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-pyrene, dihydropyridazine, pyrimidine and pyrazole derivatives

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Abstract
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 with a variety of electrophilic and nucleophilic reagents under a variety of mild conditions. The chemical structures of these compounds were confirmed by various spectroscopic methods such as (IR, 1H-NMR, 13C-NMR, mass spectra and elemental analyses). The prepared compounds were screened in vitro for their anti-microbial activity against some species of Gram-positive bacteria (Staphylococcus aureus and Bacillus subtilis) and Gram-negative bacteria (Escherichia coli and Pseudomonas aeruginosa). 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.

Graphic abstract

Keywords Heterocycles · Microwave irradiation · Spectral characteristics · Antimicrobial activities

Introduction
According to the literature survey, heterocyclic compounds containing nitrogen, sulfur and oxygen atom are found to possess a variety of biological activities. Among them, pyrazoles, cyanopyridines, pyrimidinethiones, pyranes or their fused ring systems and pyridazine are found to exhibit a wide
spectrum of biological activities. Various biological applications have been reported for pyrazoles such as anti-viral [1], anti-cancer [2], anti-microbial [3], anti-inflammatory [4], anti-depressant [5] anti-convulsant [6] analgesic and antiplatelet [7, 8]. Cyanopyridine derivatives have attracted considerable attention as they appeared of interest to possess anti-cancer [9], anti-convulsant [10] and anti-microbial [11]. Pyrimidinethiones have been found to possess anti-tubercular [12]. Pyrane and fused 4H-pyrane derivatives have attracted a great interest owing to their anti-microbial [13, 14], anti-oxidant [15], inhibitors of influenza virus sialidases [16], mutagenic activity [17], anti-cancer [18] and anti-viral [19]. Also, Pyridazine ring is a nucleus of a many of drugs available in the market like cadralazine (anti-hypertensive), minaprine (anti-depressant), hydralazine (smooth muscle relaxant), pipofezine (tricyclic antidepressant) [20, 21]. The aim of the present work, was to synthesize new pyrazole, pyridine, pyrimidine, pyrane and pyridazine derivatives by using 1-(1-hydroxynaphthalen-2-yl)-3-phenylpropane-1,3-dione as the key starting material. Followed by anti-microbial evaluations of newly synthesized products were done. In general, the novel synthesized compounds showed a moderate antimicrobial activity against the previously mentioned microorganisms.

Results and discussion

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 benzoyleacetate in the presence of zinc chloride [30]. Rather than the expected coumarin 4 as the literature [31]. The key intermediate 3 was prepared previously in the literature [32, 33]. 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 an absorption bands at 3365, 3061, 2924, 1720, 1639 cm⁻¹ for hydroxyl, aromatic, aliphatic and carbonyl function groups, respectively. The ¹H-NMR spectrum of compound 3 showed the following signals at δ = 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⁺) corresponding to a molecular formula C₁₉H₁₄O₃ (Scheme 1).

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, the reaction of compound 3 with dimethylformamidemethyldimethyacetal (DMF-DMA) in dioxane afforded the enaminone derivative 5 in a good yield as demonstrated in (Scheme 2). Establishing the structure 5 was based on its elemental analyses and spectral data. Thus, the ¹H-NMR spectrum of compound 5 showed the following signals, a singlet signal at δ = 7.19 ppm assigned to olefinic proton, a multiplet signals at δ = 7.64–8.67 ppm assigned to aromatic protons and a singlet signal at δ = 8.68 ppm assigned to hydroxyl group. Moreover, the mass spectrum revealed a molecular ion peak at m/z = 345 (M⁺) related to a molecular formula C₂₂H₁₉NO₃. Also, when compound 3 was alkylated with triethylorthoformate in refluxing acetic anhydride afforded the ethoxymethylene derivative 6. Establishing 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 δ = 1.11 (t, 3H, CH₃), 4.19 (q, 2H, CH₂), 6.33 (s, 1H, CH-olefinic), 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 \( m/z = 346 \) (M+).

Compound 5 readily reacted with cyanothioacetamide 7 as example of active methylene reagents in refluxing ethanolic sodium ethoxide yield the expected pyridinethione derivative 10 which established on its spectral data (IR, \(^1\)H-NMR, mass spectra, \(^{13}\)C-NMR and elemental analyses). So, its mass spectrum revealed a molecular ion peak at \( m/z = 384 \) (M+ + 2) corresponding to a molecular formula \( C_{23}H_{14}N_2O_2S \). Formation of pyridinethione 10 is believed to be proceed via initial addition of active methylene moiety in cyanothioacetamide on the \( \pi \)-bond system of the carbonyl group of 5 to afford the Michael adduct 8 that cyclizes by losing water molecule 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 enamimone 5 toward binucleophilic reagents was also investigated. Thus, when compound 5 was allowed to react with hydrazine hydrate a compound with a molecular formula \( C_{20}H_{14}N_2O_2 \) is formed which may be formulated as structure 14 based on spectroscopic data. Thus, the \(^1\)H-NMR spectrum of compound 14 showed a singlet signal at \( \delta = 7.22 \) assigned to CH-pyrazole, a multiplet signals at \( \delta = 7.31-8.71 \) assigned for CH aromatic and NH protons and a singlet signal at \( \delta = 8.73 \) 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 enamimone 5 with urea or thiourea to yield the expected pyrimidine derivatives 16a,b. Compounds 16a,b were established on its correct spectral data (IR, \(^1\)H-NMR, mass spectra and elemental analyses). Also, enamimone 5 reacted with guanidine hydrochloride to yield the pyrimidine derivative 18 which established on spectral data. On the other hand, the reaction of enamimone 5 with hydroxylamine hydrochloride in ethanol containing anhydrous sodium acetate afforded the isoxazole derivative 20. The structure of compound 20 was established based on its elemental analyses and spectroscopic data. Thus, the \(^1\)H-NMR spectrum of compound 20 revealed the presence of a singlet signal at \( \delta = 7.21 \) ppm corresponding to the CH-isoxazole and a multiplet signals at \( \delta = 7.31-8.70 \) ppm corresponding to aromatic protons and a singlet signal at 8.71 ppm corresponding to OH group. The mass spectrum of compound 20 revealed a molecular ion peak at \( m/z = 315 \) (M+) corresponding to a 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 hydroxylamine hydrochloride to yield the isoxazole derivative 23 in a good yield. Compound 23 was established based on its spectral data (IR, \(^1\)H-NMR, \(^{13}\)C-NMR, mass spectra) and elemental analyses. The \(^1\)H-NMR spectrum of compound 23 showed a singlet signal at \( \delta = 7.21 \) ppm assigned to CH-isoxazole, a singlet signal at \( \delta = 8.69 \) ppm assigned to OH group beside a multiplet signals at \( \delta = 7.32-8.54 \) ppm assigned to aromatic protons. The mass spectrum showed a molecular ion peak
at \( m/z = 287 \) (M\(^+\)) corresponding to a molecular formula \( \text{C}_{19}\text{H}_{13}\text{NO}_{2} \) 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 \( \text{C}_{22}\text{H}_{14}\text{N}_{2}\text{O}_{2} \) was obtained as the sole isolable product through the intermediates 24 and 25 [35]. On the other hand, the reaction of compound 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, the \(^1\text{H}-\text{NMR} \) of the structure revealed a singlet signal at \( \delta = 8.69 \text{ ppm} \) corresponding to OH group beside a multiplet signals corresponding to the aromatic protons and NH\(_2\) at \( \delta = 7.20–8.68 \text{ ppm} \). Also, the mass spectrum showed a molecular ion peak at \( m/z = 370 \) (M\(^+\)) corresponding to a molecular formula \( \text{C}_{22}\text{H}_{14}\text{N}_{2}\text{O}_{2}\text{S} \).

One-pot reaction of a mixture of compound 31 and dimentone 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 an 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 \(^1\text{H}-\text{NMR} \) of compound 35b for example showed a singlet signals at \( \delta = 0.82, 1.19 \text{ ppm} \) corresponding to 2CH\(_3\), two singlet signals at \( \delta = 2.70 \text{ ppm} \) and at \( \delta = 2.86 \text{ ppm} \) corresponding to two methylene groups of dimentone, a singlet signal at \( \delta = 3.70 \text{ ppm} \) assigned to OCH\(_3\) protons, a singlet signal at \( \delta = 4.49 \text{ ppm} \) assigned to CH-pyridine, a singlet signal at \( \delta = 7.21–8.28 \text{ ppm} \) 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 dimentone 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 molecule 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 derivatives 40a,b were synthesized in an excellent yield upon treatment of 3 with arylidinemononitrile 36a–b in the presence of a catalytic amount of
The structures of compounds 40a,b were established based on analytical and spectral data. The 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 α, β-unsaturated linkage and subsequent water elimination from carbonyl benzyol group to yield a 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 δ = 3.87 ppm assigned for OCH3, a singlet signal at δ = 8.74 ppm assigned to OH, a singlet signal at δ = 9.87 ppm assigned for NH group in addition to a multiplet signals at δ = 7.12–8.73 ppm assigned to aromatic protons [34, 39, 40]. Similarly, The reaction of compound 3 with cyclopentylidenecynothiocetamide and cyclohexyliden-cynothioacetamide 46a,b yield the azaspiro derivatives 49a,b through the intermediates 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. Compounds 54a–c were established based on spectral data (IR, 1H-NMR and mass spectra) and elemental analyses. Thus, the 1H-NMR spectrum of 54a for example revealed a singlet signal at δ = 3.99 ppm assigned to OCH3, a singlet signal at δ = 8.71 ppm assigned to OH group in addition to a multiplet signals at δ = 7.12–8.73 ppm assigned 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 C_{29}H_{20}N_{4}O_{3} 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 aeruginosa*). 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 disks of Whatman filter paper with equal diameter size (10 mm). Paper disks were sterilized in an autoclave. The paper disks 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 aeruginosa*, *Candida albicans* and *Aspergillus flavus*. The petri dishes were incubated at 36 °C. The inhibition zones were recorded after 24 h 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 antibacterial 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 Eq. (1).

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\text{% Activity index} = \frac{\text{Zone of inhibition by test compound (diameter)}}{\text{Zone of inhibition by standard (diameter)}} \times 100
\] (1)

**Scheme 8** The synthetic route of compound 49

**Scheme 9** Synthetic route to pyridazenes
Minimum inhibitory concentration (MIC) measurement

The minimum inhibitory concentration (MIC) was determined using the disk diffusion technique by preparing disks containing 1.9–1000 µg/mL of each compound against Gram-positive bacteria (Staphylococcus aureus, Bacillus subtilis) and Gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa). 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 h 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. Tables 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. aeruginosa (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. aeruginosa with also small range spectrum antifungal activity. All the other compounds (3, 35b, 26, 35c, 35a, 40a, 10, 16a, 14, and 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.

Structure–activity relationship: By analyzing the previous results, it is noted that the substitutes do not play a clear role in the biological activity. However, in most of the results it was observed that the compounds that contain electron-withdrawing groups have a higher biological activity than the compounds that contain electron-donating groups and that the biological activity depends on the formation of the new fused rings and the type of strains chosen from bacteria and fungi.

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.

Experimental

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

General procedure of the synthesis of 1-(1-hydroxy-naphthalen-2-yl)-3-phenyl-propane-1,3-dione (3)

A mixture of α-naphthol 1 (0.01 mol, 1.44 g), ethyl benzoylecetate 2 (0.01 mol, 1.92 g) and zinc chloride (0.5 gm) was exposed to microwave irradiation (Microwave assisted synthesis was performed on a CEM Microwave synthesizer, the irradiation power was 200 W as the maximum level of irradiation and a maximum level of internal vessel pressure at 250 Psi for about 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) as brown crystals: M.P.: 147–149 °C, yield: 2.65 g (91%). IR (KBr) (νmax/cm⁻¹): 3365 (OH), 3061 (Ar–H), 2924 (Aliph-H), 1720, 1639 (C=O). MS (EI, 70 eV): mlz (%) = 290 (M⁺). 1H NMR (400 MHz, DMSO-d6): δ (ppm) 4.49 (s, 2H, CH2), 7.20–8.68 (m, 11H, aromatic H), 8.69 (s, 1H, OH). Anal. Calcd. for C19H14O3 (290): C, 78.61; H, 4.86. Found: C, 78.63; H, 4.88.

Synthesis of 2-((dimethylamino)methylene)-1-(1-hydroxy-naphthalen-2-yl)-3-phenyl-propane-1,3-dione (5)

A mixture of 3 (0.01 mol, 2.9 g) and DMF-DMA (0.01 mol, 1.19 g) in dioxane (30 ml) was heated under reflux for 6 h. The reaction mixture was allowed to cool. The separated solid was filtered off, washed with ethanol and crystallized from ethanol to give (5) as pale brown crystals: M.P.: 173–175 °C, yield: 2.65 g (77%). IR (KBr)
### Antibacterial and antifungal activities of synthesized compounds

| Compound | Gram-negative bacteria (−ve) | Gram-positive bacteria (+ve) | Fungal Species |
|----------|-----------------------------|----------------------------|---------------|
|          | E. coli | P. aeruginosa | S. aureus | B. subtilis | C. albicans | A. flavus |
|          | 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 | 1 | 4.5 | 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
(ν<sub>max</sub>/cm<sup>−1</sup>): 3422 (NH), 3062 (Ar–H), 2932–2854 (Aliph-H), 1723, 1636 (2C=O). MS (EI, 70 eV): <i>m/z</i> (%) = 345 (M+). 1H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 3.00 (s, 6H, 2CH<sub>3</sub>), 7.19 (s, 1H, CH-olefinic), 7.64–8.67 (m, 11H, aromatic H), 8.68 (s, 1H, OH). 13C NMR (100 MHz, DMSO-d<sub>6</sub>): δ (ppm) 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. Anal. calcd for C<sub>22</sub>H<sub>19</sub>NO<sub>3</sub> (345): C, 76.50; H, 5.54; N, 4.06. Found: C, 76.52; H, 5.56; N, 4.08.

### Synthesis of 2-(ethoxymethylene)-1-(1-hydroxynaphthalen-2-yl)-3-phenylpropane-1,3-dione (6)

A mixture of 3 (0.01 mol, 2.9 g) and triethoxy methane (3 ml) in acetic anhydride (10 ml) was heated under reflux for 12 h. The reaction mixture was allowed to cool. The separated solid was filtered off, washed with ethanol and crystallized from ethanol to give (6) as pale brown crystals: M.P.: 120–122 °C, yield: 3.46 g (83%). IR (KBr) (ν<sub>max</sub>/cm<sup>−1</sup>): 3426 (OH), 3062 (Ar–H), 2930 (Aliph-H), 1767, 1636 (2C=O). MS (EI, 70 eV): <i>m/z</i> (%) = 346 (M+). 1H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 1.11 (t, 3H, CH<sub>3</sub>), 4.19 (q, 2H, CH<sub>2</sub>), 6.33 (s, 1H, CH-olefinic), 7.29–8.23 (m, 11H, aromatic H), 8.68 (s, 1H, OH). Anal. calcd for C<sub>24</sub>H<sub>20</sub>O<sub>4</sub> (346): C, 76.50; H, 5.54; N, 4.06. Found: C, 76.52; H, 5.56; N, 4.08.

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

| Compounds | Minimum inhibitory concentration (MIC) of the synthesized compounds (µg/mL) |
|-----------|--------------------------------------------------------------------------------|
|           | E. coli | P. aeruginosa | S. aureus | B. subtilis | C. albicans | A. flavus |
| 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       | 188.5      | 93.7        | 17.6      |
| 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       | 125        | 97.7        | 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

A mixture of 5 (0.01 mol, 3.45 g) and cyanthioacetamide 7 (0.01 mol, 1 g), in presence of sodium ethoxide (30 ml) was heated under reflux for 24 h. 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) as brown crystals: M.P.: 238–240 °C, yield: 3.35 g (87%). IR (KBr) (ν<sub>max</sub>/cm<sup>−1</sup>): 3447, 3423 (NH), 3062 (Ar–H), 2209 (CN), 1636 (C=O). MS (EI, 70 eV): <i>m/z</i> (%) = 382 (M+). 1H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 7.20–8.24 (m, 13H, aromatic H and NH), 8.70 (s, 1H, OH). 13C NMR (100 MHz, DMSO-d<sub>6</sub>): δ (ppm) 107.1, 117.0, 118.2, 122.3, 123.2, 126.3, 126.4, 126.8, 127.3, 127.3, 127.5, 128.3, 128.4, 129.1, 130.1, 130.0, 131.2, 144.6, 166.1, 168.0, 168.6, 196.0. Anal. calcd for C<sub>23</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S (382): C, 72.23; H, 3.69; N, 7.33. Found: C, 72.25; H, 3.71; N, 7.35.

### Synthesis of (1-hydroxynaphthalen-2-yl)(3-phenyl-1H-pyrazol-4-yl)methanone (14)

#### Method (A): A mixture of 5 (0.01 mol, 3.45 g) and hydrazine hydrate (10 ml) was heated under reflux for 12 h. 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).
Method (B): A mixture of 6 (0.01 mol) and hydrazine hydrate (10 ml) was heated under reflux for 12 h. 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).

as white crystals: M.P.: > 300 °C, yield: 2.50 g (79%). IR (KBr) (v_max/cm⁻¹): 3300, 3228 (NH), 3062 (Ar–H), 1670 (C=O).), MS (EI, 70 eV): m/z (%) = 341 (M⁺). 1H NMR (400 MHz, DMSO-d₆): δ (ppm) 7.22 (s, 1H, CH-pyrimidine), 7.31–8.39 (m, 12H, aromatic H), 8.67 (s, 1H, OH). 13C NMR (100 MHz, DMSO-d₆): δ ppm) 127.5, 127.6, 127.9, 128.8, 128.8, 132.4, 161.0, 163.2, 165.8, 166.3, 194.0. Anal. calc. for C₂₁H₁₄N₂O₂ (342): C, 73.68; H, 4.12; N, 8.18. Found: C, 73.91; H, 4.43; N, 8.12. 13C NMR (100 MHz, DMSO-d₆): δ ppm) 127.6, 128.2, 128.7, 128.9, 130.7, 132.7, 155.3, 162.7, 165.8, 166.3, 194.0. Anal. calc. for C₂₁H₁₅N₃O₂ (358): C, 70.37; H, 4.43; N, 4.88. Found: C, 70.39; H, 4.39; N, 4.86.

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

A mixture of 5 (0.01 mol, 3.45 g) with urea (0.01 mol, 0.6 g), thiourea (0.01 mol, 0.76 g) and guanidine hydrochloride (0.01 mol, 0.95 g), in presence of sodium ethoxide (30 ml) was heated under reflux for 12 h. The reaction mixture was 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: M.P.: > 300 °C, yield: 2.70 g (78%). IR (KBr) (v_max/cm⁻¹): 3447 (OH), 3423 (NH), 3062 (Ar–H), 1641 (C=O). MS (EI, 70 eV): m/z (%) = 314 (M⁺). 1H NMR (400 MHz, DMSO-d₆): δ (ppm) 7.21 (s, 1H, CH-pyrazole), 7.32–8.54 (m, 11H, aromatic H), 8.69 (s, 1H, OH). Anal. calc. for C₂₁H₁₅N₃O₂ (342): C, 73.91; H, 4.45; N, 12.33. Found: C, 73.91; H, 4.45; N, 12.33.

Synthesis of (1-hydroxynaphthalen-2-yl)(3-phenylisoxazol-4-yl)methanone (20)

A mixture of 5 (0.01 mol, 3.45 g), hydroxylamine hydrochloride in ethanol (30 ml) containing anhydrous sodium acetate (1 g) was heated under reflux for 24 h. 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) as brown crystals: M.P.: 150–152 °C, yield: 2.25 g (71%). IR (KBr) (v_max/cm⁻¹): 3425 (OH), 3060 (Ar–H), 1636 (C=O). MS (EI, 70 eV): m/z (%) = 315 (M⁺). 1H NMR (400 MHz, DMSO-d₆): δ (ppm) 7.21 (s, 1H, CH-isoxazole), 7.31–8.70 (m, 11H, aromatic H), 8.71 (s, 1H, OH). Anal. calc. for C₂₁H₁₄N₂O₂ (341): C, 76.18; H, 4.41; N, 4.44%. Found: C, 76.20; H, 4.18; N, 4.46%.

Synthesis 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 h. 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) as beige crystals: M.P.: 132–134 °C, yield: 2.25 g (80%). IR (KBr) (v_max/cm⁻¹): 3382 (NH), 3061 (Ar–H), MS (EI, 70 eV): m/z (%) = 287 (M⁺). MS (EI, 70 eV): m/z (%) = 287 (M⁺). 1H NMR (400 MHz, DMSO-d₆): δ ppm) 7.21 (s, 1H, CH- isoxazole), 7.32–8.54 (m, 11H, aromatic H), 8.69 (s, 1H, OH). 13C NMR (100 MHz, DMSO-d₆): δ ppm) 127.5, 127.6, 127.9, 128.8, 128.8, 130.7, 132.7, 155.3, 162.7, 165.8, 166.3, 194.0. Anal. calc. for C₂₁H₁₄N₂O₂ (341): C, 76.18; H, 4.41; N, 4.44%. Found: C, 76.20; H, 4.18; N, 4.46%.

Synthesis of 6-(1-hydroxynaphthalen-2-yl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (26)

A mixture of 3 (0.01 mol, 2.90 g), malononitrile (0.01 mol, 0.66 g) in sodium ethoxide (30 ml) was heated under reflux for 12 h. 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) as brown crystals: M.P.:
163–165 °C, yield: 2.35 g (69%). IR (KBr) \( \nu_{\text{max}}/\text{cm}^{-1} \): 3311, 3294, 3062, 2193, 1639 cm\(^{-1} \). MS (EI, 70 eV): \( m/z \) (\%) = 338 (M\(^+\)). \(^1\)H NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) (ppm) 7.16 (s, 1H, CH-Pyridine), 7.51–8.63 (m, 12H, aromatic H and NH), 8.64 (s, 1H, OH). \(^13\)C NMR (100 MHz, DMSO-\( d_6 \)): \( \delta \) (ppm) 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, 155.5, 157.8, 162.3. Anal. calcd for C\(_{22}\)H\(_{14}\)N\(_2\)O\(_2\)S (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 a mixture of 3 and 30a–c in ethanol/piperidine/ refluxing) (0.01 mol, 2.90 g), dimedone (0.01 mol, 1.40 g) 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: M.P.: 277–279 °C, yield: 4.25 g (80%). IR (KBr) \( \nu_{\text{max}}/\text{cm}^{-1} \): 3371 (OH), 3255 (NH), 3059 (Ar–H), 2954–2835 (Aliph-H), 1639, 1620 (2C=O). MS (EI, 70 eV): \( m/z \) (\%) = 529 (M\(^+\)). \(^1\)H NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) (ppm) 0.82 (s, 3H, CH\(_3\)), 1.19 (s, 3H, CH\(_3\)), 2.70 (s, 2H, CH\(_2\)), 2.86 (s, 2H, CH\(_2\)), 3.70 (s, 3H, OCH\(_3\)), 4.49 (s, 1H, CH-pyridine), 7.21–8.28 (m, 16H, aromatic H and NH), 8.45 (s, 1H, OH). \(^13\)C NMR (100 MHz, DMSO-\( d_6 \)): \( \delta \) (ppm) 29.2, 29.8, 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. Anal. calcd for C\(_{35}\)H\(_{31}\)NO\(_4\) (529): C, 79.39; H, 5.92; N, 2.66. Found: C, 79.39; H, 5.92; N, 2.66.

### General procedure for preparation of compounds (40a,b)

A mixture of 3 (0.01 mol, 2.90 g) and arylidenemalononitriles (36a-b) (0.01 mol, 1.88 and 1.70 g) in ethanol (30 ml) containing a catalytic amount of piperidine was heated under reflux for 12 h. 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).
It was obtained as brown crystals from ethanol: M.P.: 200–202 °C, yield: 4.30 g (90%). IR (KBr) (vmax/cm−1): 3447–3390 (OH, NH2), 3062 (Ar–H), 2928 (Aliph-H), 2196 (CN), 1630 (C=C=O). MS (EI, 70 eV): m/z (%) = 460 (M+), 1H NMR (400 MHz, DMSO-d6): δ (ppm) 4.20 (s, 1H, OCH3), 7.12–8.73 (m, 15H, aromatic H and NH), 8.74 (s, 1H, OH). Anal. calcd for C29H18N2O2S (458): 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, 2.90 g) and arylidenecyanothioacetamide (41a–c) (0.01 mol, 1.88, 2.18 and 2.22 g) in ethanol (30 ml) containing a catalytic amount of TEA was heated under reflux for 12 h. 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 (45a–c).

5-(1-hydroxy-2-naphthoyl)-4,6-diphenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (45a)

It was obtained as pale yellow crystals from ethanol: M.P.: 146–148 °C, yield: 3.60 g (78%). IR (KBr) (vmax/cm−1): 3444 (OH), 3390 (NH), 3059 (Ar–H), 2191 (CN), 1620 (C=C=O). MS (EI, 70 eV): m/z (%) = 458 (M+). 1H NMR (400 MHz, DMSO-d6): δ (ppm) 7.23–8.73 (m, 17H, aromatic H and NH), 8.74 (s, 1H, OH). 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-dihydropyridine-3-carbonitrile (45b)

It was obtained as pale yellow crystals from ethanol: M.P.: 150–152 °C, yield: 4.00 g (82%). IR (KBr) (vmax/cm−1): 3448, 3387, 3059, 2931, 2194, 1630 cm−1. MS (EI, 70 eV): m/z (%) = 488 (M+). 1H NMR (400 MHz, DMSO-d6): δ (ppm) 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 (ppm) 57.6, 108.2, 111.9, 118.2, 118.2, 122.3, 124.6, 124.8, 125.2, 126.4, 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. 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-dihydropyridine-3-carbonitrile (45c)

It was obtained as yellow crystals from ethanol: M.P.: 136–138 °C, yield: 3.60 g (88%). IR (KBr) (vmax/cm−1): 3390 (OH), 3255 (NH), 3059 (Ar–H), 2191 (CN), 1635 (C=O). MS (EI, 70 eV): m/z (%) = 494 (M+ + 2). 1H NMR (400 MHz, DMSO-d6): δ (ppm) 7.33–8.87 (m, 16H, aromatic H and NH), 8.74 (s, 1H, OH). Anal. calcd for C29H18N2O2S (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 (0.01 mol, 2.90 g) and 2-cyano-2-cyclopentylidenepropenoic acid (46a) (0.01 mol, 1.66 g) or 2-cyano-2-cyclohexylidenepropenoic acid (46b) (0.01 mol, 1.88 g) in ethanol (30 ml) containing a catalytic amount of piperidine was heated under reflux for 24 h. 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: M.P.: 180–182 °C, yield: 3.25 g (74%). IR (KBr) (vmax/cm−1): 3387 (OH), 3248 (NH), 3059 (Ar–H), 2935–2854 (Aliph-H), 2183 (CN), 1627 (C=C=O). MS (EI, 70 eV): m/z (%) = 440 (M+ + 2). 1H NMR (400 MHz, DMSO-d6): δ (ppm) 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, 1IH, aromatic H), 8.70 (s, 1H, OH)), 9.40 (s, 1H, NH). 13C NMR (100 MHz, DMSO-d6): δ (ppm) 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, 128.8, 132.5, 135.2, 155.3, 166.7, 193.2, 198.9. 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-1,2-dihydropyridine-3-carbonitrile (49b)

It was obtained as pale yellow crystals from dioxane: M.P.: 278–280 °C, yield: 3.95 g (87%). IR (KBr) (vmax/cm−1): 3387 (OH), 3255 (NH), 3059 (Ar–H), 2935–2854 (Aliph-H), 2183 (CN), 1627 (C=C=O). MS (EI, 70 eV): m/z (%) = 440 (M+ + 2). 1H NMR (400 MHz, DMSO-d6): δ (ppm) 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, 1IH, aromatic H), 8.70 (s, 1H, OH)), 9.40 (s, 1H, NH). 13C NMR (100 MHz, DMSO-d6): δ (ppm) 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, 128.8, 132.5, 135.2, 155.3, 166.7, 193.2, 198.9. Anal. calcd for C27H22N2O2S (438): C, 73.95; H, 5.06; N, 6.39%. Found: C, 73.97; H, 5.08; N, 6.41%.
cm\(^{-1}\))): 3394 (OH), 3325 (NH), 3062 (Ar–H), 2931–2854 (Aliph-H), 2191 (CN), 1643 (C=O). MS (EI, 70 eV): \(m/z\) (%) = 454 (\(M^+ + 2\)). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) (ppm) 0.86–1.02 (m, 4H, 2CH\(_2\)), 1.76 (s, 2H, CH\(_2\)), 1.96 (s, 1H, CH-pyridine), 2.00–2.94 (m, 4H, 2CH\(_2\)), 6.70–8.71 (m, 11H, aromatic H), 9.23 (s, 1H, OH), 9.87 (s, 1H, NH). Anal. calcd for C\(_{28}\)H\(_{24}\)N\(_2\)O\(_2\)S (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, 0.85, 0.86 and 0.77 g) (prepared from 0.02 mol of aromatic amines 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, 1.45 g) in ethanol (50 ml) containing anhydrous sodium acetate (2 gm) with continuous stirring for 1 h. 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)hydrazono)-3-phenyl propane-1,3-dione (51a)**

It was obtained as brown crystals from ethanol: M.P.: 170–172 °C, yield: 3.45 g (81%). IR (KBr) (v\(_{\text{max}}\)/cm\(^{-1}\)): 3420 (OH), 3400 (NH), 3065 (Ar–H), 2928 (Aliph-H), 1724, 1659 (2C=O). MS (EI, 70 eV): \(m/z\) (%) = 424 (\(M^+\)). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) (ppm) 3.87 (s, 3H, OCH\(_3\)), 6.68–8.25 (m, 16H, aromatic H and NH), 8.71 (s, 1H, OH). Anal. calcd for C\(_{26}\)H\(_{20}\)N\(_2\)O\(_4\) (424): C, 73.57; H, 4.75; N, 6.60. Found: C, 73.59; H, 4.77; N, 6.62.

**2-(4-chlorophenyl)-6-(1-hydroxy-2-naphthoyl)-3-imino-2-(4-methoxyphenyl)-5-phenyl-2,3-dihydropyridazine-4-carbonitrile (54b)**

It was obtained as brown crystals from dioxane: M.P.: 258–260 °C, yield: 3.60 g (75%). IR (KBr) (v\(_{\text{max}}\)/cm\(^{-1}\)): 3406 (OH), 3400 (NH), 3063 (Ar–H), 2200 (CN), 1650 (C=O). MS (EI, 70 eV): \(m/z\) (%) = 478 (\(M^+ + 2\)). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) (ppm) 6.67–8.27 (m, 16H, aromatic H and NH), 8.72 (s, 1H, OH). Anal. calcd for C\(_{28}\)H\(_{17}\)ClN\(_4\)O\(_2\) (476): C, 70.52; H, 3.59; N, 11.75%. Found: C, 70.55; H, 3.63; N, 11.78%.

**General procedure for preparation of compounds (54a–c)**

A mixture of compounds 51a–c (0.001 mol, 0.424, 0.428 and 0.408 g), ammonium acetate (3 gm) and malononitrile (0.001 mol, 0.066 g) 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 compounds (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: M.P.: 230–232 °C, yield: 3.75 g (79%). IR (KBr) (v\(_{\text{max}}\)/cm\(^{-1}\)): 3421 (OH), 3400 (NH), 3065 (Ar–H), 2928 (Aliph-H), 2200 (CN), 1650 (C=O). MS (EI, 70 eV): \(m/z\) (%) = 472 (\(M^+\)). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) (ppm) 3.99 (s, 3H, OCH\(_3\)), 6.68–8.25 (m, 16H, aromatic H and NH), 8.71 (s, 1H, OH). Anal. calcd for C\(_{29}\)H\(_{20}\)N\(_4\)O\(_3\) (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: M.P.: 272–274 °C, yield: 3.85 g (84%). IR (KBr) (v\(_{\text{max}}\)/cm\(^{-1}\)): 3406 (OH), 3400 (NH), 3063 (Ar–H), 2200 (CN), 1650 (C=O). MS (EI, 70 eV): \(m/z\) (%) = 457 (\(M^+ + 1\)). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) (ppm) 1.76 (s, 3H, CH\(_3\)), 6.67–8.27 (m, 16H, aromatic H and NH), 8.72 (s, 1H, OH). Anal. calcd for C\(_{25}\)H\(_{20}\)N\(_2\)O\(_2\) (456): C, 76.30; H, 4.42; N, 12.27. Found: C, 76.33; H, 4.45; N, 12.30.
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