

Microwave assisted the short time clean synthesis of 1,3-Diketones as Building Blocks in Heterocyclic Synthesis: A Facile Synthesis and Antimicrobial Evaluation of New Dihydropyridine, 4H-Pyrane, Dihydropyridazine, Pyrimidine and Pyrazole derivatives

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Abstract

Background: According to literature survey, the compounds bearing naphthalene moiety can be used as medical preparations because of their wide spectrum of biological activity and low toxicity. In this study, a new series of azoles or azines were synthesized from the reaction of the key intermediate 1-(1-hydroxynaphthalen-2-yl)-3-phenylpropane-1,3-dione **3** with a variety of electrophilic and nucleophilic reagents under a variety of mild conditions.

Results: The chemical structures of these compounds were confirmed by various spectroscopic methods such as (IR, ^1H -NMR, ^{13}C -NMR, mass spectral data and elemental analyses).

Conclusions: The prepared compounds were screened in vitro for their antimicrobial activity against some species of Gram-positive bacteria (***Staphylococcus aureus*** and ***Bacillus subtilis***) and Gram-negative bacteria (***Escherichia coli*** and ***Pseudomonas aeuroginosa***). Anti-fungal activities of the compounds were tested against yeast and mycelial fungi, ***Candida albicans*** and ***Aspergillus flavus***. The antimicrobial activity of this series was showed either weak or moderate activities.

Background

Heterocyclic compounds containing nitrogen, sulfur and oxygen atom are found to possess a variety of biological activities. Amongst them, pyrazoles, cyanopyridines, pyrimidinethiones and pyranes or their fused ring systems are found to exhibit a wide spectrum of biological activities, including antibacterial and antifungal activities. Various biological applications have been reported for pyrazoles such as anticancer, anti-tumor, antiviral, anti-inflammatory, antifungal, analgesic, antipyretic, antimicrobial, antihistaminic, antiplatelet, antihyperglycemic, sedative, hypnotic activity [1–6], antidepressant [7], anticonvulsant [8]. Cyanopyridine derivatives have attracted considerable attention as they appeared of interest to possess anticancer [9], anti-tumor [10] and antimicrobial [11] activities. Pyrimidinethiones have been found to possess antitubercular [12]. Pyrane and fused 4H-pyrane derivatives have attracted a great interest owing to their antimicrobial activity [13–15], inhibitors of influenza virus sialidases [16], mutagenic activity [17], antiviral [18] and anti-tumor [19]. Also Pyridazine ring is a nucleus of a many of drugs available in the market like cadralazine (antihypertensive), minaprine (antidepressant), hydralazine (smooth muscle relaxant), pipofezine (tricyclic antidepressant) [20, 21]. So, we report here the utility of **3** in the synthesis of unique heterocycles of expected biological interest.

Results And Discusion

Organic synthesis by using microwave irradiation (MW) is a new and interesting technique and is becoming popular now. The reactions under microwave irradiation take place in few minutes and no solvent is required [22–25]. In continuation to our research for chemistry developments [26–29], we report here the use of microwave irradiation for the synthesis of 1-(1-hydroxynaphthalen-2-yl)-3-phenylpropane-1,3-dione **3** in a quantitative yield (91%) from the reaction of α -naphthol and ethyl benzoylacetate in the presence of zinc chloride [30, 33]. Rather than the expected coumarin **4** as literature [31–32]. The structure of the latter product **3** was established on the basis of its elemental analyses and spectral data and chemical transformation.

Thus, the infrared spectrum of compound **3** revealed absorption bands at 3365, 3061, 2924, 1720, 1639 cm⁻¹ for hydroxyl, CH-aromatic, CH-aliphatic and carbonyl function groups, respectively; ¹H-NMR spectrum of compound **3** showed the following signals at d = 4.49 (s, 2H, CH₂), 7.20-8.68 (m, 11H, aromatic H), 8.69 (s, 1H, OH). Also, the mass spectrum of compound **3** is in agreement with the proposed structure, its showed a molecular ion peak at m/z = 290 (M⁺) in agreement with its molecular formula C₁₉H₁₄O₃ [33].

The active methylene group in compound **3** was exploited to synthesize some novel heterocyclic compounds by its reaction with some electrophilic and nucleophilic reagents. Thus, condensation of **3** with dimethylformamide-dimethylacetal (DMF-DMA) in dioxane afforded the enaminone derivative **5** in good yield as demonstrated in (scheme 2). Establishing the structure **5** was based on its elemental analyses and spectral data. Thus, ¹H-NMR spectrum of compound **5** showed the following signals, a singlet signal at d = 3.00 ppm assigned to N(CH₃)₂, a singlet signal at d = 7.19 ppm assigned to olifinic proton, a multiplet signal at d = 7.64 - 8.67 ppm assigned to aromatic protons and a singlet signal at d = 8.68 ppm assigned to hydroxyl group. Moreover, the mass spectrum revealed a molecular ion peak at m/z = 345 (M⁺) related to molecular formula C₂₂H₁₉NO₃. Also, when compound **3** was alkylated with triethylorthoformate in refluxing acetic anhydride afforded the ethoxymethylene derivative **6**. Establishing of the structure **6** was based on spectral data in addition of elemental analyses. So, its ¹H-NMR spectrum in DMSO-d₆ revealed the following signals at d = 1.11 (t, 3H, CH₃), 4.19 (q, 2H, CH₂), 6.33 (s, 1H, CH-olifinic), 7.29-8.23 (m, 11H, aromatic H), 8.68 (s, 1H, OH). The mass spectrum of the same product is in accordance with the proposed structure. Thus, it showed a molecular ion peak at 346 (M⁺).

Compound **5** readily reacted with cyanothioacetamide as example of active methylene reagents in refluxing ethanolic sodium ethoxide yield the expected pyridinethione derivative **10** which established on its spectral data (¹H-NMR, mass spectra and elemental analyses). So, its mass spectrum revealed a molecular ion peak at m/z = 384 (M⁺⁺²) corresponding to molecular formula C₂₃H₁₄N₂O₂S. Formation of pyridinethione **10** is believed to be proceed via initial addition of active methylene moiety in cyanothioacetamide on the π- bond system of carbonyl group of **5** to afford the Michael adduct **8** that cyclizes by losing water under the same reaction condition to give intermediate **9** which eliminate dimethylamine molecule to yield the final structure **10** as demonstrated in (scheme 2) [34]. Furthermore, the behavior of enaminone **5** toward binucleophilic reagents was also investigated. Thus, when **5** is allowed to react with hydrazine hydrate a compound with a molecular formula C₂₀H₁₄N₂O₂ = 314 (M⁺) is formed which may be formulated as structure **14** based on spectroscopic data. Thus ¹H-NMR spectrum of compound **14** showed a singlet signal at d = 7.22 assigned to pyrazole-H, a multiplet signals at d = 7.31-8.71 assigned for CH aromatic and NH proton and a singlet signal at d = 8.73 assigned to OH group. On the other hand, compound **6** was reacted with hydrazine hydrate to afford the product identical in all respects (mp, mixed mp, and spectral data) with those corresponding to the pyrazole derivative **14** as demonstrated in (scheme 2).

Similarly, reactions of enaminone **5** with urea or thiourea to yield the expected pyrimidine derivatives **16a,b**. Compounds **16a,b** were established on its correct spectral data (IR,¹H-NMR, mass spectra and elemental analyses). Also, enaminone **5** reacted with guanidine hydrochloride to yield the pyrimidine derivative **18** which established on spectral data. On the other hand, reaction of enaminone **5** with hydroxylamine

hydrochloride in ethanol containing anhydrous sodium acetate afforded the isoxazole derivative **20**. Structure **20** was established based on its elemental analyses and spectroscopic data. Thus, the ¹H-NMR of **20** revealed the presence of a singlet signal at δ = 7.21 ppm corresponding to the isoxazole proton and a multiplet signal at δ = 7.31-8.70 ppm corresponding to aromatic protons and a singlet signal at 8.71 ppm corresponding to OH group. The mass spectrum of compound **20** is revealed a molecular ion peak at m/z = 315 (M^+) corresponding to the molecular formula $C_{20}H_{13}NO_3$ as demonstrated in (scheme 3).

3-phenylpropane-1,3-dione derivative **3** was examined as a key precursor toward a variety of nucleophilic and electrophilic reagents aiming at exploring its synthetic potentiality. Thus, when compound **3** was reacted with hydroxyl amine hydrochloride to yield the isoxazole derivative **23** in good yield. Compound **23** was established based on its spectral data (IR, ¹H-NMR, mass spectra) and elemental analyses. ¹H-NMR of the compound **23** showed a singlet signal δ = 7.21 ppm assigned to CH-isoxazole, a singlet signal at δ = 8.69 ppm assigned to OH group beside the multiplet signal at δ = 7.32-8.54 ppm assigned to aromatic protons. The mass spectrum showed a molecular ion peak at m/z = 287 (M^+) corresponding to molecular formula $C_{19}H_{13}NO_2$ as demonstrated in (scheme 4).

The reactivity of compound **3** toward active methylene reagents was also investigated and found to afford new pyridinone derivative. Thus, when compound **3** was reacted with malononitrile in ethanolic sodium ethoxide, a product **26** with molecular formula $C_{22}H_{14}N_2O_2$ was obtained as the sole isolable product through the intermediates **24** and **25** [35]. On the other hand, reactions of **3** with a mixture of malononitrile and elemental sulfur in ethanolic piperidine afforded the expected thiophene derivative **29** as demonstrated in (scheme 5) [34]. Assignment of structure **29** for the reaction product was based on its correct elemental analyses and compatible spectroscopic data, ¹H-NMR of the structure revealed a singlet signal at δ = 8.69 ppm corresponding to OH group beside the multiplet signals corresponding to the aromatic protons and NH_2 at δ = 7.20-8.68 ppm. Also, the mass spectrum showed a molecular ion peak at m/z = 370 (M^+) corresponding to the molecular formula $C_{22}H_{14}N_2O_2S$.

One-pot reaction of a mixture of compound **31** and dimedone in the presence of ammonium acetate afforded the tetrahydroquinoline derivatives **35a-c**. Assignment of structure **35b** as example for the reaction product was based on its compatible spectroscopic data. Thus, its IR spectrum showed absorption bands at 3371, 3255 cm^{-1} for (OH/NH), 3059 cm^{-1} for (CH-arom), 2954-2835 cm^{-1} for (CH-aliph) and 1639, 1620 cm^{-1} for (2C=O) group. However, the ¹H-NMR of compound **35b** for example showed a singlet signals at δ = 0.82, 1.19 ppm corresponding to $2CH_3$, two singlet signals at δ = 2.70 ppm and at δ = 2.86 ppm corresponding to two methylene groups of dimedone, a singlet signal at δ = 3.70 ppm assigned to OCH_3 protons, a singlet signal at δ = 4.49 ppm assigned to CH-pyridine, a singlet signal at δ = 8.45 ppm assigned to OH group beside the multiplet signals at δ = 7.21-8.28 ppm assigned to aromatic protons and NH. The mass spectrum of the same compound revealed a molecular ion peak at 529 (M^+) and a number of fragments which agree with the proposed structure. The formation of **35a-c** can be understood in terms of the Michael type addition of the active methylene group in the dimedone molecule to the activated double bond in the compound **31** to yield the Michael adduct **33** and cyclized to **34**, the intermediate **34** was oxidized by loss of water to yield the final product **35** [36-38] as demonstrated in (scheme 6).

Reactions of compound **3** with some electrophilic reagents under alkaline conditions were also investigated. Thus, 4H-pyran-3-carbonitrile **40a,b** were synthesized in an excellent yield upon treatment of **3** with arylidinemalononitrile **36a-b** in the presence of a catalytic amount of piperidine. The structures of compounds **40a,b** were established based on analytical and spectral data. Products **40a,b** are apparently formed via a Michael type addition of the active methylene group in compound **3** to the activated double bond in arylidinemalononitrile **36a,b** to form the non-isolable intermediate **39** through an intramolecular cyclization and subsequent tautomerization to give **40a,b**. Also, compound **3** was reacted with arylidinecyanothioacetamide to yield the acceptable pyridinethione derivatives **45a-c**. We first assumed that the reaction product is formed via addition of active methylene to a, β -unsaturated linkage and subsequent water elimination from carbonyl benzoyl group to yield the cyclic intermediate **44** which aromatized by loss of H₂ to yield the pyridinethione **45** as demonstrated in (scheme 7). Confirmation of pyridinethiones **45** based on its compatible spectroscopic data. Thus, the ¹H-NMR spectrum of compound **45b** for example showed a singlet signal at d = 3.87 ppm assigned for OCH₃, a singlet signal at d = 8.74 ppm assigned to OH, a singlet signal at d = 9.87 ppm assigned for NH group in addition to a multiplet signal at d = 7.12-8.73 ppm assigned to aromatic protons [34, 39-40].

Similarly, reaction of **3** with cyclopentylidenecynothiocetamide and cyclohexylidenecynothioacetamido **46a,b** yield the azaspiro derivatives **49a,b** through the intermediate **47**and **48** [41] as demonstrated in (scheme 8). Establishing the spiro derivatives was based on its compatible spectroscopic data and elemental analyses.

Coupling of propane-1,3-dione derivative **3** with diazotized aromatic amines in ethanol buffered with sodium acetate at 0-5 °C afforded the aryl hydrazones **51a-c**. The aryl hydrazones were established based on its compatible spectroscopic data and elemental analyses. Condensation of **51** with malononitrile proceeded very readily by fusion in the presence of ammonium acetate to yield the pyridazine derivatives **54 a-c**. Compound **54a-c** were established based on spectral data (IR, ¹H-NMR and mass spectra) and elemental analyses. Thus, ¹H-NMR spectrum of **54a** for example revealed a singlet signal at d = 3.99 ppm assigned to OCH₃, a singlet signal at d = 8.71 ppm assigned to OH group in addition to a multiplet signal at d = 6.68-8.25 ppm corresponding to aromatic protons and NH. Also, the mass spectrum of the same compound revealed a molecular ion peak at 472 (M⁺) corresponding to the molecular formula C₂₉H₂₀N₄O₃ and a number of fragments which agree with the proposed structure [42] (scheme 9).

In vitro antimicrobial activity

The newly synthesized compounds have been screened for antibacterial activity against some species of Gram-positive bacteria (**Staphylococcus aureus** and **Bacillus subtilis**) and Gram-negative bacteria (**Escherichia coli** and **Pseudomonas aeuroginosa**). Anti-fungal activities of the compounds were tested against yeast and mycelial fungi; **Candida albicans** and **Aspergillus flavus**, respectively. Each tested compound was dissolved in DMSO making a solution concentration of 1.00 mg/mL and loaded separately in paper discs of Whatman filter paper with equal diameter size (10 mm), Paper discs were sterilized in an autoclave. The paper discs loaded with the desired concentration of the complex solution, were placed aseptically in the petri dishes containing nutrient agar medium (agar 20 g + beef extract 3 g + peptone 5 g)

inoculated with *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeuroginosa*, *Candida albicans* and *Aspergillus flavus*. The petri dishes were incubated at 36 °C. The inhibition zones were recorded after 24 hrs of incubation in case of bacteria and yeast and after 5-6 days in case of mycelial fungi. Each treatment was replicated three times [43-44]. **Ampicillin** and **clotrimazole**, were used as a common standard antibiotic and antifungal agents, respectively. They prepared using the same procedure as above at the same concentration and solvents. The % activity index was calculated for the tested compounds by using the given formula in equation (1).

See Formula 1 in Supplementary Files.

Minimum inhibitory concentration (MIC) measurement

The minimum inhibitory concentration (MIC) was determined using the disc diffusion technique by preparing discs containing 1.9-1000 µg/mL of each compound against Gram-positive *Staphylococcus aureus*, *Bacillus subtilis* and Gram-negative *Escherichia coli*, *Pseudomonas aeuroginosa*. The anti-fungal activities of the compounds were tested against two fungi *Candida albicans* and *Aspergillus flavus*. The twofold dilutions of the solution were prepared. The microorganism suspensions at 10 CFU/mL (colony forming unit/mL) concentration were inoculated to the corresponding wells. The plates were incubated at 36 °C for 24 hrs for the bacteria. The standard antibiotic **ampicillin** and antifungal **clotrimazole** was also recorded using the same procedure as above at the same concentration and solvents. At the end of the incubation period, the minimum inhibitory concentrations (MIC) values were recorded as the lowest concentration of the substance that had no visible turbidity. Control experiments with DMSO and uninoculated media were run parallel to the test compounds under the same condition. **Table 1 and 2** illustrated the results of antimicrobial and antifungal activity and it's MIC. The results which are illustrated in **Table 1** showed that most of tested compounds were active against most of micro-organisms used. Both of compounds **45c** and **5** showed no antibacterial or antifungal activity. On the other side each of compound **29** and **54a** showed maximum antibacterial and antifungal activity. Compound **51a** has no antibacterial activity against Gram-negative bacteria only, although it have broad spectrum antibacterial activity against Gram-positive bacteria and antifungal activity against *C. albicans* and *A. flavus*. On the other hands, compound **23** showed narrow spectrum antibacterial activity against *P. aeuroginosa* (a Gram-negative bacteria) and *S. aureus* (a Gram-positive bacteria) and revealed no antibacterial activity against *E. coli* (a Gram negative bacteria) and *B. subtilis* (a Gram-positive bacteria), but in case of compound **40b** it has no antibacterial activity against *B. Subtilis* only and has narrow range spectrum as antibacterial agent against *S. aureus*, *E. Coli* and *P. aeuroginosa* with also small rang spectrum antifungal activity. All the other compounds (**3, 35b, 26, 35c, 35a, 40a, 10, 16a, 14, 49a**) indicated wide range spectrum antibacterial and antifungal activity.

From **Table 2**, we observed that compounds **29, 35a, 10, 54a and 16a** showed the lowest minimum inhibitory concentrations (MIC) for most tested bacteria and fungi, while compounds **40a, 40b, 35c** and **49a** exhibited high concentrations of MIC as compared with standard antimicrobial agents used.

Experimental Section

The melting points, the elemental analyses and the spectral data were recorded as reported in reference [29].

Preparation of 1-(1-hydroxynaphthalen-2-yl)-3-phenylpropane-1,3-dione (3) : A mixture of α-naphthol **1** (0.01 mol), ethyl benzoylacetate **2** (0.01 mol) and zinc chloride (5 gm) was exposed to microwave irradiation for 5 min, the reaction mixture was allowed to reach room temperature, then diluted with ethanol with stirring and the solid product that formed, was filtrated off and crystallized from ethanol to give (**3**; 91%) as brown crystals; M.P.72-74°C; IR (KBr) ν cm⁻¹ = 3365 (OH), 3061 (CH-arom), 2924 (CH-aliph), 1720, 1639 (2C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 4.49 (s, 2H, CH₂), 7.20-8.68 (m, 11H, aromatic H), 8.69 (s, 1H, OH); ¹³C-NMR (100 MHz, DMSO-d₆) δ = 54.6, 118.6, 123.1, 124.2, 125.2, 126.0, 126.3, 127.5, 127.5, 127.7, 127.7, 128.2, 129.6, 132.6, 132.9, 135.6, 166.2, 193.2, 202.8; MS: m/z (%) 290 (M⁺). Anal. calcd for C₁₉H₁₄O₃ (290): C, 78.61; H, 4.86; O, 16.53%; Found: C, 78.63; H, 4.88.

Preparation of 2-((dimethylamino)methylene)-1-(1-hydroxynaphthalen-2-yl)-3-phenylpropane-1,3-dione (5): A mixture of **3** (0.01 mol) and DMF-DMA (0.01 mol) in dioxane (30 ml) was heated under reflux for 6 hrs. The reaction mixture was allowed to cool. The separated solid was filtered off, washed with ethanol and crystallized from ethanol to give (**5**; 77%) as pale brown crystals; M.P.173-175°C; IR (KBr) ν cm⁻¹ = 3422 (OH), 3062 (CH-aromatic), 2932-2854 (CH-aliphatic), 1723, 1636 (2C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 3.00 (s, 6H, 2CH₃), 7.19 (s, 1H, CH-oliffinic), 7.64-8.67 (m, 11H, aromatic H), 8.68 (s, 1H, OH); ¹³C-NMR (100 MHz, DMSO-d₆) δ = 44.5, 44.5, 116.2, 122.4, 124.3, 126.1, 126.7, 127.6, 127.6, 128.1, 128.1, 128.2, 128.6, 129.1, 130.1, 132.4, 132.5, 138.1, 163.2, 166.5, 194.7, 198.0; MS: m/z (%) 345 (M⁺). Anal. calcd for C₂₂H₁₉NO₃ (345): C, 76.50; H, 5.54; N, 4.06%; Found: C, 76.52; H, 5.56; N, 4.08%.

Preparation of 2-(ethoxymethylene)-1-(1-hydroxynaphthalen-2-yl)-3-phenylpropane-1,3-dione (6): A mixture of **3** (0.01 mol) and triethoxy methane (3 ml) in acetic anhydride (10 ml) was heated under reflux for 12 hrs. The reaction mixture was allowed to cool. The separated solid was filtered off, washed with ethanol and crystallized from ethanol to give (**6**; 86%) as pale brown crystals; M.P.120-122°C; IR (KBr) ν cm⁻¹ = 3426 (OH), 3062 (CH-arom), 2930 (CH-aliph), 1767, 1636 (2C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 1.11 (t, 3H, CH₃), 4.19 (q, 2H, CH₂), 6.33 (s, 1H, CH-oliffinic), 7.29-8.23 (m, 11H, aromatic H), 8.68 (s, 1H, OH); MS: m/z (%) 346 (M⁺). Anal. calcd for C₂₂H₁₈O₄ (346): C, 76.29; H, 5.24; O, 18.48%; Found: C, 76.31; H, 5.26.

Preparation of 5-(1-hydroxy-2-naphthoyl)-4-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (10): A mixture of **5** (0.01 mol) and cyanothioacetamide **7** (0.01 mol), in presence of sodium ethoxide (30 ml) was heated under reflux for 24 hrs. The solution was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off, washed with water and crystallized from dioxane to give (**10**; 88%) as brown crystals; M.p.238-240°C; IR (KBr) ν cm⁻¹ = 3447 (OH), 3423 (NH), 3062 (CH-arom), 2209 (CN), 1636 (CO) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 7.20-8.24 (m, 13H, aromatic H and NH), 8.70 (s, 1H, OH); ¹³C-NMR (100 MHz, DMSO-d₆) δ = 107.1, 117.0, 118.2, 122.3, 123.2, 126.3, 126.4, 126.8, 127.3, 127.3, 127.5, 127.5, 128.3, 128.4, 129.1, 130.0, 130.1, 132.2, 144.6, 166.1, 168.0, 168.6, 196.0; MS: m/z (%) 384 (M⁺⁺²). Anal. calcd for C₂₃H₁₄N₂O₂S (382): C, 72.23; H, 3.69; N, 7.33 %; Found: C, 72.25; H, 3.71; N, 7.35%.

Preparation of (1-hydroxynaphthalen-2-yl)(3-phenyl-1H-pyrazol-4-yl)methanone (14): Method (A): A mixture of **5** (0.01 mol) and hydrazine hydrate (10 ml) was heated under reflux for 12 hrs. The reaction mixture was

allowed to cool and poured into crushed ice. The separated solid was filtered off, washed with water and crystallized from DMF to give (**14**; 80%).

Method (B): A mixture of **6** (0.01 mol) and hydrazine hydrate (10 ml) was heated under reflux for 12 hrs. The reaction mixture was allowed to cool and poured into crushed ice. The separated solid was filtered off, washed with water and crystallized from DMF to give (**14**; 79%) as white crystals; M.P.> 300°C; IR (KBr) ν cm⁻¹ = 3300 (OH), 3228 (NH), 3062 (CH-aromatic), 1670 (CO) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 7.22 (s, 1H, CH-pyrazole), 7.31-8.71 (m, 12H, aromatic and NH), 8.73 (s, 1H, OH); MS: m/z (%) 314 (M⁺). Anal. calcd for C₂₀H₁₄N₂O₂ (314): C, 76.42; H, 4.49; N, 8.91%; Found: C, 76.44; H, 4.51; N, 8.93%.

General procedure for preparation of compounds (16a,b and 18):

A mixture of **5** (0.01 mol) with urea (0.01 mol), thiourea (0.01 mol) and guanidine hydrochloride (0.01 mol), in presence of sodium ethoxide (30 ml) was heated under reflux for 24 hrs. The solutions were allowed to cool and poured into crushed ice then acidified with HCl. The separated solids were filtered off, washed with water and crystallized from the proper solvent to give (**16a,b** and **18**).

5-(1-hydroxy-2-naphthoyl)-4-phenylpyrimidin-2(1H)-one (16a): It was obtained as beige crystals from DMF; yield (79%); M.P.> 300°C; IR (KBr) ν cm⁻¹ = 3447, 3423 (OH/NH), 3061 (CH-aromatic), 1740, 1641 (2C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 7.22 (s, 1H, CH-pyrimidine), 7.65-8.70 (m, 12H, aromatic H and NH), 8.71 (s, 1H, OH); MS: m/z (%) 342 (M⁺). Anal. calcd for C₂₁H₁₄N₂O₃ (342): C, 73.68; H, 4.12; N, 8.18 %; Found: C, 73.70; H, 4.14; N, 8.20 %.

(1-hydroxynaphthalen-2-yl)(4-phenyl-2-thioxo-1,2-dihydropyrimidin-5-yl)methanone (16b): It was obtained as brown crystals from DMF; yield (72%); M.P.> 300°C; IR (KBr) ν cm⁻¹ = 3449, 3400 (OH/NH), 1645 (C=O)cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 7.19 (s, 1H, CH-pyrimidine), 7.59-8.67 (m, 12H, aromatic H and NH), 8.68 (s, 1H, OH); MS: m/z (%) 358 (M⁺). Anal. calcd for C₂₁H₁₄N₂O₂S (358): C, 70.37; H, 3.94; N, 7.82 %; Found: C, 70.39; H, 3.96; N, 7.84 %.

(2-amino-4-phenylpyrimidin-5-yl)(1-hydroxynaphthalen-2-yl)methanone (18): It was obtained as brown crystals from dioxane; yield (71%); M.P.250-252°C; IR (KBr) ν cm⁻¹ = 3449, 3400 (OH/NH₂), 1642 (C=O)cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 6.20 (s, 2H, NH₂), 7.31-8.39 (m, 12H, aromatic H), 8.67 (s, 1H, OH); ¹³C-NMR (100 MHz, DMSO-d₆) δ = 118.0, 119.3, 123.2, 124.3, 124.8, 126.4, 126.4, 126.4, 126.6, 127.6, 128.2, 128.7, 128.9, 128.9, 130.7, 132.7, 155.3, 162.7, 165.8, 166.3, 194.0; MS: m/z (%) 341 (M⁺). Anal. calcd for C₂₁H₁₅N₃O₂ (341): C, 73.89; H, 4.43; N, 12.31%; Found: C, 73.91; H, 4.45; N, 12.33%.

Preparation of (1-hydroxynaphthalen-2-yl)(3-phenylisoxazol-4-yl)methanone (20): A mixture of **5** (0.01 mol), hydroxylamine hydrochloride in ethanol (30 ml) containing anhydrous sodium acetate (1g) was heated under reflux for 24 hrs. The reaction mixture was allowed to cool and poured into cold water (60 ml). The separated solid was filtered off and crystallized from ethanol to give (**20**; 71%) as brown crystals; M.P.150-152°C; IR (KBr) ν cm⁻¹ = 3425 (OH), 3060 (CH-aromatic), 1636 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 7.21 (s, 1H, CH-

isoxazole), 7.31-8.70 (m, 11H, aromatic H), 8.71 (s, 1H, OH); MS: m/z (%) 315 (M^+). Anal. calcd for $C_{20}H_{13}NO_3$ (315): C, 76.18; H, 4.16; N, 4.44 %; Found: C, 76.20; H, 4.18; N, 4.46 %.

Preparation of (2-(3-Phenylisoxazol-5-yl)naphthalen-1-ol (23): A mixture of **3** (0.01 mol), hydroxylamine hydrochloride (0.01 mol) in ethanol (30 ml) containing anhydrous sodium acetate (1 g) was heated under reflux for 24 hrs. The reaction mixture was allowed to cool and poured into cold water (60 ml). The separated solid was filtered off and crystallized from ethanol to give (**23**; 80%) as beige crystals; M.p.132-134°C; IR (KBr) $n\text{ cm}^{-1}$ = 3382 (OH), 3061 (CH-aromatic) cm^{-1} ; $^1\text{H-NMR}$ (DMSO-d₆) d = 7.21 (s, 1H, CH-isoxazol), 7.32-8.54 (m, 11H, aromatic H), 8.69 (s, 1H, OH); $^{13}\text{C-NMR}$ (100 MHz, DMSO-d₆) d = 99.6, 118.7, 120.6, 123.5, 124.1, 126.1, 126.3, 126.5, 126.5, 127.3, 127.5, 127.6, 127.9, 128.8, 128.8, 132.4, 161.0, 163.2, 170.1; MS: m/z (%) 287 (M^+). Anal. calcd for $C_{19}H_{13}NO_2$ (287): C, 79.43; H, 4.56; N, 4.88%; Found: C, 79.45; H, 4.58; N, 4.90%.

Preparation of 6-(1-hydroxynaphthalen-2-yl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (26): A mixture of **3** (0.01 mol), malononitrile (0.01 mol) in ethanol (30 ml) containing catalytic amount of sodium ethoxide was heated under reflux for 12 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off, washed with water and crystallized from ethanol to give (**26**; 69%) as brown crystals; M.P.163-165°C; IR (KBr) $n\text{ cm}^{-1}$ = 3311, 3294 (OH/NH), 3062 (CH-aromatic), 2193 (CN), 1639 (C=O) cm^{-1} ; $^1\text{H-NMR}$ (DMSO-d₆) d = 7.16 (s, 1H, CH-Pyridine), 7.51-8.63 (m, 12H, aromatic H and NH), 8.64 (s, 1H, OH); $^{13}\text{C-NMR}$ (100 MHz, DMSO-d₆) d = 108.3, 118.3, 118.6, 120.1, 123.4, 124.1, 125.8, 126.9, 127.1, 127.2, 127.6, 127.6, 127.9, 127.9, 128.3, 133.9, 135.2, 153.6, 155.2, 155.3, 157.8, 162.3; MS: m/z (%) 338 (M^+). Anal. calcd for $C_{22}H_{14}N_2O_2$ (338): C, 78.09; H, 4.17; N, 8.28%; Found: C, 78.11; H, 4.19; N, 8.30%.

Preparation of 2-amino-5-(1-hydroxy-2-naphthoyl)-4-phenylthiophene-3-carbonitrile (29): Equimolar amounts of **3** (0.01 mol), malononitrile and elemental sulfur (0.01 mol) in ethanol (30 ml) containing piperidine were refluxed for 15 hrs, poured onto cold water (30 ml) and acidified with HCl (pH=3). The solid product thus formed was filtered off and crystallized from ethanol to give (**29**; 80%) as yellow crtstals; M.p.130-132°C; IR (KBr) $n\text{ cm}^{-1}$ = 3421, 3400 (OH/NH₂), 3061 (CH-aromatic), 2192 (CN), 1639 (C=O) cm^{-1} ; $^1\text{H-NMR}$ (DMSO-d₆) d = 7.20-8.68 (m, 13H, aromatic H and NH₂), 8.69 (s, 1H, OH); MS: m/z (%) 370 (M^+). Anal. calcd for $C_{22}H_{14}N_2O_2S$ (370): C, 71.33; H, 3.81; N, 7.56%; Found: C, 71.35; H, 3.84; N, 7.58%.

General procedure for preparation of compounds (35a-c): A mixture of **31a-c** (which prepared by amixture of **3** and **30a-c** in ethanol/piperidine refluxing) (0.01 mol), dimedone (0.01 mol) and ammonium acetate (2 gm) was fused for 30 min. The reaction mixture was allowed to cool, then triturated with ethanol. The separated solid was filtered off, washed with water and crystallized from the proper solvent to give **35a-c**.

3-(1-hydroxy-2-naphthoyl)-7,7-dimethyl-2,4-diphenyl-4,6,7,8-tetrahydroquinolin-5(1H)-one (35a): It was obtained as yellow crystals from dioxane; yield (86%); M.P.280-282°C; IR (KBr) $n\text{ cm}^{-1}$ = 3402, 3400 (OH/NH), 3059 (CH-aromatic), 2954-2870 (CH-aliphatic), 1642, 1620 (2C=O) cm^{-1} ; $^1\text{H-NMR}$ (DMSO-d₆) d = 0.86 (s, 3H, CH₃), 0.99 (s, 3H, CH₃), 2.73 (s, 2H, CH₂), 2.89 (s, 2H, CH₂), 4.80 (s, 1H, CH-pyridine), 7.14-8.70 (m, 17H,

aromatic H and NH), 8.70 (s, 1H, OH); MS: m/z (%) 499 (M^+). Anal. calcd for $C_{34}H_{29}NO_3$ (499): C, 81.74; H, 5.85; N, 2.80%; Found: C, 81.76; H, 5.87; N, 2.82%.

3-(1-hydroxy-2-naphthoyl)-4-(4-methoxyphenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydro-quinolin-5(1H)-one (35b): It was obtained as yellow crystals from dioxane; yield (80%); M.P.277-279°C; IR (KBr) ν cm⁻¹ = 3371 (OH), 3255 (NH), 3059 (CH-aromatic), 2954-2835 (CH-aliphatic), 1639, 1620 (2C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 0.82 (s, 3H, CH₃), 1.19 (s, 3H, CH₃), 2.70 (s, 2H, CH₂), 2.86 (s, 2H, CH₂), 3.70 (s, 3H, OCH₃), 4.49 (s, 1H, CH-pyridine), 7.21-8.28 (m, 16H, aromatic H and NH), 8.45 (s, 1H, OH); ¹³C-NMR (100 MHz, DMSO-d₆) δ = 29.2, 29.2, 33.8, 41.0, 41.4, 52.3, 57.8, 107.0, 113.2, 116.3, 116.3, 122.0, 123.1, 124.3, 126.4, 126.8, 127.2, 127.6, 127.6, 127.6, 127.8, 128.0, 128.2, 128.9, 132.1, 132.1, 132.7, 137.2, 137.2, 143.6, 150.2, 159.5, 166.0, 193.4, 195.1; MS: m/z (%) 529 (M^+). Anal. calcd for $C_{35}H_{31}NO_4$ (529): C, 79.37; H, 5.90; N, 2.64; Found: C, 79.39; H, 5.92; N, 2.66.

4-(4-chlorophenyl)-3-(1-hydroxy-2-naphthoyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1H)-one (35c): It was obtained as pale yellow crystals from dioxane; yield (83%); M.P.290-292°C; IR (KBr) ν cm⁻¹ = 3356 (OH), 3271 (NH), 3059 (CH-aromatic), 2954-2870 (CH-aliphatic), 1643, 1620 (2C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 0.83 (s, 3H, CH₃), 1.20 (s, 3H, CH₃), 2.70 (s, 2H, CH₂), 2.89 (s, 2H, CH₂), 4.49 (s, 1H, CH-pyridine), 7.28-8.11 (m, 16H, aromatic H and NH), 8.50 (s, 1H, OH); MS: m/z (%) 533 (M^+). Anal. calcd for $C_{34}H_{28}ClNO_3$ (533): C, 76.47; H, 5.28; N, 2.62; Found: C, 76.49; H, 5.30; N, 2.64%.

General procedure for preparation of compounds (40a,b): A mixture of **3** (0.01 mol) and arylidenemalononitriles (**36a,b**) (0.01 mol) in ethanol (30 ml) containing catalytic amount of piperidine was heated under reflux for 12 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off, washed with water and crystallized from the proper solvent to give (**40a,b**).

2-amino-4-(4-chlorophenyl)-5-(1-hydroxy-2-naphthoyl)-6-phenyl-4H-pyran-3-carbonitrile (40a): It was obtained as brown crystals from ethanol; yield (92%); M.P.162-164 °C; IR (KBr) ν cm⁻¹:3448, 3421 (OH/NH₂), 3063 (CH-aromatic), 2929 (CH-aliphatic), 2191 (CN), 1630 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 4.40 (s, 1H, 4H-pyrane), 7.23-8.72 (m, 17H, aromatic H and NH₂), 8.74 (s, 1H, OH); ¹³C-NMR (100 MHz, DMSO-d₆) δ = 43.7, 60.3, 118.9, 122.1, 123.4, 124.2, 125.2, 125.2, 126.2, 126.8, 126.8, 126.8, 126.9, 126.9, 127.5, 127.5, 127.6, 127.6, 128.1, 128.2, 131.3, 131.3, 132.6, 133.2, 135.0, 140.8, 163.3, 165.2, 193.5; MS: m/z (%) 480 (M^++2). Anal. calcd for $C_{29}H_{19}ClN_2O_3$ (478): C, 72.73; H, 4.00; N, 5.85%; Found: C, 72.75; H, 4.02; N, 5.87%.

2-amino-5-(1-hydroxy-2-naphthoyl)-4-(4-hydroxyphenyl)-6-phenyl-4H-pyran-3-carbonitrile (40b): It was obtained as brown crystals from ethanol; yield (90%); M.P.200-202 °C; IR (KBr) ν cm⁻¹: 3447, 3390 (OH/NH₂), 3062 (CH-aromatic), 2928 (CH-aliphatic), 2196 (CN), 1630 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 4.20 (s, 1H, 4H-pyrane), 6.87 (s, 2H, NH₂), 6.90-8.71 (m, 15H, aromatic H), 8.72 (s, 1H, OH), 10.00 (s, 1H, OH); MS: m/z (%) 460 (M^+). Anal. calcd for $C_{29}H_{20}N_2O_4$ (460): C, 75.64; H, 4.38; N, 6.08%; Found: C, 75.66; H, 4.40; N, 6.10%.

General procedure for preparation of compounds (45a-c): A mixture of **3** (0.01 mol) and arylidenecyanothioacetamide (**41a-c**) (0.01 mol) in ethanol (30 ml) containing catalytic amount of TEA was heated under reflux for 12 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off, washed with water and crystallized from the proper solvent to give (**45 a-c**).

5-(1-hydroxy-2-naphthoyl)-4,6-diphenyl-2-thioxo-1,2-dihdropyridine-3-carbonitrile (45a): It was obtained as pale yellow crystals from ethanol; yield (78%); M.P.146-148 °C; IR (KBr) ν cm⁻¹: 3444 (OH), 3390 (NH), 3059 (CH-aromatic), 2191 (CN), 1620 (C=O)cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 7.23-8.73 (m, 17H, aromatic H and NH), 8.74 (s, 1H, OH); MS: m/z (%) 458 (M⁺). Anal. calcd for C₂₉H₁₈N₂O₂S (458): C, 75.96; H, 3.96; N, 6.11%; Found:C, 75.98; H, 3.98; N, 6.13%.

5-(1-hydroxy-2-naphthoyl)-4-(4-methoxyphenyl)-6-phenyl-2-thioxo-1,2-dihdropyridine-3-carbonitrile (45b): It was obtained as pale yellow crystals from ethanol; yield (82%); M.P.150-152 °C; IR (KBr) ν cm⁻¹ = 3448 (OH), 3387 (NH), 3059 (CH-aromatic), 2931 (CH-aliphatic), 2194 (CN), 1630 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 3.87 (s, 3H, OCH₃), 7.12-8.73 (m, 15H, aromatic H), 8.74 (s, 1H, OH), 9.87 (s, 1H, NH); ¹³C-NMR (100 MHz, DMSO-d₆) δ = 57.6, 108.2, 111.9, 118.2, 118.2, 118.8, 122.3, 124.6, 124.8, 125.2, 126.4, 126.8, 126.8, 127.3, 127.3, 127.5, 127.6, 128.0, 128.1, 128.7, 132.1, 132.1, 132.7, 135.2, 155.8, 160.8, 163.7, 165.2, 172.6, 193.3; MS: m/z (%) 488 (M⁺). Anal. calcd for C₃₀H₂₀N₂O₃S (488): C, 73.75; H, 4.13; N, 5.73%; Found:C, 73.77; H, 4.15; N, 5.75%.

4-(4-chlorophenyl)-5-(1-hydroxy-2-naphthoyl)-6-phenyl-2-thioxo-1,2-dihdropyridine-3-carbonitrile (45c): It was obtained as yellow crystals from ethanol; yield (88%); M.P.136-138 °C; IR (KBr) ν cm⁻¹ = 3390 (OH), 3255 (NH), 3059 (CH-aromatic), 2191 (CN), 1635 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 7.23-8.73 (m, 16H, aromatic H and NH), 8.74 (s, 1H, OH); MS: m/z (%) 494 (M⁺⁺²). Anal. calcd for C₂₉H₁₇ClN₂O₂S (492): C, 70.65; H, 3.48; N, 5.68%; Found:C, 70.67; H, 3.50; N, 5.71%.

General procedure for preparation of compounds (49a,b): A mixture of **3** (0.01mol) and 2-cyano-2-cyclopentylidene-ethaneethioamide **46a** (0.01 mol) or 2-cyano-2-cyclohexylidene-ethaneethioamide **46b** (0.01 mol) in ethanol (30 ml) containing catalytic amount of piperidine was heated under reflux for 24 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered off, washed with water and crystallized from the proper solvent to give (**49a,b**).

10-(1-hydroxy-2-naphthoyl)-9-phenyl-7-thioxo-8-azaspiro[4.5]dec-9-ene-6-carbonitrile (49a): It was obtained as pale yellow crystals from ethanol; yield (74%); M.P.180-182°C; IR (KBr) ν cm⁻¹ = 3387 (OH), 3248 (NH), 3059 (CH-aromatic), 2935-2854 (CH-aliphatic), 2183 (CN), 1627 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 0.85-1.91 (m, 4H, 2CH₂), 1.95 (s, 1H, CH-pyridine), 2.00-2.94 (m, 4H, 2CH₂), 7.14-8.69 (m, 11H, aromatic H), 8.70 (s, 1H, OH), 9.40 (s, 1H, NH); ¹³C-NMR (100 MHz, DMSO-d₆) δ = 27.8, 27.8, 38.3, 38.3, 39.0, 57.8, 116.2, 119.2, 122.3, 123.3, 123.9, 126.1, 126.4, 126.9, 127.3, 127.3, 127.5, 127.8, 128.3, 128.3, 128.8, 132.5, 135.2, 155.3, 166.7, 193.2, 198.9; MS: m/z (%) 440 (M⁺⁺²). Anal. calcd for C₂₇H₂₂N₂O₂S (438): C, 73.95; H, 5.06; N, 6.39%; Found:C, 73.97; H, 5.08; N, 6.41%.

5-(1-hydroxy-2-naphthoyl)-4-phenyl-2-thioxo-3-azaspiro[5.5]undec-4-ene-1-carbonitrile (49b): It was obtained as pale yellow crystals from dioxane; yield (87%); M.P.278-280°C; IR (KBr) ν cm⁻¹ = 3394 (OH), 3325 (NH), 3062 (CH-aromatic), 2931-2854 (CH-aliphatic), 2191 (CN), 1643 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 0.86-1.02 (m, 4H, 2CH₂), 1.76 (s, 2H, CH₂), 1.96 (s, 1H, CH-pyridine), 2.00-2.94 (m, 4H, 2CH₂), 6.70-8.71 (m, 11H, aromatic H), 9.23 (s, 1H, OH), 9.87 (s, 1H, NH); MS: m/z (%) 454 (M⁺+2). Anal. calcd for C₂₈H₂₄N₂O₂S (452): C, 74.31; H, 5.35; N, 6.19 %; Found: C, 74.33; H, 5.37; N, 6.21 %.

General procedure for preparation of compounds (51a-c): A cold suspension of aryl diazonium salts **50a-c** (0.02 mol) (prepared from 0.02 mol of aromatic amine with the appropriate quantities of sodium nitrite and hydrochloric acid) was gradually added to a cold solution (0-5°C) of **3** (0.002 mol) in ethanol (50 ml) containing anhydrous sodium acetate (2 gm) with continuous stirring for 1 hr. The resulting reaction product was filtered off, washed with water and crystallized from the proper solvent to give compounds (**51a-c**).

1-(1-hydroxynaphthalen-2-yl)-2-(2-(4-methoxyphenyl)hydrazone)-3-phenyl propane-1,3-dione (51a): It was obtained as brown crystals from ethanol; yield (81%); M.P.170-172 °C; IR (KBr) ν cm⁻¹: 3420, 3400 (OH/NH), 3062 (CH-aromatic), 2930 (CH-aliphatic), 1724, 1659 (2C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 3.87 (s, 3H, OCH₃), 6.96-8.73 (m, 15H, aromatic H), 8.74 (s, 1H, OH), 11.00 (s, 1H, NH); MS: m/z (%) 424 (M⁺). Anal. calcd for C₂₆H₂₀N₂O₄ (424): C, 73.57; H, 4.75; N, 6.60 %; Found: C, 73.59; H, 4.77; N, 6.62 %.

2-(2-(4-chlorophenyl)hydrazone)-1-(1-hydroxynaphthalen-2-yl)-3-phenylpropane-1,3-dione (51b): It was obtained as brown crystals from ethanol; yield (77%); M.P.161-162 °C; IR (KBr) ν cm⁻¹: 3449, 3419 (OH/NH), 3063 (CH-arom), 1723, 1650 (2C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 7.23-8.71 (m, 15H, aromatic H), 8.72 (s, 1H, OH), 12.00 (s, 1H, NH); MS: m/z (%) 430 (M⁺+2). Anal. calcd for C₂₅H₁₇CIN₂O₃ (428): C, 70.01; H, 4.00; N, 6.53%; Found: C, 70.02; H, 4.03; N, 6.55%.

1-(1-hydroxynaphthalen-2-yl)-3-phenyl-2-(2-p-tolylhydrazone) propane-1,3-dione (51c): It was obtained as brown crystals from ethanol; yield (71%); M.P.166-168 °C; IR (KBr) ν cm⁻¹: 3422, 3400 (OH/NH), 3063 (CH-aromatic), 2926 (CH-aliphatic), 1723, 1650 (2CO) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 1.91 (s, 3H, CH₃), 7.14-8.73 (m, 15H, aromatic H), 8.74 (s, 1H, OH), 12.00 (s, 1H, NH); MS: m/z (%) 408 (M⁺). Anal. calcd for C₂₆H₂₀N₂O₃ (408): C, 76.45; H, 4.94; N, 6.86%; Found: C, 76.46; H, 4.96; N, 6.88 %.

General procedure for preparation of compounds (54a-c): A mixture of compounds **51a-c** (0.001 mole), ammonium acetate (3 gm) and malononitrile (0.001 mole) were fused for 10 min. The solid precipitate so formed was treated with ethanol and filtered out and crystallized from the proper solvent to give (**54a-c**).

6-(1-hydroxy-2-naphthoyl)-3-imino-2-(4-methoxyphenyl)-5-phenyl-2,3-dihydropyridazine-4-carbonitrile (54a): It was obtained as brown crystals from dioxane; yield (79%); M.P.230-232 °C; IR (KBr) ν cm⁻¹: 3421, 3400 (OH/NH), 3065 (CH-aromatic), 2928 (CH-aliphatic), 2200 (CN), 1650 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 3.99 (s, 3H, OCH₃), 6.68-8.25 (m, 16H, aromatic H and NH), 8.71 (s, 1H, OH); MS: m/z (%) 472 (M⁺). Anal. calcd for C₂₉H₂₀N₄O₃ (472): C, 73.72; H, 4.27; N, 11.86%; Found: C, 73.75; H, 4.29; N, 11.88%.

2-(4-chlorophenyl)-6-(1-hydroxy-2-naphthoyl)-3-imino-5-phenyl-2,3-dihydropyridazine-4-carbonitrile (54b): It was obtained as brown crystals from dioxane; yield (79%); M.P.258-260 °C; IR (KBr) ν cm⁻¹: 3406, 3400 (OH/NH), 3063 (CH-aromatic), 2200 (CN), 1650 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 6.67-8.25 (m, 16H, aromatic H and NH), 8.71 (s, 1H, OH); MS: m/z (%) 478 (M⁺+2). Anal. calcd for C₂₈H₁₇CIN₄O₂ (476): C, 70.52; H, 3.59; N, 11.75%; Found: C, 70.55; H, 3.63; N, 11.78%.

6-(1-hydroxy-2-naphthoyl)-3-imino-5-phenyl-2-p-tolyl-2,3-dihydropyridazine-4-carbonitrile (54c): It was obtained as brown crystals from dioxane; yield (79%); M.P.272-274 °C; IR (KBr) ν cm⁻¹: 3400, 3385 (OH/NH), 3062 (CH-aromatic), 2963 (CH-aliphatic), 2202 (CN), 1650 (C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ = 1.76 (s, 3H, CH₃), 6.67-8.27 (m, 16H, aromatic H and NH), 8.72 (s, 1H, OH); MS: m/z (%) 457 (M⁺+1). Anal. calcd for C₂₉H₂₀N₄O₂ (456): C, 76.30; H, 4.42; N, 12.27%; Found: C, 76.33; H, 4.45; N, 12.30%.

Conclusion

In conclusion, compounds 3 and 5 were used as efficient precursors for the synthesis of new heterocycles including α-naphthol moiety with expected biological activities.

Declarations

Author's contributions

MAMA, SMB were responsible for the organic synthesis, and characterization experiments and department of Pharmacology, Faculty of Pharmacy, Mansoura University, Egypt for performing the antimicrobial evaluation. All authors read and +approved the final manuscript.

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Tables

Table 1. Antibacterial and antifungal activities of synthesized compounds.

Compound	Gram Negative Bacteria (-ve)				Gram Positive Bacteria (+ve)				Fungal Species			
	<i>E. coli</i>		<i>P. aeuroginosa</i>		<i>S. aureus</i>		<i>B. subtilis</i>		<i>C. albicans</i>		<i>A. flavus</i>	
	DIZ (mm)	% Activity index	DIZ (mm)	% Activity index	DIZ (mm)	% Activity index	DIZ (mm)	% Activity index	DIZ (mm)	% Activity index	DIZ (mm)	% Activity index
35c	4.1	13.7	9	33.5	13.4	52.1	12	45.6	13	44.6	15	57.0
40a	5.2	18.8	13	44.5	14.7	56.8	14.3	54.4	16.3	55.2	17.4	66.6
51a	NA	-	NA	-	10	39.6	8	32.4	13	45.7	14	49.2
29	18.4	79.9	23	94.5	25	93.5	24.8	98.9	19.1	77.3	24	88.1
10	15	64.6	17.5	70.9	22.5	86.3	19	87.9	19.3	73.8	24.8	83.7
40b	3	10.5	7	23.8	5	14.7	NA	-	4	13.5	6	24.0
14	8	29.6	10	48.7	9	26.7	6	18.9	8	25.2	13	43.4
16a	14.3	54.5	15	66.7	16.7	80.0	19.6	85.6	19	59.7	17.8	69.1
3	9	37.8	19	61.5	14	46.3	11	36.8	11	22.8	10	33.0
35a	15	70.0	20	83.9	19.7	73.8	19.6	77.3	17.6	63.5	19.4	73.6
35b	11	40.8	17.3	63.9	16.9	71.7	17.8	69.4	12.9	56.0	18	62.0
23	NA	-	4	13.8	3	8.9	NA	-	5	12.3	7	17.0
26	13	49.5	16	69.2	14	65.5	14	58.5	10	25.6	14	42.0
45c	NA	-	NA	-	NA	-	NA	-	NA	-	NA	-
49a	5	24.8	12	54.2	8	35.3	6	21.7	8	33.3	11	44.0
5	NA	-	NA	-	NA	-	NA	-	NA	-	NA	-
54a	11	77.2	27	83.9	24	84.5	31	97.6	24.7	85.3	28.5	97.0
Ampicillin	25	100	25	100	24	100	25	100	NA	-	NA	-
Clotrimazole	NA	-	NA	-	NA	-	NA	-	26	100	26	100

NA: No activity; DIZ, Diameter of inhibition zone.

Table 2. Minimum inhibitory concentrations (MIC) for selected compounds.

Compounds	Minimum Inhibitory Concentration (MIC) of the synthesized compounds ($\mu\text{g/mL}$)					
	<i>E. coli</i>	<i>P. aeuroginosa</i>	<i>S. aureus</i>	<i>B. subtilis</i>	<i>C. albicans</i>	<i>A. flavus</i>
35c	760	530	270	500	65.5	50.9
40a	780	385	260	500	48.9	29.4
51a	NA	NA	530	740	95.7	69.5
29	98.7	68.5	66.5	135	14.6	8.8
10	197.5	135	90.7	189.4	22.4	9.8
40b	NA	750	NA	NA	510	365
14	540	260	740	NA	188.5	93.7
16a	188.4	125	125	177.5	37.2	17.6
3	385	187.5	375	740	260	187.5
35a	145	92.7	135.7	240	24.4	14.7
35b	365	197.5	177.9	240	63.5	39.2
23	NA	NA	NA	NA	760	600
26	240	136	187.8	385	260	145
45c	NA	NA	NA	NA	NA	NA
49a	520	260	500	NA	125	97.7
5	NA	NA	NA	NA	NA	NA
54a	125	93.7	93.7	125	11.7	3.9
Ampicillin	125	187.5	93.7	187.5	NA	NA
Clotrimazole	NA	NA	NA	NA	7.8	5.8

NA: No activity.

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