European Journal of Chemistry

Journal webpage: www.eurjchem.com

Utility of β-diketones in heterocyclic synthesis: Synthesis of new tetrahydropyrimidinethione, pyrazole, thiophene, dihydropyridine, dihydropyrane, pyridazine derivatives and investigation of their antimicrobial activity

Mohamed Ahmed Mahmoud Abdel Reheim *, Ibrahim Saad Abdel Hafiz and Safaa Mohamed

Department of Chemistry, Faculty of Science, Arish University, Arish 45511, Egypt

** Corresponding author at: Department of Chemistry, Faculty of Science, Arish University, Arish 45511, Egypt.*
Tel.: +2.0122.2283357. Fax: +2.068.3350065. E-mail address: dr.mohamedabdelreheim@gmail.com (M.A.M.A. Reheim).

ARTICLE INFORMATION

DOI: 10.5155/eurjchem.7.3.298-308.1447

Received: 10 May 2016
Accepted: 11 June 2016
Published online: 30 September 2016
Printed: 30 September 2016

KEYWORDS

Pyrazole
Thiophene
β-Diketones
Dihydropyridine
Antimicrobial activity
Tetrahydropyrimidinethione

ABSTRACT

A series of many important diverse number of fused heterocyclic systems were prepared from the reaction of 1-(2-hydroxynaphthalen-1-yl)-3-phenylpropane-1,3-dione with some bifunctional nucleophiles, these reactions mainly proceed via condensation of 1-(2-hydroxynaphthalen-1-yl)-3-phenylpropane-1,3-dione with the aldehydic function followed by nucleophilic attack. Structures of the new compounds were established by elemental analyses and spectral data. Some of the products were also screened in vitro for their antimicrobial activity.

Cite this: *Eur. J. Chem.* **2016**, *7(3)*, 298-308

1. Introduction

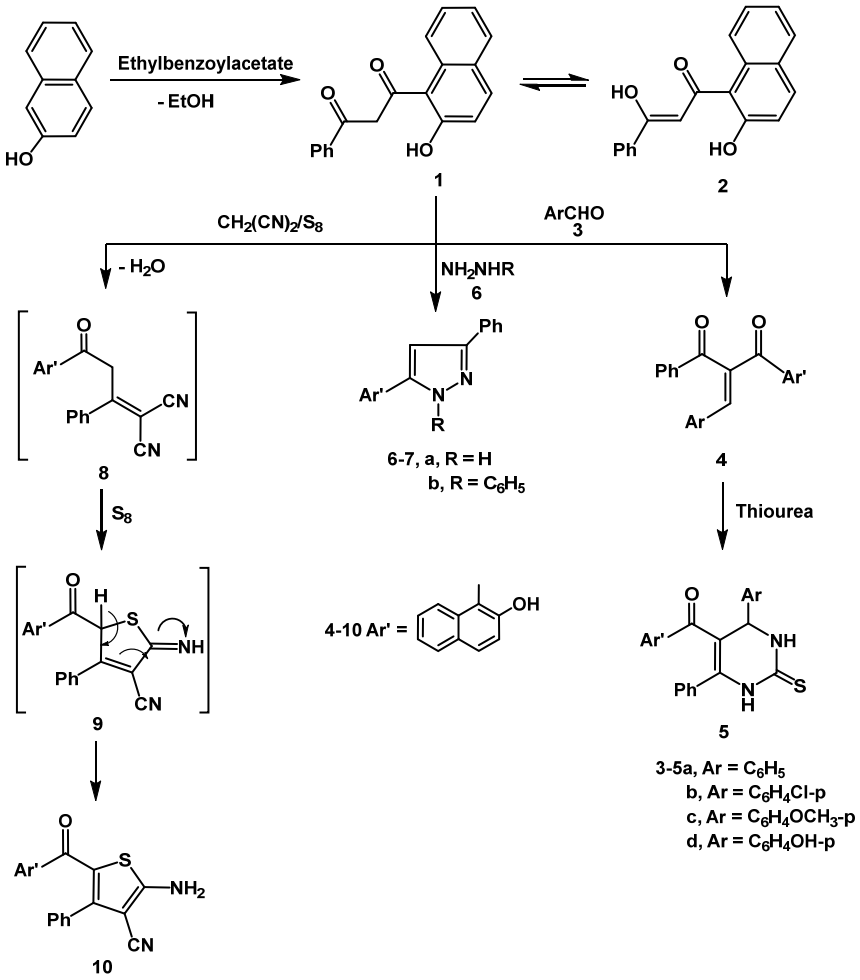
Among a wide variety of heterocyclic that have been explored for developing pharmaceutical important molecules such as pyrazoles, cyanopyridines, pyrimidinethiones and pyranes have played an important role in medicinal chemistry. Various biological applications have been reported for pyrazoles such as anticancer, antiviral, anti-inflammatory, antifungal, antimicrobial, antihistaminic, antiplatelet, analgesic, antihyperglycemic, antipyretic, anti-tumor, sedative, hypnotictivity [1-6], antidepressant [7], anticonvulsant [8]. Cyanopyridine derivatives have attracted considerable attention as they appeared of interest to possess anticonvulasnt [9], antibacterial [10,11], antitumor [12], antihypertensive [13], cardiovascular [14] and antisoriasis [15] activities. Pyrimidine thiones have been found to possess antitubercular [16], antitumor [17] and hypoglycemic [18] activities. Pyrane and fused 4H-pyrane derivatives have attracted a great interest owing to their antimicrobial activity [19-21], inhibition of influenza, virus sialidases [22], mutagenic activity [23], antiviral [24], antiprol feraction agents [25], sex-pheromones [26], antitumor [27] and anti-inflammatory agents [28]. Moreover, pyrane derivatives are well known for their antihistaminic activity [29]. Also, naphthalene is important aryl ring in many active compounds such as anti-inflammatory, anti-bacterial, anti-microbial and anti-cancer [30,31]. In view of the above observations and in continuation of our previous works in heterocyclic chemistry, we report herein a convenient and efficient synthesis of new heterocycles based on 1-(2-hydroxynaphthalen-1-yl)-3-phenylpropane-1,3-dione (**1**) as a key starting material. A selected series of these compounds were investigated for their antimicrobial activities.

2. Experimental

2.1. Instrumentation

All melting points were measured using Akofler Block instrument and are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν, cm^{-1}). The ^1H NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ at 300 MHz and 400 MHz on a Varian Gemini NMR. 1000 EX mass spectrometer at 70 eV. The purity of synthesized compounds was checked by thin layer chromatography TLC (aluminum sheets) using *n*-hexane, ethyl acetate (9: 1, *v*: *v*) eluent.

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
http://dx.doi.org/10.5155/eurjchem.7.3.298-308.1447



Scheme 1

Elemental analyses were carried out by the Microanalytical Research Center, Faculty of Science, and Microanalytical Unit, Faculty of Pharmacy, Cairo University, Egypt.

2.2. Synthesis

2.2.1. Synthesis of 1-(2-hydroxynaphthalen-1-yl)-3-phenyl propane-1,3-dione (1)

A mixture of ethyl benzoylacetate (0.01 mol) and β-naphthol (0.01 mol) was exposed to microwave irradiation for 4-6 mins, the reaction mixture was allowed to reach room temperature, then diluted with ethanol with stirring and the solid product that formed, was filtrated and crystallized from ethanol (Scheme 1). Color: Brown. Yield: 91%. M.p.: 136-138 °C. FT-IR (KBr, ν, cm^{-1}): 3434 (OH), 3056 (CH-Arom), 2967 (CH-Aliph), 1727, 1637 (2CO). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.38 (s, 2H, CH_2), 7.13-8.29 (m, 11H, aromatic H), 9.92 (s, 1H, OH). MS (EI, *m/z* (%)): 290 (M+, 18). Anal. calcd. for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86; O, 16.53. Found: C, 78.62; H, 4.88; O, 16.54%.

2.2.2. General procedure for preparation of benzylidene derivatives (4a-d)

A mixture of compound **1** (0.01 mol), appropriate aryl aldehydes (0.01 mol) in ethanol (30 mL) with catalytic amount of piperidine was heated under reflux for 3 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from ethanol to give compound **4a-d** (Scheme 1).

2-Benzylidene-1-(2-hydroxynaphthalen-1-yl)-3-phenyl propane-1,3-dione (**4a**): Color: Pale green. Yield: 61%. M.p.: 145-147 °C. FT-IR (KBr, ν, cm^{-1}): 3453 (OH), 3057 (C-H-Arom), 1726, 1637 (2C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.24 (s, 1H, CH-olefinic), 7.06-8.34 (m, 16H, Ar-H), 9.95 (s, 1H, OH). MS (EI, *m/z* (%)): 378 (M+, 6). Anal. calcd. for $C_{26}H_{18}O_3$: C, 82.52; H, 4.79; O, 12.68. Found: C, 82.51; H, 4.78; O, 12.69%.

2-(4-Chlorobenzylidene)- 1 -(2-hydroxynaphthalen-1-yl) - 3-phenylpropane-1,3-dione (**4b**): Color: Pale yellow. Yield: 72%. M.p.: 170-172 °C. FT-IR (KBr, ν, cm^{-1}): 3437 (OH), 3057 (C-H, Ar), 1725, 1637 (2C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.68 (s, 1H, CH-olefinic), 7.20-8.37 (m, 15H, Ar-H), 9.96 (s, 1H, OH). MS (EI, *m/z* (%)): 414 (M^++2, 80). Anal. calcd. for $C_{26}H_{17}ClO_3$: C, 75.64; H, 4.15; O, 11.63. Found: C, 75.63; H, 4.14; O, 11.64%.

1-(2-Hydroxynaphthalen-1-yl)-2-(4-methoxybenzylidene)-3-phenylpropane-1,3-dione (**4c**): Color: Green. Yield: 69%. M.p.: 160-162 °C. FT-IR (KBr, ν, cm^{-1}): 3453 (OH), 3056 (C-H, Arom.), 2922 (C-H Aliph.), 1720, 1637 (2C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.84 (s, 3H, OCH_3), 5.20 (s, 1H, CH-olefinic), 7.54-8.30 (m, 15H, Ar-H), 9.94 (s, 1H, OH). MS (EI,

m/z (%)): 408 (M^+, 20). Anal. calcd. for $C_{27}H_{20}O_4$: C, 79.40; H, 4.94; O, 15.67. Found: C, 79.37; H, 4.91; O, 15.65%.

2-(4-Hydroxybenzylidene)-1- (2-hydroxynaphthalen-1-yl)-3-phenylpropane-1,3-dione (**4d**): Color: Pale yellow. Yield: 70 %. M.p.: 176-177 °C. FT-IR (KBr, ν, cm^{-1}): 3453 (OH), 3046 (C-H, Arom.), 1730, 1636 (2C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.48 (s, 1H, CH-olefinic), 7.59-8.38 (m, 15H, Ar-H), 9.95 (s, 1H, OH), 9.97 (s, 1H, OH). MS (EI, *m/z* (%)): 394 (M^+, 60). Anal. calcd. for $C_{26}H_{18}O_4$: C, 79.17; H, 4.60; O, 16.23. Found: C, 79.14; H, 4.55; O, 16.20%.

2.2.3. General procedure for preparation of tetrahydro pyrimidinethion derivatives (5a-d)

To boiling solution of compound **4a-d** (0.01 mol) and thiourea (0.01 mol) in ethanolic potassium hydroxide (30 mL, 10%), was added. The reaction mixture was refluxed for 20 h, then allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from ethanol to give compound **5a-d** (Scheme 1).

(4,6-Diphenyl-2-thioxo-1,2,3, 4-tetrahydropyrimidin-5-yl)(2-hydroxynaphthalen-1-yl)methanone (**5a**): Color: Yellow. Yield: 73 %. M.p.: 150-152 °C. FT-IR (KBr, ν, cm^{-1}): 3447, 3400 (OH/NH), 3058 (C-H, Arom.), 2964 (C-H, Aliph.), 1637 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.35 (s, 1H, CH-pyrimidine), 7.11-8.37 (m, 18H, Ar-H + 2NH), 9.97 (s, 1H, OH). MS (EI, *m/z* (%)): 436 (M^+, 5). Anal. calcd. for $C_{27}H_{20}N_2O_2S$: C, 74.29; H, 4.62; N, 6.42. Found: C, 74.30; H, 4.63; N, 6.41%.

(4-(4-Chlorophenyl)-6-phenyl-2-thioxo-1, 2, 3, 4-tetrahydro pyrimidin-5-yl)(2-hydroxynaphthalen-1-yl)methanone (**5b**): Color: Yellow. Yield: 77 %. M.p.: 177-179 °C. FT-IR (KBr, ν, cm^{-1}): 3400, 3374 (OH/NH), 3061 (C-H, Arom.), 2934 (CH Aliph.), 1685 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.35 (s, 1H, CH-pyrimidine), 7.21-8.38 (m, 17H, Ar-H + 2NH), 9.97 (s, 1H, OH). MS (EI, *m/z* (%)): 470 (M^+, 22). Anal. calcd. for $C_{27}H_{19}ClN_2O_2S$: C, 68.86; H, 4.07; N, 5.95. Found: C, 68.85; H, 4.06; N, 5.96%.

(2-Hydroxynaphthalen-1-yl)(4-(4-methoxyphenyl)-6-phenyl-2-thioxo-1,2,3, 4-tetrahydropyrimidin-5-yl)methanone (**5c**): Color: Pale yellow. Yield: 81 %. M.p.: 157-159 °C. FT-IR (KBr, ν, cm^{-1}): 3444, 3400 (OH/NH), 3057 (C-H, Arom.), 2965 (C-H, Aliph.), 1637 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.80 (s, 3H, OCH_3), 4.40 (s, 1H, CH-pyrimidine), 7.11-8.35 (m, 17H, Ar-H + 2NH), 9.96 (s, 1H, OH). MS (EI, *m/z* (%)): 466 (M^+, 20). Anal. calcd. for $C_{28}H_{22}N_2O_3S$: C, 72.08; H, 4.75; N, 6.00. Found: C, 72.02; H, 4.70; N, 6.06%.

(2-Hydroxynaphthalen-1-yl)(4-(4-hydroxyphenyl)-6-phenyl-2-thioxo-1,2,3, 4-tetrahydropyrimidin-5-yl)methanone (**5d**): Color: Yellow. Yield: 80 %. M.p.: 170-172 °C. FT-IR (KBr, ν, cm^{-1}): 3443, 3400 (OH/NH), 3057 (C-H Arom.), 2965 (C-H Aliph.), 1637 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.36 (s, 1H, CH-pyrimidine), 7.21-8.38 (m, 17H, Ar-H + 2NH), 9.95 (s, 1H, OH), 9.97 (s, 1H, OH). MS (EI, *m/z* (%)): 452 (M^+, 17). Anal. calcd. for $C_{27}H_{20}N_2O_3S$: C, 71.66; H, 4.45; N, 6.19. Found: C, 71.63; H, 4.41; N, 6.15%.

2.2.4. General procedure for preparation of compounds (7a,b)

A mixture of compound **1** (0.01 mol) and hydrazine hydrate or phenyl hydrazine in ethanol (30 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, washed with water and crystallized from ethanol to give compound **7a**,**b** (Scheme 1).

1-(3-Phenyl-1H-pyrazol-5-yl)naphthalen-2-ol (**7a**): Color: Pale brown. Yield: 55 %. M.p.: 182-184 °C. FT-IR (KBr, ν, cm^{-1}): 3417 (OH), 3202 (NH), 3050 (C-H Arom.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.85 (s, 1H, CH-pyrazole), 6.96-8.10 (m, 11H, Ar-H), 10.10 (hump, 1H, OH),12.95 (s, 1H, NH). MS (EI, *m/z* (%)): 286 (M^+, 50). Anal. calcd. for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.73; H, 4.95; N, 9.80%.

1-(1, 3-Diphenyl-1H-pyrazol-5-yl)naphthalen-2-ol (**7b**): Color: Brown. Yield: 62 %. M.p.: 202-204 °C. FT-IR (KBr, ν, cm^{-1}): 3417 (OH), 3065 (C-H Arom.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.11 (s, 1H, CH-pyrazole), 7.21-8.38 (m, 16H, Ar-H), 9.97 (s, 1H, OH). MS (EI, *m/z* (%)): 362 (M^+, 56). Anal. calcd. for $C_{25}H_{18}N_2O$: C, 82.85; H, 5.01; N, 7.73. Found: C, 82.83; H, 5.09; N, 7.76%.

2.2.5. Synthesis of 2-amino-5-(2-hydroxy-1-naphthoyl)-4-phenylthiophene-3-carbonitrile (10)

Equimolar amounts of compound **1** (0.01 mol), malononitrile and elemental sulfur (0.01 mol) in ethanol (30 mL) containing piperidine (1.2 mL) were refluxed for 15 hrs, poured onto cold water (30 mL) and acidified with HCl (pH = 3). The solid product thus formed was filtered and crystallized from dioxane (Scheme 1). Color: Yellow. Yield: 86 %. M.p.: 178-180 °C. FT-IR (KBr, ν, cm^{-1}): 3440 (OH), 3331, 3202 (NH_2), 3058 (C-H Arom.), 2212 (C≡N), 1638 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.20-8.38 (m, 11H, Ar-H), 9.97 (s, 1H, OH), 12.02 (s, 2H, NH_2). MS (EI, *m/z* (%)): 372 (M^++2, 22). Anal. calcd. for $C_{22}H_{14}N_2O_2S$: C, 71.33; H, 3.81; N, 7.56. Found: C, 71.35; H, 3.84; N, 7.59%.

2.2.6. Synthesis of 6-(2-hydroxynaphthalen-1-yl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (12)

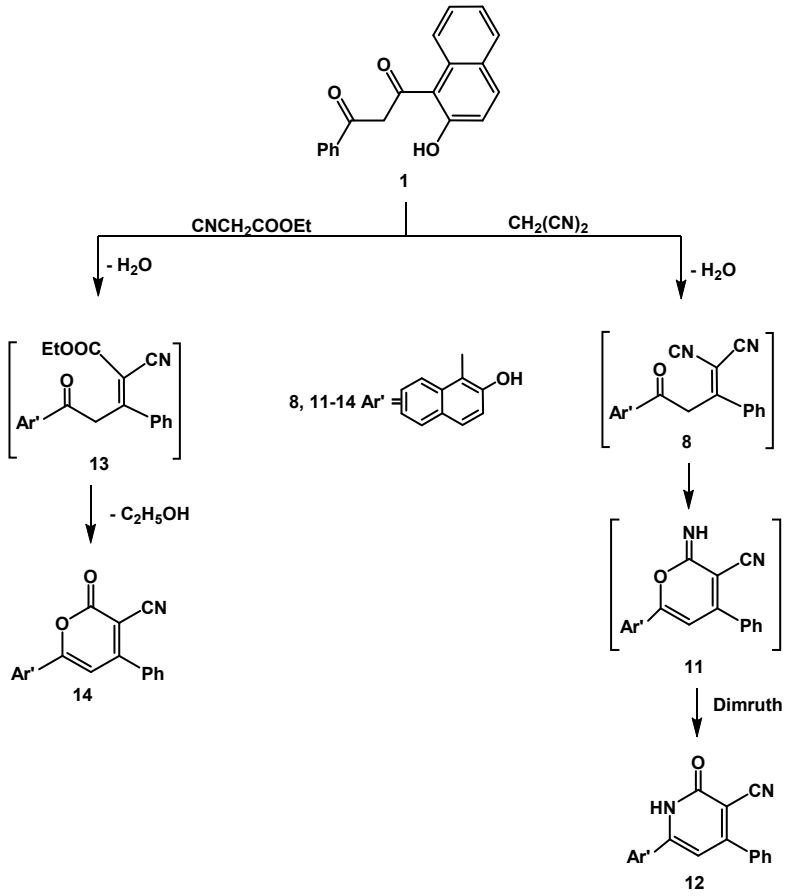
A mixture of compound **1** (0.01 mol), malononitrile (0.01 mol) in ethanol (30 mL) containing catalytic amount of piperidine was heated under reflux for 24 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from ethanol (Scheme 2). Color: Pale yellow. Yield: 76 %. M.p.: 146-148 °C. FT-IR (KBr, ν, cm^{-1}): 3408 (OH), 3400 (NH), 3060 (C-H Arom.), 2192 (C≡N), 1636 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.09 (s, 1H, =CH), 7.20-8.39 (m, 11H, Ar-H), 9.70 (s, 1H, NH), 9.98 (s, 1H, OH). MS (EI, *m/z* (%)): 338 (M^+, 17). Anal. calcd. for $C_{22}H_{14}N_2O_2$: C, 78.09; H, 4.17; N, 8.28. Found: C, 78.04; H, 4.13; N, 8.25%.

2.2.7. Synthesis of 6-(2-hydroxynaphthalen-1-yl)-2-oxo-4-phenyl-2H-pyran-3-carbonitrile (14)

A mixture of compound **1** (0.01 mol), ethylcyanoacetate 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, washed with water and crystallized from the ethanol (Scheme 2). Color: Pale yellow. Yield: 83 %. M.p.: 160-162 °C. FT-IR (KBr, ν, cm^{-1}): 3450 (OH), 3062 (C-H Arom.), 2196 (C≡N), 1658 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.92-8.38 (m, 12H, Ar-H), 9.20 (s, 1H, OH). MS (EI, *m/z* (%)): 339 (M^+, 27). Anal. calcd. for $C_{22}H_{13}NO_3$: C, 77.87; H, 3.86; N, 4.13. Found: C, 77.83; H, 3.83; N, 4.10%.

2.2.8. General procedure for preparation of pyrano-3-carbonitrile derivatives (19a-d)

A mixture of compound **1** (0.01 mol) and arylidine malononitrile **15a-d** (0.01 mol) in ethanol (40 mL) containing catalytic amount of piperidine (1.2 mL) was refluxed for 6 hrs, The reaction mixture was allowed to cool and poured in to cold water (30 mL) and acidified with HCl (pH = 3). The solid product was collected and crystallized from ethanol to give compound **19a-d** (Scheme 3).



Scheme 2

2-Amino-5-(2-hydroxy-1-naphthoyl)-4,6-diphenyl-4H-pyran-3-carbonitrile (**19a**): Color: Brown. Yield: 81 %. M.p.: 168-170 °C. FT-IR (KBr, ν, cm^{-1}): 3448 (OH), 3420, 3400 (NH_2), 3064 (C-H Arom.), 2932 (CH Aliph.), 2197 (C≡N), 1640 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.35 (hump, 1H, 4H-pyrane), 7.20-8.37 (m, 18H, Ar-H + NH_2), 9.97 (s, 1H, OH). MS (EI, *m/z* (%)): 444 (M^+, 40). Anal. calcd. for $C_{29}H_{20}N_2O_3$: C, 78.36; H, 4.54; N, 6.30. Found: C, 78.37; H, 4.55; N, 6.32%.

2-Amino-4-(4-chlorophenyl)-5- (2-hydroxy-1-naphthoyl)-6-phenyl-4H-pyran-3-carbonitrile (**19b**): Color: Pale yellow. Yield: 77 %. M.p.: 160-162 °C. FT-IR (KBr, ν, cm^{-1}): 3447 (OH), 3420, 3400 (NH_2), 3058 (C-H Arom.), 2191 (C≡N), 1639 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.36 (hump, 1H, 4H-pyrane), 7.17-8.34 (m, 17H, Ar-H + NH_2), 9.95 (s, 1H, OH). MS (EI, *m/z* (%)): 480 ((M^++2), 8). Anal. calcd. for $C_{29}H_{19}ClN_2O_3$: C, 72.73; H, 4.00; N, 5.85. Found: C, 72.75; H, 4.05; N, 5.88%.

2-Amino-5-(2-hydroxy-1-naphthoyl)-4- (4-methoxyphenyl)-6-phenyl-4H-pyran-3-carbonitrile (**19c**): Color: Pale yellow. Yield: 85 %. M.p.: 216-218 °C. FT-IR (KBr, ν, cm^{-1}): 3450 (OH), 3345, 3210 (NH_2), 2924 (C-H Aliph.), 2193 (C≡N), 1624 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.83 (s, 3H, OCH_3), 4.40 (hump, 1H, 4H-pyrane), 7.07-8.29 (m, 17H, Ar-H+NH_2), 9.93 (s, 1H, OH). MS (EI, *m/z* (%)): 474 ((M^+), 20). Anal. calcd. for $C_{30}H_{22}N_2O_4$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.90; H, 4.63; N, 5.88%.

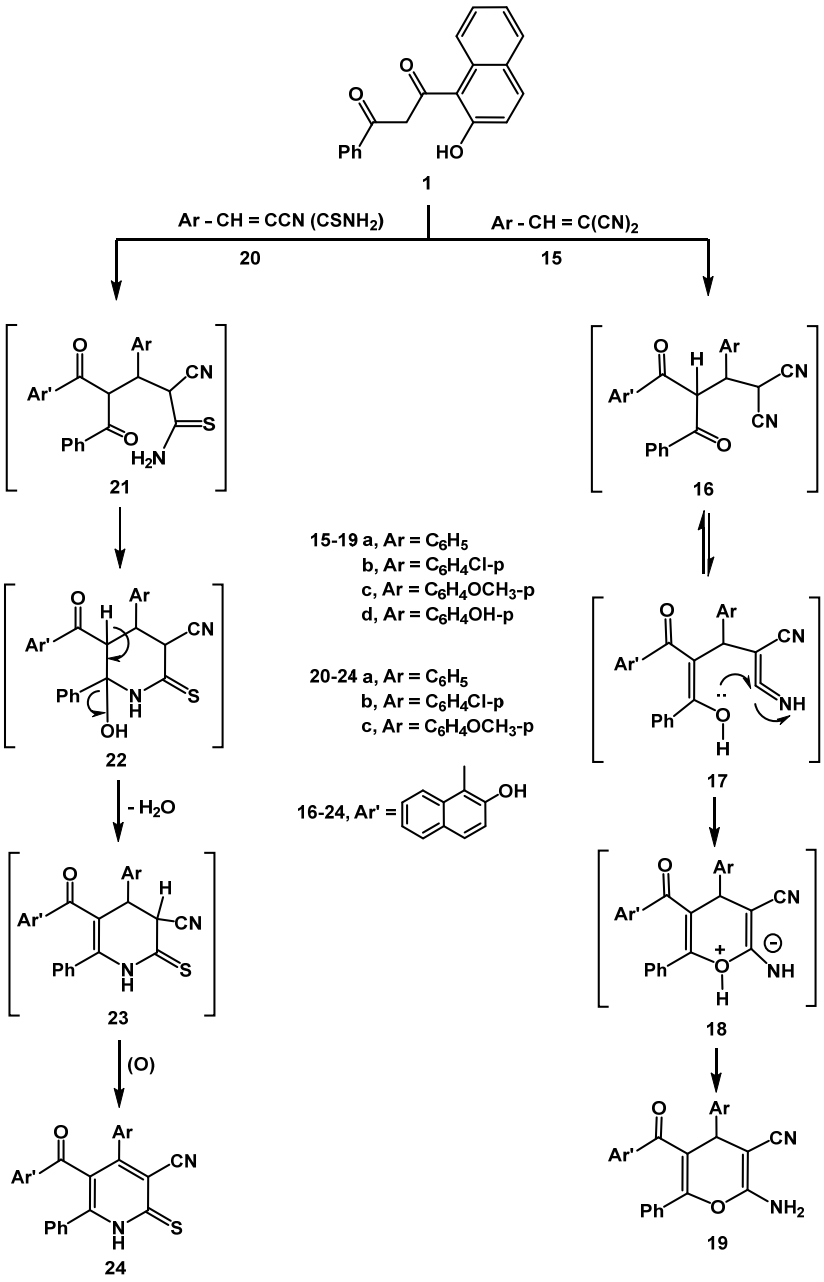
2-Amino-5-(2-hydroxy-1-naphthoyl)-4- (4-hydroxyphenyl)-6-phenyl-4H-pyran-3-carbonitrile (**19d**): Color: Brown. Yield: 79 %. M.p.: 163-165 °C. FT-IR (KBr, ν, cm^{-1}): 3347 (OH), 3300, 3222 (NH_2), 3063 (CH Arom.), 2934 (C-H Aliph.), 2199 (C≡N), 1624 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.50 (s, 1H, 4H-pyrane), 6.92 (s, 2H, NH_2), 6.94-8.38 (m, 15H, Ar-H), 9.98 (s, 1H, OH), 10.02 (s, 1H, OH). MS (EI, *m/z* (%)): 460 ((M^+), 37). Anal. calcd. for $C_{29}H_{20}N_2O_4$: C, 75.64; H, 4.38; N, 6.08. Found: C, 75.17; H, 4.39; N, 6.09%.

2.2.9. General procedure for preparation of dihydropyridine thion derivatives (24a-c)

A mixture of compound **1** (0.01 mol) and arylidene cyanothioacetamide derivatives **20a-c** (0.01 mol) in ethanol with catalytic amount of piperidine was heated under reflux for 10 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from ethanol to give compound **24a-c** (Scheme 3).

5-(2-Hydroxy-1-naphthoyl)-4, 6-diphenyl-2-thioxo-1, 2-di hydropyridine-3-carbonitrile (**24a**): Color: Yellow. Yield: 76 %. M.p.: 173-175 °C. FT-IR (KBr, ν, cm^{-1}): 3434 (OH), 3400 (NH), 3071 (C-H Arom.), 2189 (C≡N), 1634 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.58-8.36 (m, 17H, Ar-H + NH), 9.96 (s, 1H, OH). MS (EI, *m/z* (%)): 459 ((M^+ +1), 50). Anal. calcd. for $C_{29}H_{18}N_2O_2S$: C, 75.96; H, 3.96; N, 6.11. Found: C, 75.93; H, 3.90; N, 6.10%.

4-(4-Chlorophenyl)-5- (2-hydroxy-1-naphthoyl)-6-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**24b**): Color: Yellow. Yield: 70 %. M.p.: 173-175 °C. FT-IR (KBr, ν, cm^{-1}): 3464 (OH), 3433 (NH), 3070 (C-H Arom.), 2193 (C≡N), 1634 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.15-8.32 (m, 16H, Ar-H + NH), 9.94 (s, 1H, OH). MS (EI, *m/z* (%)): 494 ((M^++2), 5). Anal. calcd. for $C_{29}H_{17}ClN_2O_2S$: C, 70.66; H, 3.48; N, 5.68. Found: C, 70.60; H, 3.44; N, 5.69%.



Scheme 3

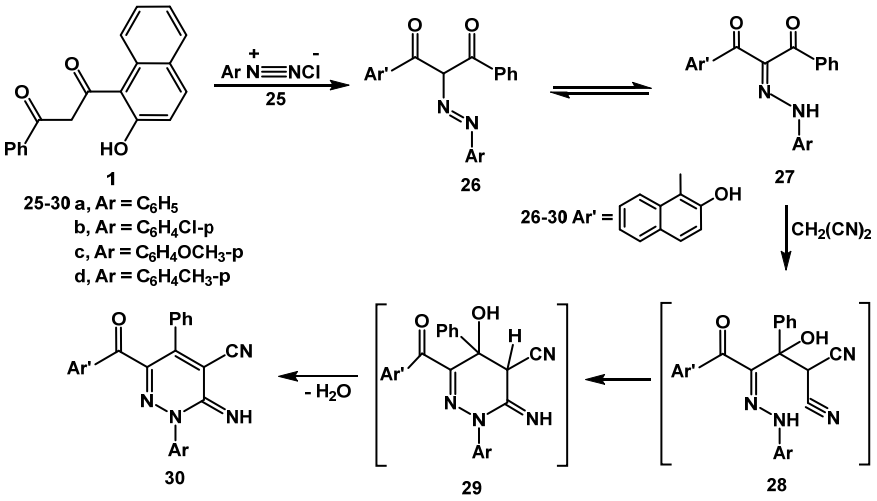
5-(2-Hydroxy-1-naphthoyl)-4- (4-methoxyphenyl)-6-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**24c**): Color: Yellow. Yield: 69 %. M.p.: 178-180 °C. FT-IR (KBr, ν, cm^{-1}): 3408 (OH), 3400 (NH), 3072 (C-H Arom.), 2924 (CH Aliph.), 2190 (C≡N), 1634 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.90 (s, 3H, OCH_3), 7.16-8.33 (m, 16H, Ar-H + NH), 9.95 (s, 1H, OH). MS (EI, *m/z* (%)): 488 ((M^+), 12). Anal. calcd. for $C_{30}H_{20}N_2O_3S$: C, 73.75; H, 4.13; N, 5.73. Found: C, 73.77; H, 4.15; N, 5.77%.

2.2.10. General procedure for preparation of compounds (27a-d)

To a stirred cold solution of aryldiazonium chlorides **25a-d** (0.01 mol, prepared by treating aniline derivatives (0.01 mol) with sodium nitrite (0.01 mol) in HCl, ethanol (30 mL) and catalytic sodium acetate, the active methylene reagent **1** was added gradually. The stirring was continued for two hrs. The solid product so formed was filtered off, washed with water several times, dried and crystallized from ethanol to give compound **27a-d** (Scheme 4).

1-(2-Hydroxynaphthalen-1-yl)-3-phenyl-2- (2-phenylhydrazono)propane-1, 3-dione (**27a**): Color: Red. Yield: 88 %. M.p.: 156-158 °C. FT-IR (KBr, ν, cm^{-1}): 3387 (OH), 3300 (NH), 3063 (C-H Arom.), 1743, 1634 (2C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.60-8.37 (m, 17H, Ar-H + NH), 9.97 (s, 1H, OH). MS (EI, *m/z* (%)): 394 ((M^+), 55). Anal. calcd. for $C_{25}H_{18}N_2O_3$: C, 76.13; H, 4.60; N, 7.10. Found: C, 76.15; H, 4.63; N, 7.13%.

2-(2-(4-Chlorophenyl)hydrazono)-1-(2-hydroxynaphthalen-1-yl)-3-phenylpropane-1,3-dione (**27b**): Color: Orange.



Scheme 4

Yield: 80 %. M.p.: 152-154 °C. FT-IR (KBr, ν, cm^{-1}): 3384 (OH), 3300 (NH), 3061 (C-H Arom.), 1743, 1635 (2C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.90-8.36 (m, 16H, Ar-H + NH), 9.96 (s, 1H, OH). MS (EI, *m/z* (%)): 430 ((M$^+$+2), 35). Anal. calcd. for $C_{25}H_{17}ClN_2O_3$: C, 70.02; H, 4.00; N, 6.53. Found: C, 70.09; H, 4.07; N, 6.55%.

1-(2-Hydroxynaphthalen-1-yl)-2- (2-(4-methoxyphenyl) hydrazono)-3-phenylpropane-1,3-dione (**27c**): Color: Red. Yield: 79 %. M.p.: 158-160 °C. FT-IR (KBr, ν, cm^{-1}): 3387 (OH), 3300 (NH), 3061 (C-H Arom.), 2923 (CH Aliph.), 1743, 1634 (2C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.86 (s, 3H, OCH_3), 7.12-8.70 (m, 16H, Ar-H + NH), 9.97 (s, 1H, OH). MS (EI, *m/z* (%)): 424 (M$^+$, 8). Anal. calcd. for $C_{26}H_{20}N_2O_4$: C, 73.57; H, 4.75; N, 6.60. Found: C, 73.58; H, 4.74; N, 6.61%.

1-(2-Hydroxynaphthalen-1-yl)-3-phenyl-2-(2-p-tolylhydrazono)propane-1,3-dione (**27d**): Color: Red. Yield: 73 %. M.p.: 170-172 °C. FT-IR (KBr, ν, cm^{-1}): 3437 (OH), 3400 (NH), 3072 (C-H Arom.), 2921 (CH Aliph.), 1743, 1634 (2C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.06 (s, 3H, CH_3), 7.17-8.33 (m, 16H, Ar-H + NH), 9.95 (s, 1H, OH). MS (EI, *m/z* (%)): 409 ((M$^+$+1), 17). Anal. calcd. for $C_{26}H_{20}N_2O_3$: C, 76.46; H, 4.94; N, 6.86. Found: C, 76.44; H, 4.95; N, 6.87%.

2.2.11. General procedure for preparation of dihydro pyridazine derivatives (30a-d)

A mixture of compounds **27a-d** (0.001 mole), ammonium acetate (1 g) and malononitrile (0.001 mole) was fused in domestic microwave oven for 3 minutes. The solid precipitate so formed was treated with ethanol and filtered out and crystallized from ethanol to give compound **30a-d** (Scheme 4).

6-(2-Hydroxy-1-naphthoyl)-3-imino-2, 5-diphenyl-2, 3-di hydropyridazine-4-carbonitrile (**30a**): Color: Brown. Yield: 87 %. M.p.: 185-187 °C. FT-IR (KBr, ν, cm^{-1}): 3419 (OH), 3350 (NH), 2203 (C≡N), 1680 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.14-8.31 (m, 17H, Ar-H + NH), 9.94 (s, 1H, OH). MS (EI, *m/z* (%)): 442 (M$^+$, 35). Anal. calcd. for $C_{28}H_{18}N_4O_2$: C, 76.01; H, 4.10; N, 12.66. Found: C, 76.07; H, 4.11; N, 12.67%.

2-(4-Chlorophenyl)-6- (2-hydroxy-1-naphthoyl)-3-imino-5-phenyl-2,3-dihydropyridazine-4-carbonitrile (**30b**): Color: Pale yellow. Yield: 75 %. M.p.: 192-194 °C. FT-IR (KBr, ν, cm^{-1}): 3417 (OH), 3213 (NH), 2203 (C≡N), 1680 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.19-8.36 (m, 15H, Ar-H), 9.96 (s, 1H, OH), 10.00 (s, 1H, NH). MS (EI, *m/z* (%)): 478 ((M$^+$+2), 13). Anal. calcd. for $C_{28}H_{17}ClN_4O_2$: C, 70.52; H, 3.59; N, 11.75. Found: C, 70.50; H, 3.58; N, 11.73%.

6-(2-Hydroxy-1-naphthoyl)-3-imino-2-(4-methoxyphenyl)-5-phenyl-2, 3-dihydropyridazine-4-carbonitrile (**30c**): Color: Brown. Yield: 74 %. M.p.: 186-188 °C. FT-IR (KBr, ν, cm^{-1}): 3382 (OH), 3300 (NH), 3070 (CH Arom.), 2929 (CH Aliph.), 2193 (C≡N), 1634 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.83 (s, 3H, OCH_3), 7.13-8.30 (m, 16H, Ar-H + NH), 9.93 (s, 1H, OH). MS (EI, *m/z* (%)): 472 (M$^+$, 5). Anal. calcd. for $C_{29}H_{20}N_4O_3$: C, 73.72; H, 4.27; N, 11.86. Found: C, 73.70; H, 4.23; N, 11.84%.

6-(2-Hydroxy-1-naphthoyl)-3-imino-5-phenyl-2-p-tolyl-2, 3-dihydropyridazine-4-carbonitrile (**30d**): Color: Brown. Yield: 87 %. M.p.: 184-186 °C. FT-IR (KBr, ν, cm^{-1}): 3385 (OH), 3300 (NH), 3071 (CH Arom.), 2924 (CH Aliph.), 2193 (C≡N), 1635 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.76 (s, 3H, CH_3), 6.67-8.37 (m, 16H, Ar-H + NH), 9.96 (hump, 1H, OH). MS (EI, *m/z* (%)): 456 (M$^+$, 7). Anal. calcd. for $C_{29}H_{20}N_4O_2$: C, 76.30; H, 4.42; N, 12.27. Found: C, 76.33; H, 4.45; N, 12.29%.

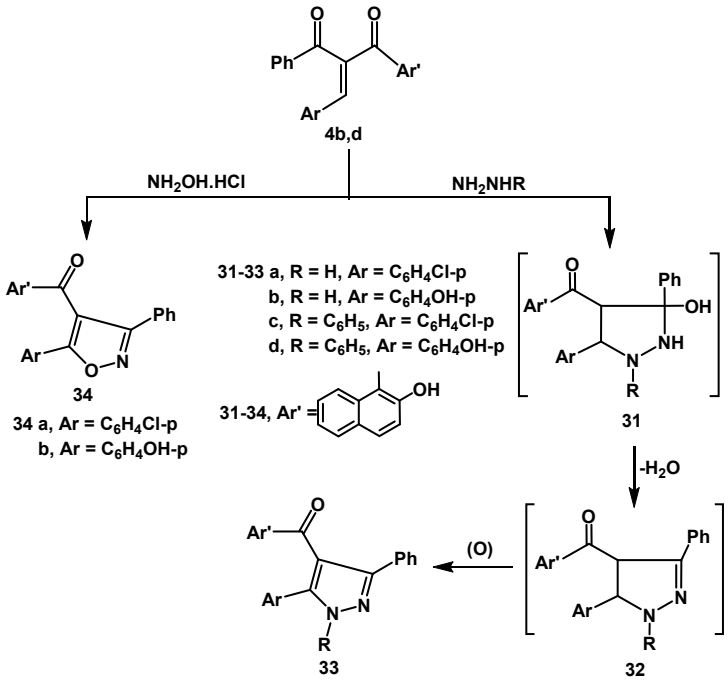
2.2.12. General procedure for preparation of pyrazol derivatives (33a-d)

A mixture of compound **4b**,**d** (0.01 mol) and hydrazine hydrate or phenyl hydrazine (0.01 mol) in ethanol (30 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, washed with water and crystallized from dioxane to give compound **33a-d** (Scheme 5).

(5-(4-Chlorophenyl)-3-phenyl-1H-pyrazol-4-yl) (2-hydroxy naphthalen-1-yl)methanone (**33a**): Color: Pale yellow. Yield: 68 %. M.p.: 188-190 °C. FT-IR (KBr, ν, cm^{-1}): 3418 (OH), 3204 (NH), 3051 (C-H Arom.), 1618 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.83-8.08 (m, 15H, Ar-H), 9.97 (s, 1H, OH), 12.93 (s, 1H, NH). MS (EI, *m/z* (%)): 426 (M$^+$+2, 15). Anal. calcd. for $C_{26}H_{17}ClN_2O_2$: C, 73.50; H, 4.03; N, 6.59. Found: C, 73.52; H, 4.08; N, 6.60%.

(2-Hydroxynaphthalen-1-yl) (5-(4-hydroxyphenyl)-3-phenyl-1H-pyrazol-4-yl)methanone (**33b**): Color: Brown. Yield: 72 %. M.p.: 182-184 °C. FT-IR (KBr, ν, cm^{-1}): 3446 (OH), 3205 (NH), 3051 (C-H Arom.), 1618 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.88-8.11 (m, 15H, Ar-H), 10.03 (s, 1H, OH), 12.92 (s, 1H, NH), 13.58 (s, 1H, OH). MS (EI, *m/z* (%)): 408 (M$^+$+2, 10). Anal. calcd. for $C_{26}H_{18}N_2O_3$: C, 76.83; H, 4.46; N, 6.89. Found: C, 76.85; H, 4.49; N, 6.91%.

(5-(4-Chlorophenyl)-1, 3-diphenyl-1H-pyrazol-4-yl)(2-hydro xynaphthalen-1-yl)methanone (**33c**): Color: Pale yellow. Yield: 80 %. M.p.: 190-192 °C.



Scheme 5

FT-IR (KBr, ν, cm^{-1}): 3386 (OH), 3063 (C-H Arom.), 1635 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.18-8.35 (m, 20H, Ar-H), 9.96 (s, 1H, OH). MS (EI, *m/z* (%)): 502 (M$^+$+2, 4). Anal. calcd. for $C_{32}H_{21}ClN_2O_2$: C, 76.72; H, 4.23; N, 5.59. Found: C, 76.74; H, 4.25; N, 5.61%.

(2-Hydroxynaphthalen-1-yl) (5-(4-hydroxyphenyl)-1, 3-di phenyl-1H-pyrazol-4-yl)methanone (**33d**): Color: Brown. Yield: 72 %. M.p.: 184-186 °C. FT-IR (KBr, ν, cm^{-1}): 3450 (OH), 3056 (C-H Arom.), 1638 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.67-8.39 (m, 20H, Ar-H), 9.96 (s, 1H, OH), 9.98 (s, 1H, OH). MS (EI, *m/z* (%)): 482 (M$^+$, 18). Anal. calcd. for $C_{32}H_{22}N_2O_3$: C, 79.65; H, 4.60; N, 5.81. Found: C, 79.64; H, 4.58; N, 5.80%.

2.2.13. General procedure for preparation of isoxazole derivatives (34a,b)

A mixture of compound **4b**,**d** (0.01 mol), hydroxylamine hydrochloride in glacial acetic acid (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 and crystallized from ethanol to give compound **34a**,**b** (Scheme 5).

(5-(4-Chlorophenyl)-3-phenylisoxazol-4-yl)(2-hydroxy naphthalen-1-yl)methanone (**34a**): Color: Pale yellow. Yield: 71 %. M.p.: 158-160 °C. FT-IR (KBr, ν, cm^{-1}): 3447 (OH), 3058 (C-H Arom.), 1640 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.16-8.33 (m, 15H, Ar-H), 9.95 (s, 1H, OH). MS (EI, *m/z* (%)): 427 (M$^+$+2, 11). Anal. calcd. for $C_{26}H_{16}ClNO_3$: C, 73.33; H, 3.79; N, 3.29. Found: C, 73.30; H, 3.74; N, 3.27%.

(2-Hydroxynaphthalen-1-yl) (5-(4-hydroxyphenyl)-3-phenyl isoxazol-4-yl)methanone (**34b**): Color: Pale yellow. Yield: 69 %. M.p.: 163-165 °C. FT-IR (KBr, ν, cm^{-1}): 3446 (OH), 3060 (C-H Arom.), 1640 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.58-8.36 (m, 15H, Ar-H), 9.94 (s, 1H, OH), 9.97 (s, 1H, OH). MS (EI, *m/z* (%)): 407 (M$^+$, 3). Anal. calcd. for $C_{26}H_{17}NO_4$: C, 76.65; H, 4.21; N, 3.44. Found: C, 76.64; H, 4.23; N, 3.45%.

2.2.14. Synthesis of 2-(ethoxymethylene)-1-(2-hydroxy naphthalen-1-yl)-3-phenylpropane-1,3-dione (35)

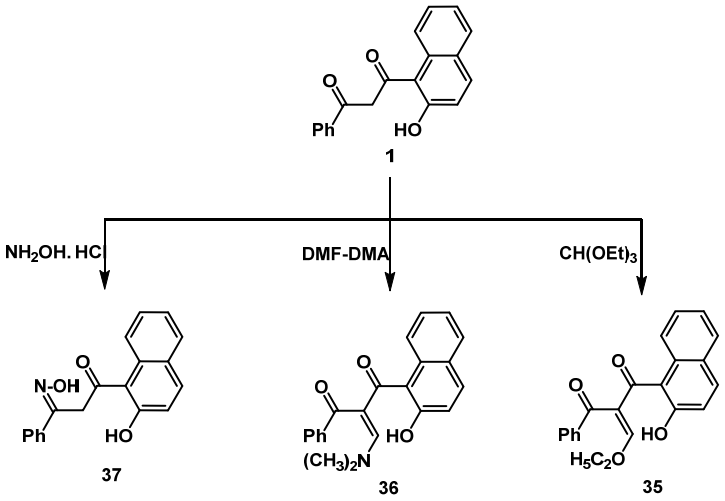
A mixture of compound **1** (0.01 mol) and triethoxy-methane (3 mL) in acetic anhydride (10 mL) was heated under reflux for 6 hrs. The reaction mixture was allowed to cool. The separated solid was filtered, washed with ethanol and crystallized from ethanol (Scheme 6). Color: Brown. Yield: 53 %. M.p.: 164-166 °C. FT-IR (KBr, ν, cm^{-1}): 3383 (OH), 3068 (CH, Arom.), 2932-2852 (CH, Aliph.), 1738, 1635 (2CO). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.11 (t, 3H, CH_3), 4.35 (q, 2H, CH_2), 6.90 (s, 1H, CH-olefinic), 7.17-8.04 (m, 11H, Ar-H), 9.97 (s, 1H, OH). MS (EI, *m/z* (%)): 347 (M$^+$+1, 13). Anal. calcd. for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24; O, 18.48. Found: C, 76.28; H, 5.20; O, 18.43%.

2.2.15. Synthesis of 2-((dimethylamino)methylene)-1-(2-hydroxynaphthalen-1-yl)-3-phenylpropane-1,3-dione (36)

A mixture of compound **1** (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, washed with ethanol and crystallized from ethanol (Scheme 6). Color: Pale yellow. Yield: 57 %. M.p.: 158-160 °C. FT-IR (KBr, ν, cm^{-1}): 3437 (OH), 3058 (CH, Arom.), 2960-2852 (CH, Aliph.), 1638 (CO). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.56 (s, 6H, $2CH_3$), 7.17 (s, 1H, CH-olefinic), 7.58-8.35 (m, 11H, Ar-H), 9.96 (s, 1H, OH). MS (EI, *m/z* (%)): 345 (M$^+$, 20). Anal. calcd. for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.51; H, 5.56; N, 4.11%.

2.2.16. Synthesis of 3-(hydroxyimino)-1-(2-hydroxy naphthalen-1-yl)-3-phenylpropan-1-one (37)

A mixture of compound **1** (0.01 mol), hydroxylamine hydrochloride in glacial acetic acid (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).



Scheme 6

$$\%\ Activity\ Index = \frac{\text{Zone of inhibition by test compound (diametre)}}{\text{Zone of inhibition by standard (diametre)}} x100 \qquad (1)$$

The separated solid was filtered and crystallized from ethanol (Scheme 6). Color: Pale brown. Yield: 76 %. M.p.: 145-147 °C. FT-IR (KBr, ν, cm^{-1}): 3427 (OH), 3079 (C-H Arom.), 2925 (CH Aliph.), 1638 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.40 (s, 2H, CH_2), 7.18-8.35 (m, 12H, Ar-H + OH), 9.96 (s, 1H, OH). MS (EI, *m/z* (%)): 305 (M^+, 45). Anal. calcd. for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.75; H, 4.96; N, 4.61%.

2.3. Pharmacology

2.3.1. In-vitro antimicrobial activity

The newly synthesized compounds and its derivatives 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 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 aeruginosa*, *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 [32]. 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).

2.3.2. Minimum inhibitory concentration 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) concentrations 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 [33,34]. Control experiments with DMSO and uninoculated media were run parallel to the test compounds under the same condition.

3. Results and discussion

3.1. Synthesis

In continuation of this work and as a part of our biological chemistry program [35-38], we reported here the utility of 1-(2-hydroxynaphthalen-1-yl)-3-phenylpropane-1,3-dione (**1**) in the synthesis of unique heterocyclic of expected biological interest. Thus, β-diketone (**1**) is prepared in a quantitative yield in a demostic microwave oven from the reaction of 2-naphthol and ethylbenzoylacetate. β-diketone (**1**) underwent several chemical transformations aiming at exploring its synthetic potentiality. Thus, β-diketone (**1**) reacted with aryl aldehydes **3a-d** to afford the condensation products **4a-d** (Scheme 1). Structures of compounds **4a-d** were established using their elemental and spectral data. Compounds **4a-d** are allowed to react with thiourea to afford tetrahydropyrimidine thions **5a-d** [39] (Scheme 1). Structures of tetrahydro pyrimidinethions **5a-d** were established using their elemental and spectral data. For example, the IR spectrum of compound **5a** revealed an absorption band at 3447 cm^{-1} corresponding to OH group and a band at 3400 cm^{-1} corresponding to NH group and a band at 1637 cm^{-1} corresponding to carbonyl group. The ^{1}H NMR of the same product revealed to the presence of a signal at δ 4.35 ppm corresponding to aliphatic proton at

pyrimidine ring, a multiplet signal at δ 7.11-8.37 ppm corresponding to Ar-Hand amino function and a signal at δ 9.97 ppm corresponding to OH function. The mass spectrum of the same product is in accordance with the proposed structure. Furthermore, the behavior of β-diketone (**1**) toward nitrogen nucleophile was also investigated. Thus, β-diketone (**1**) reacted with hydrazine and phenylhydrazine to afford substituted pyrazoles **7a**,**b**. Establishing structure pyrazoles **7a**,**b** was based on their elemental and spectral data [40,41] (Scheme 1). In addition to this the behaviour of β-diketone (**1**) toward a mixture of active methylene and elemental sulfur was also investigated. Thus, β-diketone (**1**) reacted with malononitrile and elemental sulfur to afford the thiophene derivative **10** (Scheme 1). The formation of thiophene **10** from the reaction of diketone (**1**) and malononitrile is beleived to be formed via initial addition of malononitrile on the double bond system of carbonyl group of diketone **1** and subsequent elimination of water to afford the non-isolable intermediate **8**. The intermediate **8** reacted with elemental sulfur to afford thiophene **10** via intermediacy of compound **9** (Scheme 1). Establishing structure thiophene **10** was based on its elemental analysis and spectral data. The IR spectrum of compound **10** revealed an absorption band at 3440 cm^{-1} corresponding to OH group and a band at 2212 cm^{-1} corresponding to CN group and a band at 1638 cm^{-1} corresponding to carbonyl group. The mass spectrum of the same product is in accordance with the proposed structure.

The behaviour of β-diketone (**1**) toward active methylene reagent was also investigated. Thus, β-diketone reacted with malononitrile to afford the dihydropyridine derivative **12** (Scheme 2). The formation of dihydropyridine derivative **12** from the reaction of diketone (**1**) and malononitrile is beleived to be formed via initial addition of malononitrile on the double bond system of carbonyl group of diketone and subsequent elimination of water to afford the non-isolable intermediate **8**. The intermediate **8** tautomerizes and cyclizes under the same reaction condition to afford the non-isolable intermediate **11** which underwent Dimruth rearrangement to afford compound **12** (Scheme 2). Establishing structure **12** was based on its elemental analysis and spectral data. The IR spectrum of compound **12** revealed an absorption band at 2192 cm^{-1} corresponding to CN group and a band at 1636 cm^{-1} corresponding to carbonyl group. The mass spectrum of the same product is in accordance with the proposed structure. Thus, it revealed a molecular ion peak at 338 *m/z* (M^+) and a number of fragments corresponding to the proposed structure. The product obtained from the reaction of β-diketone with malononitrile prompted us to investigate further the behaviour of β-diketone with ethylcyanoacetate. Thus, when compound **1** is allowed to react with ethylcyanoacetate under the same reaction condition afforded the pyranone derivative **14** whose structure was based on its spectral analysis. The formation of pyranone derivative **14** is beleived to be formed via initial addition of ethylcyanoacetate on the double bond system of compound **1** and subsequent elimination of water to afford the non-isolable intermediate **13**. The intermediate **13** tautomerizes and cyclizes under the same reaction condition to afford the pyranone derivative **14** (Scheme 2).

On the other hand the behaviour of β-diketone (**1**) toward some electrophilic reagents was also investigated. Thus, β-diketone reacted with arylidenemalononitrile **15a-d** under reflux to afford the pyrane derivatives **19a-d** (Scheme 3). The formation of pyrane derivatives is beleived to be formed via intial addition of active methylene of compound **1** on the double bond system of arylidenemalononitrile to afford the acyclic intermediate **16** which tautomerizes into compound **17** that cyclizes under the same reaction condition to afford compound **18** that tautomerizes into pyrane derivative **19** (Scheme 3). Establishing structure **19a-d** were based on their elemental and spectral analysis. Similarly, β-diketone reacted with arylidene cyanothioacetamide **20a-c** to afford the dihydropyridinethione derivatives **24a-c** (Scheme 3). Establishing structure **24a-c** were based on their elemental analysis and spectral data.

Coupling of β-diketone (**1**) with aryl diazonium salts **25a-d** in ethanol containing sodium acetate afforded the hydrazo form compound **27a-d** based on spectral data. Compounds **27a-d** reacted with malononitrile to afford pyridazine derivatives **30a-d**. Establishing structure **30** was based on its elemental and spectral data. For example, the IR spectrum of compound **30c** revealed the presence of a band at 3382 cm^{-1} corresponding to OH group, a band at 3300 cm^{-1} corresponding to NH group, a band at 2193 cm^{-1} corresponding to C≡N group and a band at 1634 cm^{-1} corresponding to C=O group. ^1H NMR of the same product revealed the presence of a signal at δ 3.83 ppm corresponding to OCH_3, a multiplet signal at δ 7.13-8.30 ppm corresponding to Ar-Hand amino function and a singlet signal at δ 9.93 ppm corresponding to OH group. The mass spectrum of the same product is in accordance with the proposed structure. Thus, it revealed a molecular ion peak at 472 *m/z* (M^+) beside a number of fragments agree with the proposed structure. Formation of pyridazine derivatives from the reaction of malononitrile and the hydrazo compounds **27** is beleived to be formed via initial addition of malononitrile on the double bond of carbonyl group of compound **27** to afford the acyclic intermediate **28**, that cyclizes and loses water to give compound **30** under the same reaction condition (Scheme 4).

Once more the behaviour of nitrogen nucleophile toward β-diketones **4b**,**d** was also investigated. Thus, when β-diketones **4b**,**d** are allowed to react with hydrazine and phenyl hydrazine pyrazoles derivative **33a-d** were obtained via intermediacy of compound **31** and **32** (Scheme 5). Establishing structures of compound **33a-d** were based on their elemental and spectral data. Similarly, β-diketones **4b**,**d** reacted with hydroxyl amine hydrochloride to afford isoxazole derivative **34** (Scheme 5). Establishing structures of compound **34a**,**b** were based on their elemental and spectral data.

Refluxing of compound **1** with triethylorthoformate in the presence of acetic anhydride yielded 2-(ethoxymethylene)-1-(2-hydroxynaphthalen-1-yl)-3-phenylpropane-1,3-dione, **35**. The IR spectrum of compound **35** showed bands at 3383 (OH), 3068 (CH-arom), 2932-2852 (CH-aliph) and 1738, 1635 (2CO) cm^{-1}. The ^1H NMR spectrum of compound **35** in DMSO-d_6 revealed signals at δ 1.11 (t, 3H, CH_3), 4.35 (q, 2H, CH_2), 6.90 (s, 1H, CH-olefinic), 7.17-8.04 (m, 11H, aromatic H), 9.97 (s, 1H, OH). β-diketone (**1**) react with dimethylformamidedimethyl-acetal (DMF-DMA) to yield 2-(dimethylamino) methylene)-1-(2-hydroxynaphthalen-1-yl)-3-phenylpropane-1,3-dione, **36** in excellent yield. The structure of the latter product was established on the basis of its elemental analysis and spectral data. For example, its ^1H NMR spectrum displayed three signals at δ 3.56, 7.17 and 9.96 ppm attributed to magnetically nonequivalent $N(CH_3)_2$ group, CH-olefinic and OH proton respectively. In addition to this a multiplet signals at δ 7.58-8.35 ppm corresponding to aromatic hydrogen atoms. Also hydroxylamine hydrochloride reacted with β-diketone (**1**) in refluxing glacial acetic acid containing anhydrous sodium acetate to afford 3-(hydroxyimino)-1-(2-hydroxy naphthalen-1-yl)-3-phenylpropan-1-one, **37** in excellent yield (Scheme 6).

3.2. Pharmacology

The newly synthesized compounds have been tested for antibacterial activity against Gram-negative bacteria (*Escherichia coli* & *Pseudomonas aeuroginosa*) and Gram-positive bacteria (*Bacillus subtilis*), and antifungal activity against yeast (*Candida albicans*) and myelial fungi (*Aspergillus flavus*) by the cup-plate method and agar diffusion disc method for determining MIC (Minimum inhibitory concentration).

Table 1. 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
5b	3	14.3	8	34.8	12	50.0	10	43.5	11	45.8	14	56.0
19b	4	19.0	10	43.5	14	58.3	12	52.2	13	54.2	16	64.0
27c	NA	-	NA	-	9	37.5	7	30.4	10	41.7	12	48.0
10	17	80.9	21	91.3	22	91.7	23	100.0	18	75.0	21	84.0
33a	13	61.9	17	73.9	20	83.3	20	86.9	17	70.8	20	80.0
19c	2	9.5	5	21.7	4	16.7	NA	-	3	12.5	5	20.0
33d	6	28.6	11	47.8	7	29.2	4	17.4	7	29.2	10	40.0
33c	11	52.4	16	69.6	18	75.0	19	82.6	14	58.3	17	68.0
1	7	33.3	13	56.5	11	45.8	9	39.1	5	20.8	8	32.0
5d	14	66.7	19	82.6	17	70.8	18	78.3	15	62.5	18	72.0
4b	9	42.8	14	60.9	16	66.7	16	69.6	12	50.0	15	60.0
34a	NA	-	3	13.0	2	8.3	NA	-	2	8.3	3	12.0
4c	10	47.6	15	65.2	15	62.5	13	56.5	6	25.0	10	40.0
24b	NA	-	NA	-	NA	-	NA	-	NA	-	NA	-
34b	5	23.8	12	52.2	8	33.3	5	21.7	8	33.3	11	44.0
36	NA	-	NA	-	NA	-	NA	-	NA	-	NA	-
33b	16	76.2	20	86.9	21	87.5	22	95.6	20	83.3	23	92.0
Ampicillin	21	100	23	100	24	100	23	100	NA	-	NA	-
Clotrimazole	NA	-	NA	-	NA	-	NA	-	24	100	25	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 (µg/mL)					
	E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*	*C. albicans*	*A. flavus*
5b	750	500	250	500	62.5	46.9
19b	750	375	250	500	46.9	23.4
27c	NA	NA	500	750	93.7	62.5
10	93.7	62.5	62.5	125	15.6	5.8
33a	187.5	125	93.7	187.5	23.4	7.8
19c	NA	750	NA	NA	500	375
33d	500	250	750	NA	187.5	93.7
33c	187.5	125	125	187.5	31.2	15.6
1	375	187.5	375	750	250	187.5
5d	125	93.7	125	250	23.4	11.7
4b	375	187.5	187.5	250	62.5	31.2
34a	NA	NA	NA	NA	750	500
4c	250	125	187.5	375	250	125
24b	NA	NA	NA	NA	750	750
34b	500	250	500	NA	125	93.7
36	NA	NA	NA	NA	NA	NA
33b	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.

Ampicillin and clotrimazole were used as standards for comparison of antibacterial and antifungal activity, respectively. 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 tasted compounds were active against most of microorganisms used. Both of compound **24b** and **36** showed no antibacterial or antifungal activity. On the other side each of compound **10** and **33b** showed maximum antibacterial and antifungal activity. Compound **27c** has no antibacterial activity against Gram-negative bacteria only, although it has broad spectrum antibacterial activity against Gram-positive bacteria and antifungal activity against *C. albicans* and *A. flavus*. On the other hands, compound **34a** 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 **19c** 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 rang spectrum antifungal activity. All the other compounds (**1**, **4b**, **4c**, **5b**, **5d**, **19b**, **33a**, **33c**, **33d**, **34b**) indicated wide range spectrum antibacterial and antifungal activity.

From Table 2, we observed that compounds **10**, **5d**, **33a**, **33b** and **33c** showed the lowest minimum inhibitory concentrations (MIC) for most tested bacteria and fungi, while compounds **19b**, **19c**, **33c** and **34b** exhibited high concentrations of MIC as compared with standard antimicrobial agents used.

4. Conclusion

In conclusion, the results of the present study indicate that the 1-(2-hydroxynaphthalen-1-yl)-3-phenylpropane-1,3-dione (**1**) was used as an efficient precursor for the synthesis of new heterocycles with expected biological activities.

Acknowledgements

I wish to express my sincere thanks and gratitude to all members Department of Chemistry, Faculty of Science, Arish University, Arish, Egypt

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