_{14}BrN_3O_2$. C, 53.35; H, 3.92; N, 11.67. Found (%): C, 53.02; H, 3.63; N, 11.22.

Synthesis of 3-(2-(4-bromophenyl)-2-hydrazonoethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (17). A mixture of compound **4** (3.45 g; 0.01 mol) and hydrazine hydrate 98% (1.5 mL; 0.04 mol) in ethanol (50 mL) was refluxed for 2 h. The reaction mixture was allowed to cool and the separated product was filtered. Crystallization of the crude product from toluene then drying, afforded **17** (yellow powder, 2.80 g (78%) yield, mp 290°C). IR (cm^{-1}): 3372, 3308 (NH), 3053(CH aromatic), 2896 (CH aliphatic), 1679 (C=O) and 1603 (C=N). ^{1}H-NMR: δ, ppm (DMSO-d_6): 3.04 (dd, J = 6 Hz, 1H, methylene proton), 2.75 (dd, J = 6 Hz, 1H, other methylene proton), 4.20 (dd, J = 6 Hz, 1H, methine proton) 6.65-8.51 (m, 8H, aromatic protons), 8.02 (s, 2H, for – NH groups), 8.87 (s, 2H, for NH_2). ^{13}C-NMR: δ, ppm (DMSO-d_6); 172.7 (C=O of quinoxalinone), 161.4 (C=N adjacent to aroyl moiety), 135.8, 134.1, 130.5, 128.6, 127.2, 125.9, 123.5,

122.1, 119.1, 117.6 (2 benzene ring carbons), 64.7 (CH_2–**C**H–NH), 35.3 (CH_2). *Anal*. Calcd (%): $C_{16}H_{15}BrN_4O$. C, 53.50; H, 4.21; N, 15.60. Found (%): C, 53.22; H, 3.96; N, 15.32.

Synthesis of 4-(1*H*-benzo[*d*]imidazol-1-yl)-6-(4-bromophenyl)-2-(2,3,4,5,6-pentahydroxyhexanoyl)-4, 5-dihydropyridazin-3(2*H*)-one (18). A mixture of pyridazinone **13a** (3.7 g; 0.01 mol) and 1,5-[d]-gluconic acid lactone (1.7 g; 0.01 mol) in pyridine (40 mL) was refluxed for 2 h. The reaction mixture was allowed to cool then poured into ice-water. The collected solid was filtered off, washed well with water. Crystallization from ethanol then drying, afforded **18** (white powder, 3.88 g 71% yield, mp 248°C). IR (cm^{-1}): (OH), 2932, 2864 (CH), 1676, 1652 (2C=O). ^{1}H-NMR: δ, ppm (DMSO-d_6) 1.87, 1.96 (dd, 2H, CH_2C=N), 2.29 (S, 1H, CH–CO), 3.54–4.35 (m, CH, 6H, in gluconic chain), 7.67–8.06 (m – 8H, ArH), 8.75 (5 s, 5H, OH groups). ^{13}C-NMR: δ, ppm (DMSO-d_6); 175.8, 160.3 (2C=O), 144.5 (N–C=N in imidazole moiety), 143.7 (C=N in pyridazinone ring), 134.3, 132.9, 132.5, 130.2, 128.6, 125.7, 123.1, 122.5, 119.8, 117.4(2 benzene ring carbons), 70.5 (CH–N), 40.2 (CH_2 in pyridazinone).63–36 (5 carbons in gluconic chain). *Anal*. Calcd (%): $C_{23}H_{23}BrN_4O_7$. C, 50.47; H, 4.24; N, 10.24. Found (%): C, 50.25; H, 4.01; N, 10.11.

Synthesis of 2-acetyl-4-(1*H*-benzo[*d*]imidazol-1-yl)-6-(4-bromophenyl)-4,5-dihydropyridazin-3(2*H*)-one (19). A mixture of pyridazinone **13a** (3.7 g, 0.01 mol) and acetic anhydride (9.42 mL; 0.1 mol) was refluxed on boiling water bath for 2 h. The reaction mixture was allowed to cool and the separated product was filtered. Crystallization of the crude product from ethyl acetate then drying, afforded **19** (faint brown powder, 3.08 g (75%) yield, mp 270°C). IR (cm^{-1}): 1647 (C=O). ^{1}H-NMR: δ, ppm (DMSO-d_6): 1.92, 2.02 (dd, 2H, CH_2 in pyridazinone ring), 2.31 (s, 3H, CH_3), 4.16, 4.21 (dd, 1H, CH in pyridazinone ring), 7.67–8.06 (m, 8H, ArH), 8.14 (s, 1H, CH in imidazole ring).^{13}C-NMR: δ, ppm (DMSO-d_6); 170.5, 162.2 (2C=O), 143.6 (N–C=N in imidazole moiety), 141.2 (C=N in pyridazinone ring), 134.4, 132.6, 131.2, 130.4, 128.9, 126.4, 124.1, 122.5, 119.6, 117.2 (2 benzene ring carbons), 68.7 (CH–N), 40.3 (CH_2 in pyridazinone), 19.6 (CH_3). *Anal*. Calcd (%): $C_{19}H_{15}BrN_4O_2$. C, 55.49; H, 3.68; N, 13.62. Found (%): C, 55.36; H, 3.40; N, 13.43.

Synthesis of ethyl-2-(3-(4-bromophenyl)-6-oxopyridazin-1(6*H*)-yl) acetate (20). A mixture of pyridazinone **13a** (3.7 g, 0.01 mol) and ethyl chloroacetate (5 mL; 0.03 mol) and anhydrous potassium carbonate (4.1 g; 0.03 mol) in (50 mL) acetone were refluxed on water bath for 24 h. The excess solvent was distilled under reduced pressure. The residue was treated with water, filtered, washed with water, and crystallized from ethanol then drying, afforded **20** (colorless needles, 2.62 g (78%) yield, mp170°C). IR (cm^{-1}): 2983 (CH), 1754, and 1670 (2C=O). ^{1}H-NMR: δ, ppm (DMSO-d_6): 1.17 (t, J = 6 Hz, 3H, CH_3 of ethyl ester), 4.13 (q, J = 6 Hz, 2H, CH_2 of ester), 4.92(s, 2H, N–CH_2CO), 6.91, 7.09 (2d, 2H, olefinic protons in pyridazinone moiety), 7.66–7.81 (dd, 4H, ArH). ^{13}C-NMR: δ, ppm (DMSO-d_6); 167.3 (C=O of ester), 159.7 (C=O in pyridazinone ring), 143.4 (C=N in pyridazinone ring), 135.2, 131.5, 128.2, 123.3 (benzene ring carbons), 130.3, 132.6 (2 CH in pyridazinone ring), 61.5 (CH_2 of ester), 54.6 (CH_2-N), 14.5 (CH_3 of ester). *Anal*. Calcd (%): $C_{14}H_{13}BrN_2O_3$. C, 49.87; H, 3.89; N, 8.31. Found (%): C, 49.53; H, 3.61; N, 8.07.

Synthesis of 2-(3-(4-bromophenyl)-6-oxopyridazin-1(6*H*)-yl) acetohydrazide (21). A mixture of the ester **20** (3.37 g, 0.01 mol) and hydrazine hydrate (1.5 mL; 0.03 mol) in ethanol (50 mL) was refluxed for 2 h. The reaction mixture was allowed to cool and the separated product was filtered. Crystallization of the crude product from dioxane then drying, afforded **21** (white powder, 2.58 g (80%) yield, mp 232°C). IR (cm^{-1}): 3483, 3382, 3252, 3125 (NH and NH_2), and1652 (C=O). ^{1}H-NMR: δ, ppm (DMSO-d_6): 4.29(s, 2H, N–CH_2CO), 4.72 (d, J = 6 Hz 2H, NH_2 exchangeable with D_2O), 5.41, 5.07 (2d, 2H, olefinic protons in pyridazinone moiety), 7.06–7.85 (m, 4H, ArH), 9.31 (s, 1H, NH exchangeable with D_2O) ^{13}C-NMR: δ, ppm (DMSO-d_6); 166.8 (C=O of hydrazide), 159.0 (C=O in pyridazinone ring), 143.3 (C=N in pyridazinone ring), 133.9, 130.4, 128.7, 123.1 (benzene ring carbons), 130.6, 132.8 (2 CH in pyridazinone ring), 53.4 (CH_2–N). EIMS: *m/z* (%) = 323, 0.9% (M + 1). *Anal*. Calcd (%): $C_{12}H_{11}BrN_6O_2$. C, 44.60; H, 3.43; N, 17.34. Found (%): C, 44.95; H, 3.30; N, 17.46.

Synthesis of 6-(4-bromophenyl)-2-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxoethyl)pyridazin-3(2*H*)-one (22). A mixture of the hydrazide **21** (3.23 g; 0.01 mol) and acetyl acetone (1 mL; 0.01 mol) and few drops of piperidine in ethanol (20 mL) were refluxed for 4 h. The reaction mixture was allowed to cool, and the separated product was filtered. Crystallization of the crude product from ethanol then drying, afforded **22** (faint yellow powder, 2.43 g (63%) yield, mp 220°C). IR (cm^{-1}): 1666 (C=O).^{1}H-NMR: δ, ppm (DMSO-d_6): 2.39 (s, 3H, CH_3 in pyrazole ring), 2.45 (s, 3H, CH_3 in pyrazole ring), 4.12 (s, 2H, CH_2), 6.08 (s, 1H, CH in pyrazole ring), 6.60 (d, J = 6 Hz 1H, CH in pyridazinone moiety), 6.39 (d, 1H, CH in pyridazinone moiety), 7.67–8.08 (m, 4H, ArH). ^{13}C-NMR: δ, ppm (DMSO-d_6); 163.8 (C=O in side chain), 159.6 (C=O in pyridazinone ring), 151.8, 145.3, 142.87 (carbons in pyrazole ring), 143.2 (C=N in pyridazinone ring), 133.1, 131.7, 128.2, 123.5(benzene ring carbons), 130.4, 132.6 (2 CH in pyridazinone ring), 52.5 (CH_2–N), 26.2, 16.5 (2 CH_3 in pyrazole ring). *Anal*. Calcd (%): $C_{17}H_{15}BrN_4O_2$. C, 52.73; H, 3.90; N, 14.47. Found (%): C, 52.52; H, 3.44; N, 14.11.

Synthesis of 6-(4-bromophenyl)-2-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)pyridazin-3(2*H*)-one (23). A mixture of the hydrazide **21** (3.23 g; 0.01 mol) and acetyl chloride (2.1 mL; 0.03 mol) in pyridine (30 mL) was refluxed for 3 h. The reaction mixture was allowed to cool then poured into ice and HCl, and the separated product was filtered. Crystallization of the crude product from a suitable solvent then drying, afforded **23** (dark brown, 2.01 g (58%) yield, mp >360°C). IR (cm^{-1}): 1666 (C=O). ^{1}H-NMR: δ, ppm (DMSO-d_6): 2.65 (s, 3H, CH_3 in oxadiazole ring), 4.25 (s, 2H, CH_2), 6.60 (d, J = 6 Hz, 1H, CH in pyridazinone moiety), 6.39 (d, 1H, CH in pyridazinone moiety), 7.67–8.08 (m, 4H, ArH). ^{13}C-NMR: δ, ppm (DMSO-d_6); 159.4 (C=O in pyridazinone ring), 148.7, 145.2 (carbons in oxadiazole ring), 143.5 (C=N in pyridazinone ring), 133.4, 130.2, 128.7, 123.9 (benzene ring carbons), 130.5, 132.3 (2 CH in pyridazinone ring), 52 (CH_2–N) 20.4 (CH_3 in oxadiazole ring). *Anal*. Calcd (%): $C_{14}H_{11}BrN_4O_2$. C, 48.43; H, 3.19; N, 16.14. Found (%): C, 48.34; H, 2.95; N, 16.04.

Synthesis of 2-(3-(4-bromophenyl)-6-oxopyridazin-1(6*H*)-yl)-*N*′-(4-nitrobenzylidene) acetohydrazide (24). A mixture of the hydrazide **21** (4.1 g; 0.01 mol) and 4-nitrobenzaldehyde (1.51 g; 0.01 mol) and few drops of piperidine in ethanol (20 mL) were refluxed for 4 h. The reaction mixture was allowed to cool, and the separated product was filtered. Crystallization of the crude product from acetic acid then drying, afforded **24** (yellow powder, 2.87 g (63%) yield, mp 278°C). IR (cm^{-1}): 3201 (NH), and 1673 (C=O). ^{1}H-NMR: δ, ppm (DMSO-d_6): 4.33 (s, 2H, CH_2), 6.54 (d, J = 6 Hz, 1H, CH in pyridazinone moiety), 6.42 (d, J = 6 Hz 1H, CH in pyridazinone moiety), 7.67–7.84 (m, 8H, 2 ArH), 8.8 (d, J = 6 Hz 1H, CH=N) 8.12 (s, 1H, NH exchangeable with D_2O) ^{13}C-NMR:

δ, ppm (DMSO-d_6); 166.1 (C═O of hydrazide), 159.8 (C═O in pyridazinone ring), 143.6 (C═N in pyridazinone ring), 142.3 (C═N in hydrazide) 148.5, 138.7, 135.3, 133.8, 132.5, 130.9, 123.3, 119.2 (2 benzene ring carbons), 130.4, 132.9 (2 CH in pyridazinone ring), 53.3 (CH_2–N). *Anal*. Calcd (%): $C_{19}H_{14}BrN_5O_4$. C, 50.02; H, 3.09; N, 15.35. Found (%): C, 49.82; H, 2.89; N, 15.06.

Synthesis of (*E*)-ethyl 3-(2-(2-(3-(4-bromophenyl)-6-oxopyridazin-1(6*H*)-yl)acetyl)hydrazono)butanoate. (25). A mixture of the hydrazide **20** (3.23 g; 0.01 mol) and EAA (1.2 mL; 0.01 mol) and few drops of piperidine in ethanol (30 mL) were refluxed for 4 h. The reaction mixture was allowed to cool, and the separated product was filtered. After that the mother liquor was allowed to evaporate, the formed compound was separated. It was **25** (white crystals, 0.43 g (10%) yield, mp 160°C). IR (cm^{-1}): 3424(NH), 1751and 1666(2C═O). ^{1}H-NMR: δ, ppm (DMSO-d_6): 1.21 (t, J = 6 Hz, 3H, CH_3 of ester), 1.87 (s, 3H, CH_3), 2.29 (s, 2H, CH_2), 4.15 (q, J = 6 Hz, 2H, CH_2 of ester), 4.95 (s, 2H, N–CH_2CO), 7.12, 7.16 (m, 2H, olefinic proton in pyridazinone moiety), 7.67–8.08 (m, 4H, ArH), 8.46 (s, 1H, NH). ^{13}C-NMR: δ, ppm (DMSO-d_6); 166.3 (C═O of hydrazide), 163.7(C═O of ester), 159.6 (C═O in pyridazinone ring), 143.2 (C═N in pyridazinone ring), 153.6(C═N in hydrazide), 133.1, 131.2, 128.5, 123.9 (benzene ring carbons), 130.4, 132.2 (2 CH in pyridazinone ring), 60.6 (CH_2 of ester), 53.5 (CH_2–N), 42.7(C–CH_2–CO), 14.3 (CH_3 in ester), 12.1 (N═C–CH_3). *Anal*. Calcd (%): $C_{18}H_{19}BrN_4O_4$. C, 49.67; H, 4.40; N, 12.87. Found (%): C, 49.33; H, 3.98; N, 12.55.

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REFERENCES AND NOTES

[1] Onoue, K.; Shintou, T.; Zhang, C. S.; Itoh, I. Chem Lett, 2006, 35(1), 22.

[2] Vitorović-Todorović, M. D.; Juranić, I. O.; Mandić, L. M.; Drakulić B. J. Bioorg Med Chem 2010, 18, 1181.

[3] Koehler, T.; Friedrich, G.; Nuhn, P. Agents Actions 1991, 32, 70.

[4] Koehler, T.; Heinisch, M.; Kirchner, M.; Peindhardt, G.; Hirschelmann, R.; Nuhn, P. Biochem Pharmacol, 1992, 44(4), 805.

[5] Juranic, Z.; Stevovi, L. J.; Drakuli, B.; Stanojkovi, T.; Radulaovi, S.; Juranic, I. J Serb Chem Soc 1999, 64, 505.

[6] Drakulic, B. J.; Stanojkovic, T. P.; Zizak, Z. S.; Dabovic, M. M. Eur J Med Chem 2011, 46, 3265.

[7] Khachatryan, R. A.; Khachikyan, R. J.; Karamyan, N. V.; Panosyan, G. A.; Indzhikyan, M. G. Chem Heterocycl Compd 2004, 40, 446.

[8] Sammour, A.; Elhashash, M. J Prakt Chem, 1972, 314, 906.

[9] Sammour, A.; Elhashash, M. Egypt J Chem 1973, 16, 381.

[10] Elhashash, M.; Hosni, G.; Elkady, M. Rev Roum Chim 1979, 24, 839.

[11] Elhashash, M.; Mahmoud, M.; El-fiky, H. Rev Roum Chim 1979, 24, 1191.

[12] Elhashash, M.; Elkady, M. Y.; Mohamed, M. M. Indian J Chem 1979, 18B, 136.

[13] Elhashash, M.; El-sayed, G. A.; El-Kady, S. S.; Mohamed, S. A.; Egypt J Chem 2008, 1, 103.

[14] Kassab, E. A.; Elhashash, M. A.; Ahmed, E. A. Egypt J Chem 2006, 49, 753.

[15] Risk, S. A.; Elhashash, M.; Mostafa, K. K.; Egypt J Chem, 2008, 51, 611.

[16] Youssef, A. S. A.; Marzouk, M. I.; Madkour, H. M. F.; El-Soll, A. M. A.; Elhashash, M. A. Can J Chem, 2003, 83, 251.

[17] Youssef, A. S.; Madkour, H. M.; Marzouk, M. I.; El-Soll, A. M. A.; Elhashash, M. A. Afinidad 2003, 61, 304.

[18] Upreti, M.; Pant, S.; Dandia, A.; Pant, U. C. Phosphorus Sulfur Silicon 1996, 113, 165.

[19] Nesmeyanov, A. N.; Rybinskaya, M. I.; Rybin, A. I. USP Khim 1967, 36, 1089.

[20] Khachikyan, R. D.; Karamyan, N. V.; Panosyan, G. A.; Indzhikyan, M. G. IZV Akad Nauk Ser Khim 2005, 1923.

[21] Abadi, A. H.; Eissa, A. A. H.; Hassan, G. S. Chem Pharm Bull 2003, 51, 838.

[22] Boiani, M.; Cerecetto, H.; Gonalez, M.; Risso, M.; Olea–Azar, C.; Piro, O. E.; Castellano, E. E.; de Cerain, A. L.; Ezpeleta, O.; A. Monge-Vega, Eur J Med Chem 2001, 36, 771.

[23] Somani, R. R., Shirodkar, P. Y.; Kadom, V. J. Drug Des Discov 2008, 5(6) 364.

[24] Jacob, A. M. Thumpakkara, R. K.; Prathapan, S.; Jose, B. Tetrahedron 2005, 61, 4601.

[25] Piaz, V. D.; Vergelli, C.; Giovannoni, M. P.; Scheideler, M. A.; Petrane, G.; Zaratin, P. Farmaco 2003, 58, 1063.

[26] Khachikyan, R. D.; Karamyan, N. V.; Panosyan, H. A.; Injikyana, M. H.; Russ Chem Bull Int Ed 2005, 54(8), 1982.

[27] El-Hashash, M. A.; El-Sayed, G. A.; El-Kady, S. S.; Mohamed, S. A. Egypt J Chem 2008, 51(1), 103.

[28] EL-Hashash, M. A.; Rizk, S. A.; El-Badry, Y. A. IJBMSP 2012, 2(1), 28.