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Synthesis, Reactions, and Antimicrobial Evaluation of 2-(1,3-dioxoisoindolin-2-yl)acetohydrazide derivatives

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Abstract

New 2-(1,3-dioxoisoindolin-2-yl)acetohydrazide derivatives were synthesized, characterized and evaluated as antimicrobial agents. Phathalic anhydride was reacted with aminoacetoactate to afford phthalimide derivative which reacted with hydrazine hydrate to give New 2-(1,3-dioxoisoindolin-2-yl)acetohydrazide derivative **1**. Compound **1** is used as precursor to synthesize various derivatives depending on types of reactants. Spectroscopic and analytical measurements are used to confirm structures of new products. Antimicrobial evaluation of new derivatives were done.

Keywords: acetohydrazide, triazole, thiazolidinone, benzo[e][1,3]thiazine, Antimicrobial Evaluation

Introduction

Derivatives of phthalimide and thiazolidinone have the potential to be antimicrobial antimycobacterial, anti-inflammatory agents, analgesic, anticonvulsant, and anticancer activities.[1-3] Thiazolidinone scaffold is a versatile substance that can be found in a variety of clinically useful medications.[4, 5] These phthalimide and thiazolidinone derivatives have varied biological applications such as antimicrobial activity antimalarial activity, anticancer activity and antiarrhythmic activity. Besides, Acetic acid and α-methyl acetic acid derivatives as mentioned in literature possess high potency degree as antiinflammation drugs.[6-10]

Literature survey indicated that nitrogen-rich heterocycles such as triazoles, thiadiazoles, and oxadiazoles have attracted attention of many researchers as they have notable biological properties, especially cytotoxic effects.[11-13] These molecules of azoles revealed very intensive antmicrobial, antitumor and anticancer activities. Furthermore, hybrid of thiadiazole-phthalimide and triazole-phthalimide moieties have afforded remarkable cytotoxic effects.[14-16]

Heterocyclic compounds that have five and six membered ring are considered as a pivotal scaffold of targeted drugs in pharmaceutical and medicinal chemistry, this is a results of their resemblance with many biologically efficient compounds in our body. Also, they provide many medicinal and biological applications such as antimicrobial, anticonvulsant, antibacterial, anticancer, anti-inflammatory and antifungal effects.[17, 18]

Pyrimidine and thiopyrimidine scaffolds have been attracted by many researchers because of chemotherapeutic and biological efficiency. Compounds containing pyrimidine ring system are pivotal derivatives that have a wide efficiency of pharmaceutical and medicinal activities such as antibacterial, anticancer, anxiolytic, antiviral, antioxidant, and antidepressant activities[19-25].

According to above survey, the objective in this work is to synthesize a series of phthalimide derivatives containing a various heterocyclic rings such as thiazolidinone ring, triazole, benzo[e][1,3]thiazine and another, and tested antibacterial activity of these novel derivatives which expected to possess a high biological activity.

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Experimental

Electrothermal 9100 instrument is used to measure melting points and they are uncorrected. Elemental analysis was calculated on Vario Elementar at MicroAnalytical Unit, Cairo University-Egypt, the results appeared in expected theoretical range (± 0.4 %). FT-IR (KBr) have been measured at JASCO FTIR-4600 Fourier Transform Infrared Spectrophotometer while Routine NMR was recorded on a BURKER-300 MHz Spectrometers at room temperature in DMSO. Mass spectra of all compounds were measured with a GC Finnigan MAT SSQ-7000 mass spectrometer. TLC silica gel-precoated aluminum sheets are used to follow up of the reactions. IUPAC system is used to detect the chemical compounds names. The isolated crystallized pure materials are the reported yields. Literature conventional procedures are used to purify solvents. 2-(1H-indol-3-yl)acetohydrazide (**1**) was prepared and was used without further purification.

Preparation of 2-((5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)isoindoline-1,3-dione (2)

Starting material **1** (0.01 mol) in ethanolic KOH and Carbon disulfide (0.015 mol) were refluxed with constant stirring on water bath at 70ºC for 10h until reaction completion (no evolution of H_2S). This mixture was evaporated, was added to iced water then dilute HCl was added for acidification to get a precipitate that was filtered with washing with water, dried over suction and recrystallized from ethanol; yield 56% as yellow crystals, m.p.280- 283ºC. It used in the next reaction without purification.

Preparation of 2-((4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)isoindoline-1,3-dione (3)

0.03mol Hydrazine hydrate in 10 ml ethanol was added portion-wise to a stirred solution of 0.01 mol of 2 in (5mL) DMF refluxing for 9h. The reaction mixture monitoring by TLC. The precipitate was obtained, was filtered with washing with ethanol, dried and recrystallized from acetone; yield 32% as pale yellow crystals, m.p.: 188-190ºC [26], FT-IR (KBr): 3440-3330, 3290 (NH, NH_2), 1648, 1636 (C=N), 1224 (C=S) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-D6): δ 3.10 (s, 2H, NH_2, D_2O exchangeable), 4.62 (s, 2H, CH_2), 7.62-7.82 (*2d*, 4H, Ar-H), 8.72 (s, 1H, NH, D_2O exchangeable) ppm. ^{13}CNMR (75 MHz, DMSO-D6): δ 172.9 (C=S), 168.2 (C=O), 161.0 (C=N), 138.2, 125.4, 124.3 (CH, aromatic) ppm. MS (*m/z*, (relative abundance, %)): 275 (M^+, 30); AnalCalcd, for $C_{11}H_9N_5O_2S$ (275.29): C, 47.99; H, 3.30; N, 25.44; S, 11.65; Found: C, 47.51; H, 3.25; N, 25.20; S, 11.35.

Preparation of potassium 2-(2-(1,3-dioxoisoindolin-2-yl)acetyl)hydrazine-1-carbodithioate (4) and 2-((5-mercapto-1,3,4-thiadiazol-2-yl)methyl)isoindoline-1,3-dione (5)

CS_2 (0.005 mol) was poured drop-wise to a mixture of KOH (0.0025 mol) in absolute ethanol (50mL) and compound **1** (0.0025 mol). The reaction mixture stirred at r.t. for 28h. The solid residues that precipitated were filtered off, washed with petroleum ether then ethanol, dried and recrystallized from ethanol to give product **4**. It used in the next reaction without purification.

Compound 4 (0.01 mol) was poured drop-wise to 20mL very cold concentrated sulfuric acid at r.t. for 5h with stirring. The reaction, after completion (TLC), was added potion wise to ice water with stirring with neutralization with Ammonium hydroxide to get a solid product that dried over suction after filtration with water washing, then it was recrystallized from ethanol to afford compound **5**; yield 46% as buff crystals, m.p233-235ºC, FT-IR (KBr): 2500 (SH), 1660 (C=O), 1648, 1624 (C=N) cm^{-1}. ^{1}HNMR (300 MHz, DMSO-D6): δ 1.85 (s, 1H, SH, exchangeable with D_2O), 5.06 (s, 2H, CH_2), 7.61-7.82 (*2d*, 4H, Ar-H) ppm. ^{13}CNMR (75 MHz, DMSO-D6): δ 192.9 (C-S), 168.1 (C=O), 161.2 (C=N), 138.2, 125.4 (CH, aromatic) ppm. MS (*m/z*, (relative -abundance, %)): 277 (M^+, 31); AnalCalcd., for $C_{11}H_7N_3O_2S_2$ (277.32): C, 47.64; H, 2.54; N, 15.15; S, 23.12; Found: C, 47.22; H, 2.34; N, 15.36; S, 23.30.

Preparation of 2-((4-methyl-5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)methyl)isoindoline-1,3-dione (6)

To a mixture of KOH (0.006 mol) in absolute ethanol (30mL) and compound **5** (0.002 mol), add methyl iodide (2g) drop-wise with stirring. The reaction on a water bath was heated for 28h at 60ºC. Then poured onto iced-water to afford a precipitate that was dried over suction and recrystallized (ethanol) to get product 6 (buff crystals) with a yield 50%, m.p211-213ºC, FT-IR (KBr): 1660 (C=O), 1642, 1623 (C=N), 1225 (C=S) cm^{-1}. ^{1}HNMR (300 MHz, DMSO-D6): δ 3.52 (*s*, 3H, CH_3), 5.10 (s, 2H, CH_2), 7.36-7.44 (*2d*, 4H, Ar-H) ppm. MS (*m/z*, (relative abundance, %)): 291 (M^+, 27); AnalCalcd.: $C_{12}H_9N_3O_2S_2$ (291.33): C, 49.47; H, 3.11; N, 14.42; S, 22.01; Found: C, 49.25; H, 3.07; N, 14.38; S, 22.08.

Preparation of 2-((5-(methylthio)-1,3,4-thiadiazol-2-yl)methyl)isoindoline-1,3-dione (7)

The foregoing method was applied using stirring at r.t. for 8h and it was recrystallized from ethyl acetate-petroleum ether to give product **7**; (pale brown, 42%), m.p187-189ºC, FT-IR (KBr): 1662 (C=O), 1623

(C=N) cm^{-1}. ^{1}HNMR (300 MHz, DMSO-D6): δ 2.52 (*s*, 3H, CH_3), 5.13 (s, 2H, CH_2), 7.36-7.44 (*2d*, 4H, Ar-H) ppm. MS (*m/z*, (relative abundance, %)): 291 (M^+, 30); AnalCalcd., for $C_{12}H_9N_3O_2S_2$ (291.34): C, 49.47; H, 3.11; N, 14.42; S, 22.01; Found: C, 49.21; H, 3.09; N, 14.39; S, 22.10.

Synthesis of 5-(1,3-dioxoisoindolin-2-yl)dihydropyridazine-3,4,6(5H)-trione (8)

To 0.25 g Sodium metal in absolute ethanol; 1 mmol hydrazide **1** and (1.5mL; 1.1mmol) diethyloxalate were added then the mixture was stirred with refluxing for 12h. The reaction was left to room temperature to cool, HCl was added to afford a precipitate which was dried over suction and was recrystallized from the proper solvent to have 8 (Yellowish brown, 68%;) m.p. 111-113 oC; FT-IR (KBr): 3446 (NH), 1728, 1719, 1690, 1665 (C=O), 1655 (C=N) cm^{-1}. ^{1}HNMR (300 MHz, DMSO-D6): δ 5.50 (*s*, 1H, CH), 6.81-7.80 (*2d*, 4H, Ar-H), 8.50 (*s*, 1H, NH), 9.20 (*s*, 1H, NH) ppm. MS (*m/z*, (relative abundance, %)): 273 (M^+, 35); AnalCalcd. for $C_{12}H_7N_3O_2$ (273.20): C, 52.76; H, 2.58; N, 15.38; Found: C, 52.55; H, 2.42; N, 15.25.

Synthesis of 2-(1,3-dioxoisoindolin-2-yl)acetyl azide (9)

Acid hydrazide **1** (10mmol) in 20mL hydrochloric acid was stirred at 0-5ºC with addition of $NaNO_2$ sodium nitrite (portion-wise) till effervesce ceased. With continues stirring of reaction for 1h to get a solid that was dried over suction after washing with water then it was recrystallized from ethanol to get product **9.** Data analyses are in accordance with previously reported results [27]. Yellow powder, yield 55%. FT-IR (KBr,): 2210 (N_3), 1711, 1682, 1660 (C=O), 1645 (C=N) cm^{-1}. MS (*m/z*, (relative abundance, %)): 230 (M^+, 60); AnalCalcd., for $C_{10}H_6N_4O_3$ (230.18): C, 52.18; H, 2.63; N, 24.34; Found: C, 52.25; H, 2.58; N, 24.15.

Preparation of N,2-bis(1,3-dioxoisoindolin-2-yl)acetamide (10)

0.01 mol Compound 1 and 0.01mol phthalic anhydride in glacial acetic acid were stirred with refluxing for 12h (TLC). Remove glacial acetic acid with vacuum then reaction residue was added to cold water to get a precipitate which dried over suction after washing it with water, and was recrystallized from proper solvent to afford compound 10. Yield 40% as dark brown crystals (ethanol), m.p148-50ºC, FT-IR (KBr): 3204 (NH), 1705, 1700, and 1682 (C=O), 1640 (C=N) cm^{-1}; ^{1}HNMR (300 MHz, DMSO-D6): δ 4.64 (s, 4H, CH_2- CH_2), 7.64 (br. s, 1H, NH, exchangeable with D_2O), 7.74-7.52 (*2d*, 8H, Ar-H) ppm; ^{13}CNMR (75 MHz, DMSO-D6): δ 168.2, 164.1, 161.3 (C=O), 138.3, 125.5, 124.4, (CH, aromatic), 46.6 (CH_2) ppm. MS (*m/z*, (relative abundance, %)): 349 (M^++1, 61); AnalCalcd., for $C_{18}H_{11}N_3O_5$(349.30): C, 61.89; H, 3.17; N, 12.03; Found: C, 61.75; H, 3.09; N, 12.10.

Preparation of 2-chloro-N'-(2-(1,3-dioxoisoindolin-2-yl)acetyl)acetohydrazide (11)

Anhydrous K_2CO_3 (0.01 mol) and compound **1** (0.01 mol) in 15 mL acetone were stirred then add chloroacetyl chloride (0.01 mol) drop-wise with stirring for 10h at r.t (TLC). The excess anhydrous K2CO3 was filtered and the filtrate concentrated under vaccum the precipitate washed with petroleum ether. Yellow precipitated was obtained and recrystallized from methanol; yield 40% as yellow crystals, m.p. 144-146ºC, FT-IR (KBr, cm^{-1}): 3240, 3230 (br. NHs), 1696, 1684 (C=O). ^{1}HNMR (300 MHz, DMSO-D6): δ 4.66 (s, 2H, CH_2), 4.29 (s, 2H, CH_2), 7.82-7.51 (*2d*, 4H, Ar-H), 8.30 (br., 1H, NH, D_2O exchangeable), 8.70 (s, 1H, NH, D_2O exchangeable) ppm. MS (*m/z*, (relative abundance, %)): 295 (M^+, 27); AnalCalcd., for $C_{12}H_{10}ClN_3O_4$(295.68): C, 48.75; H, 3.41; Cl, 11.99; N, 14.21; Found: C, 48.47; H, 3.33; Cl, 11.85; N, 14.23.

Preparation of 2-(1,3-dioxoisoindolin-2-yl)-N'-(3-thioxo-1,2,3,6-tetrahydro-1,2,4-triazin-5-yl)acetohydrazide (12)

0.01 mol of 11 and 0.01 mol anhydrous K2CO3 in 15 mL DMF, thiosemicarbazide (0.01 mol) was added with stirring and reaction was refluxed for 15h. The reaction was cooled to room temperature then added to iced water to get a precipitate that was filtrated and recrystallized from ethanol to get 12 (brown crystals; 37%) m.p.177-179 oC, FT-IR (KBr,): 3340, 3320, 3310, 3275 (br. NHs), 1685, 1635 (C=O), 1629 (C=N), 1231 (C=S) cm^{-1}. ^{1}HNMR (300 MHz, DMSO-D6): δ 3.48 (s, 2H, CH_2), 4.65 (s, 2H, CH_2), 6.90 (br,s 1H, NH, D_2O exchangeable), 7.31-7.39 (*2d*, 4H, Ar-H), 8.00 (s, 1H, NH, D_2O exchangeable), 8.45 (br. s, 1H, NH, D_2O exchangeable) ppm. MS (*m/z*, (relative abundance, %)): 332 (M^+, 44); AnalCalcd., for $C_{13}H_{12}N_6O_3S$: (332.34) C, 46.98; H, 3.64; N, 25.29; S, 9.65; Found: C, 46.88; H, 3.55; N, 25.35; S, 9.45.

Synthesis of 2-(1,3-dioxoisoindolin-2-yl)-N'-(1-(thiophen-2-yl)ethylidene)acetohydrazide (13)

2-Acetyl thiophene (1mmol) was added compound 1 (1mmol) absolute EtOH (20mL) was refluxed for 9h in the presence of triethyl amine (few drops). The reaction mixture monitoring by TLC. After cooling, a precipitate that was formed, was dried after filtration to recrystallize it with acetone to give compound 13; (brownish yellow, 45%), m.p. >300ºC, FT-IR (KBr): 3254 (br. NH), 1675, 1642 (C=O), 1635 (C=N) cm^{-1}. ^{1}HNMR (300 MHz, DMSO-D6): δ 1.43 (s, 3H, CH_3), 4.64 (s, 2H, CH_2), 7.12-7.52 (m,

3H, thiophene H), 7.84-7.61 (*2d*, 4H, Ar-H), 9.45 (br. s, 1H, NH, D_2O exchangeable) ppm. ^{13}CNMR (75 MHz, DMSO-D6): δ 169.1, 168.3, 163.5 (C=O), 142.0 (C-S), 138.3 (C=N), 138.3, 130.1, 127.7, 127.4, 125.5, 124.4 (CH, aromatic), 14.8 (CH_3) ppm. MS (*m/z*, (relative abundance, %)): 327 (M^+, 44); AnalCalcd. for $C_{16}H_{13}N_3O_3S$: (327.36): C, 58.71; H, 4.00; N, 12.84; S, 9.79; Found: C, 58.62; H, 4.12; N, 12.56; S, 9.70.

Synthesis of 2-(1,3-dioxoisoindolin-2-yl)-N'-(4-fluorobenzylidene)acetohydrazide (14)

Hydrazide **1** (0.01 mol), and p-fluorobenzaldehyde (0.01mol) in absolute ethanol (20mL) was heated in the presence of triethyl amine (few drops) for 10h (TLC). Then it cooled to get a precipitate that dried over suction and recrystallized from ethanol to give compound 14; yield 41% as brown crystals, m.p.190-192 oC, FT-IR (KBr,): 3190 (br. NH), 1680 (C=O), 1637 (C=N), 1600 (C=C) cm-1. 1HNMR (300 MHz, DMSO-D6): δ 7.16-7.37 (m, 8H, Ar-H), 7.71 (s, 1H, CH=N), 9.50 (br. s, 1H, NH, D2O exchangeable) ppm. 13CNMR (75 MHz, DMSO-D6): δ 168.2, 168.0, 163.5 (C=O), 148.3 (C=N), 132.5, 130.4, 127.7, 125.5, 124.4, 115.5 (CH, aromatic) ppm. MS (*m/z*, (relative abundance, %)): 325 (M^+, 49); Anal. Calcd., for $C_{17}H_{12}FN_3O_3$ (325.30): C, 62.77; H, 3.72; F, 5.84; N, 12.92; Found: C, 62.67; H, 3.51; F, 5.64; N, 12.77.

Preparation of 3-((1,3-dioxoisoindolin-2-yl)methyl)thiazolidine-2,4-dione (15)

A mixture of the azide **9** (0.43 g; 1 mmol), and thioglycolic acid (0.12g, 2mmol) in 15mL of dry benzene. The mixture was reflux for the end of 9 (TLC), then under vacuum, it was concentrated, cooled, to get a precipitate that it was filtered, and crystallized to give 15. (white powder; 79%); m.p. 173-174oC[28]; FT-IR (KBr): 1825, 1780, 1723 (C=O), 1612 (C=C) cm^{-1}. ^{1}HNMR (300 MHz, DMSO-D6): δ 3.60 (*s*, 2H, CH_2), 4.60 (*d*, 2H, CH_2), 7.51-7.40 (*2d*, 4H, Ar-H) ppm; MS (*m/z*, (relative abundance, %)): 276 (M^+, 35); AnalCalcd. for $C_{12}H_8N_2O_4S$ (276.27): C, 52.17; H, 2.92; N, 10.14; S, 11.60; Found: C, 52.25; H, 2.63; N, 10.31; S, 11.41

Preparation of 2-(2-oxo-2-(3-oxobenzo[d]isothiazol-2(3H)-yl)ethyl)isoindoline-1,3-dione (16)

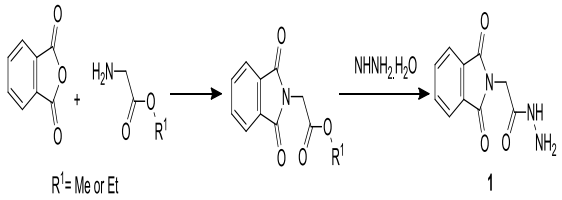
The preparation method of **15** was done except thiosalicylic acid (1.5mmol) was added instead of to get product **16** as yellow precipitate with yield 63%; m.p. 122-124 ^{o}C; FT-IR (KBr): 1833, 1755, 1718 (C=O) cm^{-1}. ^{1}HNMR (300 MHz, DMSO-D6): δ 5.20 (*s*, 2H, CH_2), 7.27-7.85 (*m*, 8H, Ar-H) ppm; MS (*m/z*, (relative abundance, %)): 338 (M^+, 35); Anal.Calcd.for $C_{17}H_{10}N_2O_4S$ (338.34): C, 60.35; H, 2.98; N, 8.28; S, 9.48; Found: C, 60.24; H, 2.77; N, 8.35; S, 9.52.

Preparation of 2-(2-oxo-2-(3-oxo-1,3-dihydro-2H-indazol-2-yl)ethyl)isoindoline-1,3-dione (17)

(0.68 g, 5 mmol) of anthranilic acid with Azide **9** (5 mmol) in of dry dioxane were refluxed for 5h (TLC) to get a solid that was collected and was recrystallized from ethanol to afford **17**. Yellow crystals; Yield 65%; m.p. 123-124 ^{o}C; FT-IR (KBr): 3444 (NH), 1833, 1755, 1718 (C=O) cm^{-1}. ^{1}HNMR (300 MHz, DMSO-D6): δ 5.20 (*s*, 2H, CH_2), 6.30 (*s*, 1H, NH), 7.20-7.92 (*m*, 8H, Ar-H) ppm; MS (*m/z*, (relative abundance, %)): 321 (M^+, 25); AnalCalcd.for $C_{17}H_{11}N_3O_4$ (321.29): C, 63.55; H, 3.45; N, 13.08; Found: C, 63.43; H, 3.56; N, 13.12.

Results and Discussion

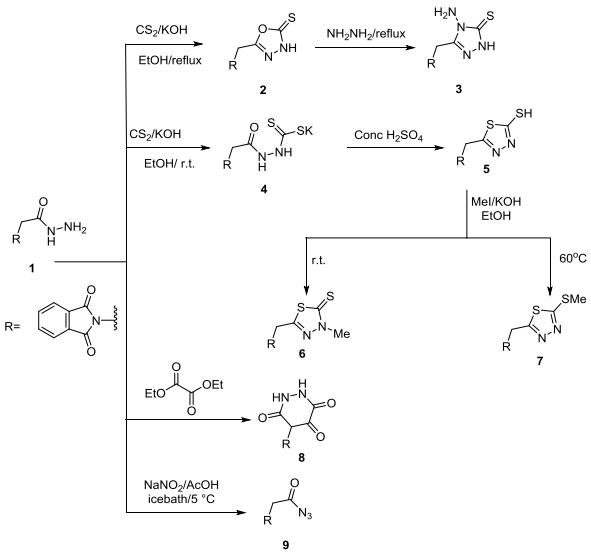
Phthalic anhydride reacted with alkyl glycinate (methyl or ethyl) to afford alkyl 2-(1,3-dioxoisoindolin-2-yl)acetate (methyl or ethyl) in a good yield which reacted with hydrazine hydrate to afford 2-(1,3-dioxoisoindolin-2-yl)acetohydrazide (**1**) in an excellent yield (Scheme 1). Data analyses are in accordance with previously reported results [29-32].



Scheme1

2-(1,3-Dioxoisoindolin-2-yl)acetohydrazide (**1**) is used as precursor to synthesize a panel of new efficient compounds such as 1,2,4-triazole, 1,3,4-thiadiazole, pyridazinetrione and another thiazolidine-2,4-dione, benzo[e][1,3]thiazine and quinazolinedione ring systems.

Compound **1** reacted with carbon disulfide in ethanolic potassium hydroxide solution at reflux temperature to compound **2** that reacted in DMF with hydrazine hydrate in absolute ethanol at reflux temperature to give compound **3** [26](Scheme 1). While compound **1** was reacted under the same condition at room temperature to afford compound **4** that cyclized in conc. sulfuric acid to thiadiazole derivative **5**(Scheme 1). Compound **5** was methylated with methyl iodide in ethanolic potassium hydroxide solution to afford compounds **6** and **7** respectively according to reaction conditions [33](Scheme 1).



Scheme 2

Structures of compounds **2-7** were elucidated in accordance with elemental and spectroscopic analyses. Routes for the formation mechanism of such compounds is depicted in literature [34]. Compound **3** revealed absorption bands in its IR (cm^{-1}, KBr) at 3440-3330, 3290 (NH, NH_2), 1648, 1636 (C=N), 1224 (C=S). Also, 1HNMR (270 MHz, DMSO-D6) δ 3.11 (s, 2H, NH_2, D_2O exchangeable), 4.62 (s, 2H, CH_2), 7.62-7.82 (*2d*, 4H, Ar-H), 8.72 (br. s, 1H, NH, D_2O exchangeable) ppm. ^{13}CNMR (DMSO-D6): δ 192.9 (C-S), 168.1 (C=O), 161.2 (C=N), 138.2, 125.4 (CH, aromatic) ppm (*cf.* Experimental).

Also, 5-(1H-indol-3-yl)dihydropyridazine-3,4,6(5H)-trione (**8**) was synthesized through reaction of compound **1** diethyloxalate and Na metal in absolute ethanol at reflux for 12h (Scheme 1). While 2-(1H-indol-3-yl)acetyl azide (**9**) was prepared via reaction of hydrazide **1** in acidic medium with addition of sodium nitrite portion-wise till effervesces (Scheme 1). Their structures were elucidated through elemental and spectroscopic analyses (*cf.* Experimental).

Mechanism of azide formation from hydrazides is depicted in the following figure which indicted that after diazotisation the adjacent N donates the lone pair to the N^{2+} group making the final product as azide (Figure 1).[35]

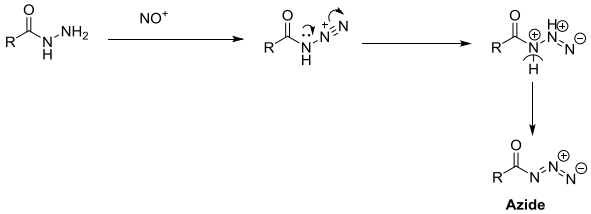
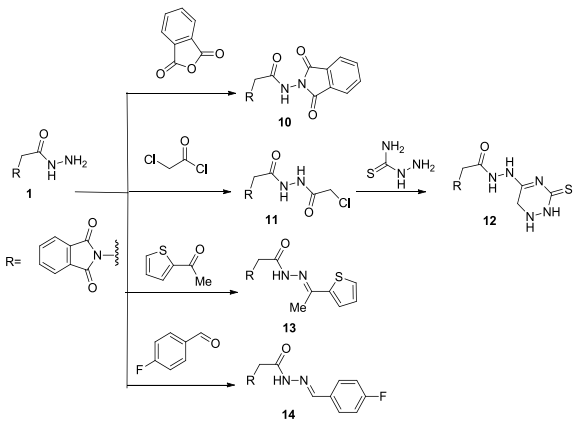


Figure 1: Mechanism of azide formation from hydrazides

Condensation reaction was done between hydrazide **1** and phthalic anhydride in glacial acetic acid at reflux temperature to afford N,2-bis(1,3-dioxoisoindolin-2-yl)acetamide (**10**), while compound **1** reacted with chloroacetyl chloride which was added drop-wise with stirring in presence of anhydrous K_2CO_3 to give compound **11**, this compound reacted with thiosemicarbazide in DMF at reflux to afford compound **12** (Scheme 3).

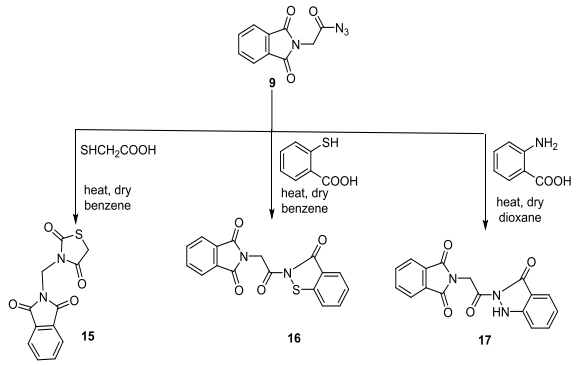


Scheme 3

Also, 2-acetyl thiophene and p-fluorobenzaldehyde reacted with hydrazide **1** in presence of triethylamine at reflux to afford Schiff base derivatives **13** and **14**, respectively (Scheme 3). Structures of compounds **10**-**14** were elucidated according to their elemental and spectroscopic analyses (cf. Experimental).

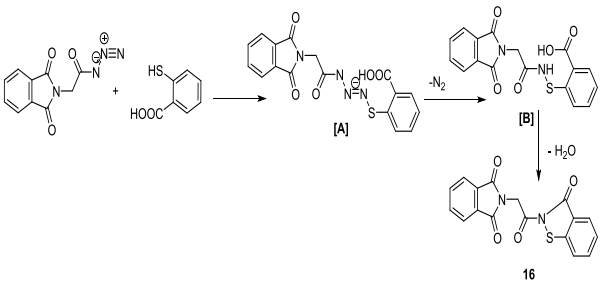
2-(1,3-Dioxoisoindolin-2-yl)acetyl azide (**9**) as starting material is used in reaction with thioglycolic acid, thiosalicylic acid, or anthranilic acid to afford thiazolidine-2,4-dione derivative 15, benzo[e][1,3]thiazine derivative 16, and quinazoline-2,4(1H,3H)-dione derivative respectively (Scheme 4). [36]Structures of compounds **15**-**17** were elucidated according to their elemental and spectroscopic analyses (cf. Experimental).

Azide derivative **9** reacted with thioglycolic acid in dry benzene under refluxing to afford new 3-((1,3-dioxoisoindolin-2-yl)methyl)thiazolidine-2,4-dione (**15**). In the same manner, 3-oxobenzo[d]isothiazol-2(3H)-yl **16** and 3-oxo-1,3-dihydro-2H-indazol-2-yl **17** derivatives had been obtained via reaction of azide **9** with thiosalicylic acid and anthranilic acid, respectively under the same conditions (Scheme 4).[37, 38]



Scheme 4

Proposed mechanistic framework for formation of compounds **15-17** is depicted in Scheme 5, intermolecular coupling between thiol and azide terminal nitrogen to form thiotriaz-2-en-1-ide intermediate [A] which extrude nitrogen molecule to afford acetamidothio benzoic acid intermediate [B] that is cyclized via extrusion of water molecule to afford compound **16** (Scheme 5).



Scheme 5

Antimicrobial Activity

Using agar cup plate method, most of our products were investigated for antimicrobial activity on four different test microbes (*Staphylococcus aureus* as Gram positive, *Escherichia coli* as Gram negative, and *Candida albicans* as yeast in comparison with reference antibiotics that were antimicrobial Cephradine and antifungal Nizo-arm. Table 1 showed the results that indicated that, some of the investigated products showed strong antifungal activity against *Candida albicans* by measuring inhibition zone diameter in millimeter. Also, compounds **15-17** have strong antibacterial activity against two types of bacteria together with *Candida albicans*. Also, starting material **1** showed no activity against *Candida albicans* or bacteria. Compounds **5, 7** showed no activity against *Staphylococcus aureus* (Gram +ve) and showed a good activity against *Candida albicans* with inhibition zone of (18mm and 16mm), respectively. Most of compounds showed no activity against *Escherichia coli* (Gram -ve) except compounds **3, 5, 8**, and **15-17**.

Table 1. Antimicrobial activity of all compounds against microorganisms

Sample Name	Clear zone (ϕmm)		
	Staphylococcus aureus	***Escherichia coli***	***Candida albicans***
1	**10**	**11**	**12**
3	13	14	17
5	**0**	16	18
7	**0**	**0**	16
8	12	16	15
9	13	**0**	**30**
10	12	**0**	**21**
12	15	**0**	**20**
13	12	**0**	**23**
14	13	12	**28**
15	**18**	**16**	**23**
16	**21**	**17**	**20**
17	**22**	**15**	**21**
Ref.*	**17**	**15**	**20**

**Reference antibiotics are antimicrobial Cephradine and antifungal Nizo-arm.*

Conclusion

The reactions of hydrazide derivative with different reagents revealed formation of various products depending on the nature of the reagents. The preferred site of attack is the less steric hydrazide. The synthesized compounds were evaluated for their antimicrobial activities. The antimicrobial activity of most of the new compounds showed moderate selectivity against fungi. Compounds **15-17** showed a good activity against *Staphylococcus aureus, Escherichia coli* and *Candida albicans.* The antimicrobial activity of the active compounds is a consequence of the biological and pharmacological activity due to presence of new added moieties and not related to phthalimide derivatives as starting material which has no antimicrobial activity.

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