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SYNTHESIS OF NOVEL PYRAZOLE, OXAZOLE, AND PYRIDINE DERIVATIVES USING MIXED CHALCONE

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Abstract

In in order to develop new pyrazole, oxazole, and pyridine derivatives involving naphthalene and furan moieties, 3-(furan-2-yl)-1-(naphthalen-2-yl)prop-2-en-1-one 1 was condensed with various nitrogen and carbon nucleophiles. The related dihydropyridine was produced by cyclizing chalcone 1 with malononitrile in ammonium acetate and ethanol that were refluxing, and the resulting derivatives were produced by condensing the resulting product with various carbon electrophilic reagents. All of the newly synthesised substances were identified by spectroscopic and elemental evidence.

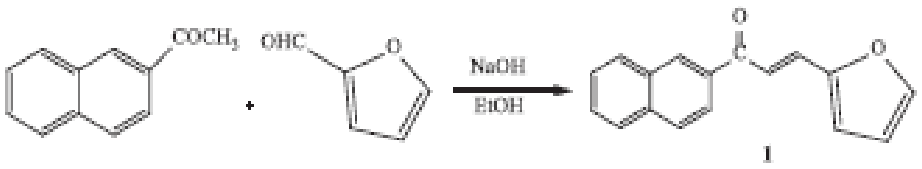
Keywords: naphthalene and furan moieties, nucleophiles, dihydropyridine, chalcone, reagents

Introduction

Heterocycles are an enormous and varied class of compounds in organic science. Particularly, Pyrazole, oxazole, and pyridine are significant heterocyclic chemical utilized both in synthetic and therapeutic processes. The pharmaceutical industry uses pyridine , pyrazole or oxazole a stable chemical, in particular for its anticancer, antifungal, antiviral, antibacterial, antioxidant, and electronic applications. α,β-Unsaturated ketones, such as pyrazoline and pyrimidine derivatives, are well-known intermediates for the synthesis of several heterocyclic compounds. According to a recent literature study, several pyrazoline compounds exhibit antibacterial [1], anti-inflammatory [2], and antifungal [3] properties. The pyrimidine nucleus is a pivotal part of organic substances such as nucleic acids and vitamin B1. Additionally, due to their biological performance as anti-HIV, anti-tubercular, and antidiabetic agents, several pyrimidine derivatives have exceptional therapeutical value [4,5]. In this analysis, we reported the synthesis of a range of pyrazole and pyridine derivatives in the context of the above facts and our ongoing efforts focused on the discovery and development of new heterocyclic molecules [6–11].

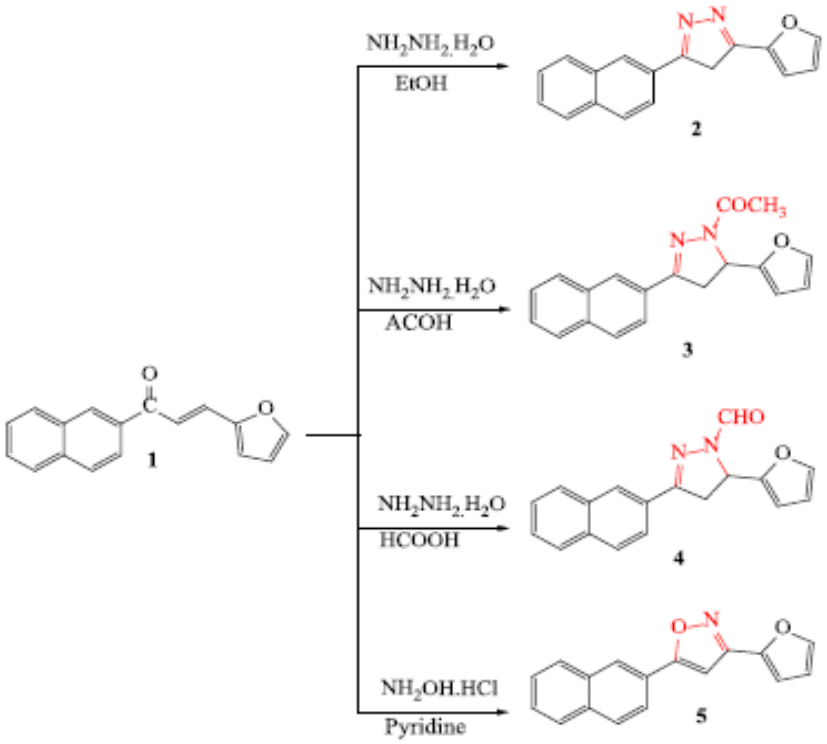
Results and Discussion

Due to the presence of the carbonyl group conjugated with the double bond, chalcones have a higher level of reactivity. This shows that the carbonyl group and the double bond are both potential sites for nucleophilic reactions with chalcones. Particularly interesting are the interactions with binucleophiles that produce a wide variety of cyclized molecules [12].
The base-catalyzed Claisen-Schmidt condensation of 1-(naphthalen-2-yl)ethan-1-one and furan-2-carbaldehyde led to the formation of 3-(Furan-2-yl)-1-(naphthalen-2-yl)prop-2-en-1-one (Scheme 1). Its infrared (IR) spectra, which displayed a typical peak for a conjugated carbonyl group at 1658 cm^{-1}, validated the structure.



Scheme: 1 Chalcone-1 Synthesis

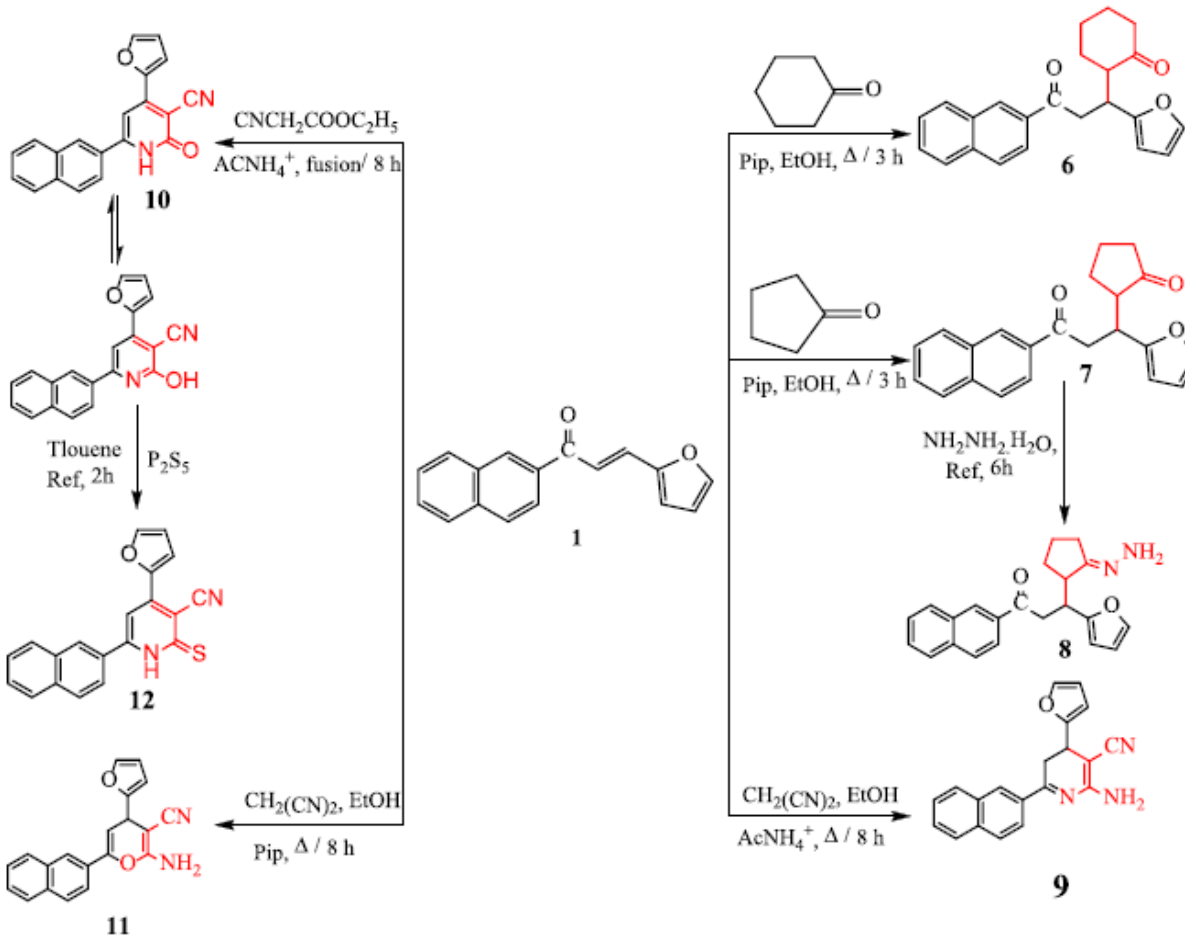
The reaction of,-unsaturated ketones with hydrazine hydrate and its derivatives (Scheme 2) is one of the most simple methods for generating pyrazolines [13, 14]. The synthesis of pyrazoline derivatives 2-4 involved the aza-Michael addition of hydrazine to chalcone 1, followed by a 5-exo-trig ring cyclization and dehydration, in the presence of ethanol, glacial acetic acid, and formic acid.



Scheme: 2 Synthesis of compounds 2–5

Mass spectra, IR, 1H-NMR, and elemental studies all verified the accuracy of the structures of compounds 2-4. Compounds 2-4's IR spectra displayed bands near 1625 cm^{-1}, which is where the C-N bond is formed. Compounds 3 and 4 also had CO-attributed bands at 1654 and 1647 cm^{-1}, respectively. In addition to signals at 5.72 and 5.68 for compounds 3 and 4, respectively, the existence of CH_2 proton at 2.67-2.80, 3.55-3.74, and 3.45-3.79 ppm in the 1H-NMR spectra of compounds 2 and 4 verified the design of the pyrazole ring. Additionally, compounds 3 and 4 had signals for CH3 and CHO proton, respectively, at 2.44 and 8.95 ppm.

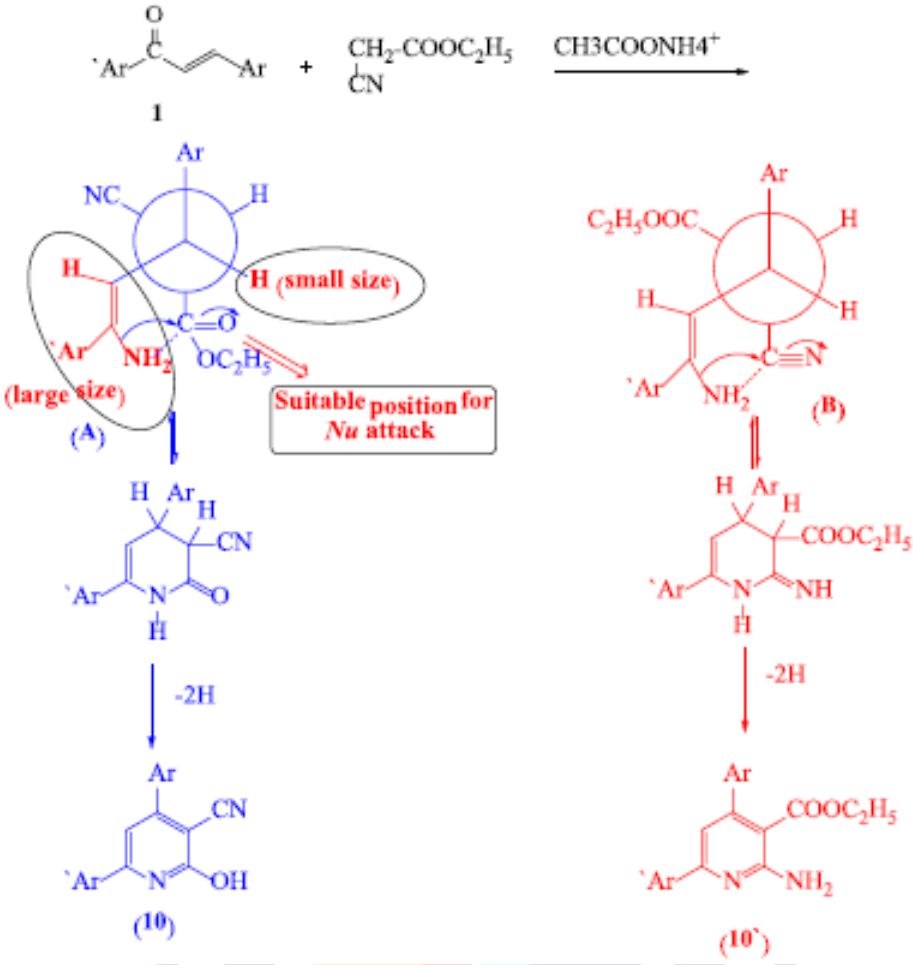
Additionally, the reaction of chalcone 1 with hydroxylamine hydrochloride produced the compounds 5, [15–18], and the 1H-NMR spectra of compound 5 was consistent with the expected structure since it displayed a signal at δ 6.96 for the CH of the isoxazole ring. Compounds 6 and 7 were produced via the reaction of chalcone 1 with cyclohexanone and cyclopentanone, respectively. Spectroscopic data that indicated bands in the infrared spectrum at 1731, 1773 and 1677, 1737 cm^{-1} that were assigned to 2CO, respectively, were used to confirm the structures of compounds 6 and 7. Compound 6's 1H-NMR spectra revealed signals at δ 1.34-2.57, 2.39, 3.46, and 3.71 ascribed to the CH, $COCH_2$, and cyclohexanone ring ($4CH_2$+CH) groups, respectively. The cyclopentanone ring is responsible for the signals in the 1H-NMR spectra of component 7 at ppm values of δ 1.50-2.51, 2.57-3.71, and 4.01-4.18 ($3CH_2$+CH, CH_2CO, and CH protons, respectively). The result of 7 reacting with hydrazine hydrate was compound 8. The NH_2 group appeared in the IR spectra at 3408 cm^{-1} (Scheme 3).



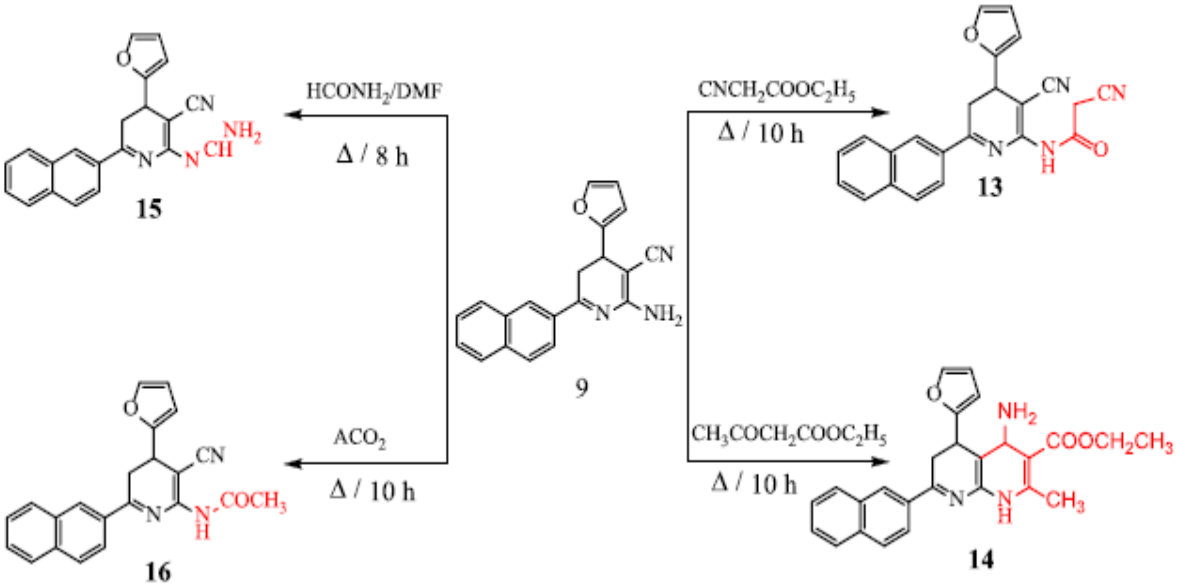
Scheme: 3 Synthesis of compounds 6–11

The cyanopyridine derivatives are typically produced by condensation of chalcone with malononitrile and ethyl cyanoacetate in refluxing ethanol in the presence of ammonium acetate [19]. These activities involve the cyanopyridine derivatives 9 and 10, which are obtained by treating chalcone 1 with malononitrile and ethyl cyanoacetate, respectively. In addition, chalcone and malononitrile combined with ethanol and piperidine produced 11. By capturing their spectral information, the structures of them were confirmed.
In the IR spectra of compounds 9 and 11, bands at 3122, 3121 and 2202, 2203 cm^{-1} were identified as belonging to the NH_2 and CN groups, respectively. Compounds 9 and 11 both had singlet signals in their 1H-NMR spectra at δ 5.50 and 5.32, which were both ascribed to NH_2 protons, respectively. However, bands at 3116, 2220, and 1652 cm^{-1} in the IR spectra of compound 10 were assigned to the NH, CN, and CO groups, respectively. A singlet was seen in the 1H-NMR spectra at δ 4.32 and 12.68 ppm, which was ascribed to an NH proton and an OH proton, respectively. The aforementioned spectrum measurements showed that compound 10 exhibits lactam-lactim tautomerism (Scheme 4).

The following can be used to explain why pyridones 10 are more prevalent: The ester group on one asymmetric carbon atom in conformation (A) is sandwiched between a small-sized group (H) and a large-sized group (-CH═CArNH$_2$) on the other asymmetric carbon, making this conformation the more stable and preferred (lowest energy) conformation. It requires the lowest activation energy and is more amenable to nucleophilic attack by nitrogen nucleophile on the ester group than conformation (B) [20]. In dry benzene, reaction 10 with P_2S_5 produced 4-(furan-2-yl)-6- (naphthalen-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile 12. Spectral measurements (see the Experimental section) supported the structure of compound 12 (Scheme 5). To create the dihydropyridine derivatives 13–16, compound 9 was condensed with several carbon electrophiles, including ethyl cyanoacetate, ethyl chloroacetate, formamide, and acetic anhydride (Scheme 4).



Scheme: 4 Mechanism of formation of compound 10



Scheme: 5 Synthesis of compounds 6–11

The IR spectra of 13 revealed bands at 3306, 3164, and 1640 cm^{-1} that, respectively, belong to the NH and CO groups. Compound 13's 1H-NMR results showed signals at δ 2.68 and 5.37 ppm that were ascribed to CH2 and NH protons, respectively. Compound 14's IR spectra showed bands at 3357 and 1740 cm^{-1}, which correspond to the NH and CO groups, respectively. Compound 14's 1H-NMR displayed signals for NH2 and CH2 protons at δ 4.22 and 5.42 ppm, respectively. Dihydropyridine derivative 15's 1H-NMR signal was at δ 5.56 ppm, which is consistent with NH2 protons. The dihydropyridine derivative 16 also exhibited IR bands at 3358 and 1710 cm^{-1}, which were associated with the NH and CO groups, respectively. Its 1H-NMR spectra showed signals at at δ 2.01 and 5.41 ppm that, respectively, corresponded to CH_3 and NH protons. All of the products (1–16) have a molecular ion peak (m/z) in their mass spectra, which is compatible with the structure of each chemical (See the section on experiments).

Conclusions

In this study, some functionalized derivatives of 3-(furan-2-yl)-1-(naphthalen-2-yl) prop-2-en-1-one chalcone were obtained by condensing it with hydrazine, hydroxylamine, cyclohexanone, cyclopentanone, ethyl cyanoacetate, and malononitrile, respectively. All the synthesized derivatives were characterized by spectral data. In addition, the synthesized products would be screened for their *in vitro* anticancer properties.

Experimental

All melting points were determined uncorrected using a Gallenkamp melting point equipment. On a Pye-Unicam SP-3-300 IR spectrophotometer (KBr Dicks), the IR spectra were captured and represented in wave number (cm^{-1}). While 13C-NMR spectra were performed at 75 MHz, 1H-NMR spectra were done at 400 MHz on a Varian Mercury VX-300 and BrukerAvance III NMR spectrometer, respectively. In deuterated dimethyl sulfoxide, tetramethylsilane was utilised as an internal standard (DMSO-d6). Chemical shifts are expressed in ppm. The acronyms are as follows: s, singlet; d, doublet; and m, multiple. The values of the coupling constant (J) are all specified in hertz. Using a Shimadzu GCMS-QP-1000EX mass spectrometer, the mass spectra were captured at 70 eV. On the Carbon-Hydrogen-Nitrogen (CHN) analyzer, elemental analyses were done, and all components were within ±0.4 of the theoretical values. Thin-layer chromatography (TLC) sheets coated with Merck 60 F254 plates' UV fluorescent silica gel were used to monitor the reactions. UV lighting and various solvents were used as the mobile phases to see the results. By using conventional methods, all solvents and reagents were dried and purified. The elemental analysis of all freshly produced compounds was suitable.

Formation of 3-(furan-2-yl)-1-(naphthalen-2-yl)prop-2-en-1-one (1).
10-mL of 10% sodium hydroxide solution was added to a combination of 2-acetylnaphthalene (10 mmol) and furfural (10 mmol) in 30-mL of ethanol, which was then stirred at 5–10°C for three hours. The precipitate was recovered by filtering and recrystallized in ethanol to produce **1** as a light yellow crystal.
Yield 95%; light yellow crystal; mp 91–93°C (EtOH); IR (cm^{-1}) *v*: 3060 (CH aromatic), 2845 (CH aliphatic), 1658 (CO); 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.53–6.54 (m, 1H, of the furan ring), 6.74 (d, 1H, of the furan ring), 7.53 (d, 1H, Ar–H, *J* = 8.8 Hz), 7.25–8.12 (m, 5H, Ar–H of the naphthalene ring, +1H of the furan ring +2H of the CH═CH), 8.55 (s, 1H, Ar–H of the naphthalene ring); 13C-NMR (100 MHz, $CDCl_3$): δ 114.7, 115.9, 120.3, 126.7, 127.4, 127.9, 128.3, 128.9, 129.4, 129.8, 130.9, 131.6, 132.5, 135.6, 144.5, 153.5, 187.3; MS (*m/z*): 249 (M^++1, 3%), 248 (M^+, 19%).
$C_{17}H_{12}O_2$, *Anal. calculated* (248.3): C, 82.24; H, 4.87. Found: C, 82.09; H, 4.53%.

Formation of 3-(furan-2-yl)-5-(naphthalen-2-yl)-4*H*pyrazole (2).
1 (10 mmol) and hydrazine hydrate (20 mmol) were combined with 20 mL of ethanol and refluxed for 8–10 hours. After cooling and being poured over ice, the reaction mixture was acidified with diluted hydrochloric acid. The resultant precipitate was separated by filtration, washed with water, dried, and recrystallized from ethanol to produce **2**.
Yield 74%; black crystal; mp 133–135°C (EtOH); IR (cm^{-1}) *v*: 3031 (CH aromatic), 1655, 1626 (C═N); 1HNMR (400 MHz, CDCl3) δ (ppm): 2.67–2.80 (m, 2H, CH_2 of the pyrazole ring), 6.37–6.93 (m, 2H of the furan ring), 7.25–8.10 (m, 6H, Ar–H of the naphthalene ring +d, 1H of the furan ring), 8.12 (s, 1H, Ar–H of the naphthalene ring); 13C-NMR (100 MHz, $CDCl_3$): δ 32.5, 111.9, 112.3, 127.7 (2), 129.2, 129.6, 129.9, 130.9, 135.4, 137.8, 139.3, 140.1, 144.5, 163.5 (2) 153.5; MS: *m/z* (%): 262.10 (M^++2, 100), 260 (M^++2,100%).

$C_{17}H_{12}N_2O$, *Anal. calculated* (260.3): C, 78.44; H, 4.65; N, 10.76. Found: C, 78.33; H, 4.70; N, 10.52%.

Formation of 1-(5-(furan-2-yl)-3-(naphthalen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one (3).
In 20 ml of glacial acetic acid, a combination of **1** (10 mmol) and hydrazine hydrate (20 moles) was refluxed for 6 to 8 hours. After cooling, the reaction mixture was poured over ice cubes. The precipitate produced was filtered, rinsed with water, dried, and recrystallized from ethanol to yield **3**.
Yield 83%; brownish-red crystal; mp 132–134°C (EtOH); IR (cm^{-1}) *v*: 3055 (CH aromatic), 2925 (CH aliphatic), 1654 (CO amide); 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.44 (s, 3H, CH_3), 3.55–3.74 (m, 2H, CH_2 of the pyrazole ring), 5.74 (d, 1H, CH of the pyrazole ring), 6.31–6.75 (m, 2H, furan ring), 7.25–8.10 (m, 6H, Ar–H + d, 1H of the furan ring), 8.47 (s, 1H, Ar–H of the naphthalene ring); 13C-NMR (100 MHz, $CDCl_3$): δ 24.5, 39.2, 53.4, 111.4, 112.8, 127.2 (2), 127.6, 128.6, 129.9, 130.2 (2), 130.4, 134.4, 136.8, 141.3, 144.5, 151.6, 167.5; MS: *m/z* (%): 305 (M^++1, 100), 304 (M^+, 22).
$C_{19}H_{16}N_2O_2$, *Anal. calculated* (304.3): 74.98; H, 5.30; N, 9.20. Found: 74.58; H, 5.32; N, 9.18%.

Formation of 5-(furan-2-yl)-3-(naphthalen-2-yl)-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde (4).
Formic acid (20 ml) was added to a mixture of 1 (10 mmol) and hydrazine hydrate (20 mmol) and refluxed for 8 hours. After cooling, the reaction mixture was poured over ice. The precipitate produced was removed by filtering, washed with water, dried, and recrystallized from ethanol to obtain **4**.
Yield 72%; brown crystal; mp 141–143°C (EtOH); IR (cm^{-1}) *v*: 3052 (CH aromatic), 2923 (CH aliphatic), 1647 (CO); 1H-NMR (400 MHz, DMSO-*d*6) δ (ppm): 3.45– 3.79 (m, 2H, CH_2 of the pyrazole ring), 5.68 (m, 1H, of the pyrazole ring), 6.34–641 (m, 2H, of the furan ring), 7.25–8.15 (m, 6H, Ar–H + d, 1H of the furan ring), 8.46 (s, 1H, Ar–H of the naphthalene ring), 8.95 (s, 1H, CHO); 13C-NMR (100 MHz, $CDCl_3$): δ 39.1, 51.3, 111.7, 112.3, 127.8 (2), 128.4, 128.6, 129.4, 131.2 (2), 130.5, 134.3, 137.8, 142.9, 115.5, 152.6, 158.5; MS: *m/z* (%): 292 (M^++2, 100), 290 (M^+, 30).
$C_{18}H_{14}N_2O_2$, *Anal. calculated* (290.3): C, 74.47; H, 4.86; N, 9.65. Found: C, 74.23; H, 4.80; N, 9.58%.

Formation of 3-(furan-2-yl)-5-(naphthalen-2-yl)isoxazole (5).
In glacial acetic acid (20 ml), a combination of 1 (10 mmol), hydroxylamine hydrochloride (10 mmol), and fussed sodium acetate was refluxed for 6 to 8 hours. After cooling, the reaction mixture was poured over ice cubes. The produced precipitate was removed, washed with water, dried, and recrystallized from ethanol to generate **5.**
Yield 84%; yellow-brown crystal; mp 207–209°C (EtOH); IR (cm^{-1}) *v*: 3055 (CH aromatic), 1655 (C═N); 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.69 (s, 1H, ═CH isoxazole ring), 7.12–7.24 (m, 1H of the furan ring), 7.27–8.18 (m, 6H, Ar–H + 2H of the furan ring), 8.81 (s, 1H, Ar–H of the naphthalene ring); 13C-NMR (100 MHz, $CDCl_3$): δ 99.3, 111.2, 112.5, 125.1, 126.5, 127.8 (2), 128.4 (2), 131.6, 133.5, 134.3,134.9, 143.9, 150.5, 158.6, 168.5; MS: *m/z* (%): 260 (M^+-1, 14%), 261 (M^+, 100%), 119 (25%).
$C_{17}H_{11}NO_2$, *Anal. calculated* (261.3): C, 78.15; H, 4.24; N, 5.36. Found: C, 77.68; H, 4.35; N, 5.30%.

General steps for compound 6 and compound 7 development.
Two drops of piperidine were added, along with a combination of **1** (10 mmol) and/or cyclohexanone, cyclopentanone (10 mmol), and ethanol (20 mL). After cooling and 16–18 hours of refluxing, the reaction mixture was poured over ice that had been crushed. In order to get **6** and **7**, the obtained precipitate was filtered out, washed with water, dried, and recrystallized from ethanol, respectively.

2-(1-(Furan-2-yl)-3-(naphthalen-2-yl)-3-oxopropyl)cyclohexan-1-one (6).
Yield 81%; buff crystal; mp 207–210°C (EtOH); IR (cm^{-1}) *v*: 3057 (CH aromatic), 2931(CH aliphatic), 1731,1773 (CO); 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.34–2.57 (m, 8H, $4CH_2$ of the cyclohexanone ring), 2.39 (m, 1H, CH of the cyclohexanone ring), 3.46 (m, 1H, CH), 3.71(m, 2H, CH2), 6.36 (d, 1H of the furan ring), 6.76 (d, 1H of the furan ring), 7.19–8.76 (m, 7H, Ar–H + d, 1H of the furan ring); 13C-NMR (100 MHz, $CDCl_3$): δ 16.3, 20.7 (2), 29.8, 38.8, 56.7, 106.3, 111.2, 125.1, 126.5, 127.5, 127.8, 128.5, 128.8, 129.7, 129.9, 132.6 (2), 134.5, 143.6, 156.5, 195.5, 216; MS: *m/z* (%): 346.4 (M^+, 14%), (226 100%), 119 (25%). $C_{23}H_{22}O_3$, *Anal. calculated* (346.4): C, 79.74; H, 6.40. Found: C, 79.82; H, 6.65%.

2-(1-(Furan-2-yl)-3-(naphthalen-2-yl)-3-oxopropyl) cyclopentan-1-one (7).
Yield (79%); buff crystal; mp 120–122°C (MeOH); IR (cm^{-1}) *v*: 3054 (CH aromatic), 2953 (CH aliphatic), 1677 (CO), 1737 (CO); 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.50–2.51 (m, 7H of the cyclopentanone

ring), 3.57–3.71 (m, 2H, CH_2), 4.01–4.18 (m, 1H, CH), 6.24 (d, 1H, furan ring), 7.25 (d, 1H, furan ring), 7.28–8.02 (m, 6H, Ar–H + 1H of the furan ring), 8.49 (s, 1H, Ar–H of the naphthalene ring); 13C-NMR (100 MHz, $CDCl_3$): δ 24.4, 25.4 (2), 29.6, 41.8, 44.7, 55.7, 106.3, 111.2, 125.1, 125.5, 126.4, 127.5, 128.5, 129.3, 131.9, 132.6, 134.5, 143.6, 155.5, 168.5, 210; MS: *m*/*z* (%): 332 (M^+, 14), 333 (M^++1, 38).
$C_{22}H_{20}O_3$, *Anal. calculated* (332.4): C, 79.50; H, 6.07. Found: C, 79.22; H, 5.92%.

Formation of 3-(furan-2-yl)-3-(2-hydrazonocyclopentyl)-1-(naphthalen-2-yl)propan-1-one (8).
It was refluxed for 6 to 8 hours with a combination of **7** (10 mmol) and hydrazine hydrate (20 mmol) in ethanol (20 mL). The reaction mixture was cooled, placed over ice, and then treated with hydrochloric acid to make it acidic. The precipitate was then dried, filtered, washed with water, and recrystallized from the ethanol to obtain **8**.
Yield 78%; Brown-yellow crystal; mp 168–170°C (EtOH); IR (cm^{-1}) *v*: 3408 (NH2), 3054 (CH aromatic), 2875 (CH aliphatic),1672 (CO); 1H-NMR (400 MHz, DMSO-*d*6) δ (ppm): 1.74–2.08 (m, 7H of the cyclopentanone ring), 2.8–3.05 (m, 1H, CH), 3.31–3.56 (m, 2H, CH_2), 3.84 (br. s, 2H, NH_2), 6.15 (d, 1H, furan ring), 7.29 (d, 1H, furan ring), 7.27–8.05 (m, 6H, Ar–H + 1H of the furan ring), 8.08 (s, 1H, Ar–H of the naphthalene ring); 13C-NMR (100 MHz, $CDCl_3$): δ 24.5 (2), 28.7, 29.5, 43.7, 44.4, 106.3, 111.2, 125.3, 126.5, 127.5, 128.4, 128.9, 129.1, 129.6, 133.4 (2), 134.4, 142.6, 155.5, 159.5, 198.4; MS: *m*/*z* (%): 346 (M^+, 5%), 226 (38%), 107 (100%).
$C_{22}H_{22}N_2O_2$, *Anal. calculated* (346.4): C, 76.28; H, 6.40; N, 8.09. Found: C, 76.00; H, 6.46; N, 8.15%.

Formation of 2-amino-4-(furan-2-yl)-6-(naphthalen-2-yl)-4,5-dihydropyridine-3-carbonitrile (9).
During an 8-hour reflux process in ethanol, a combination of **1** (10 mmol), malononitrile (10 mmol), and ammonium acetate (30 mmol) as catalyst was used. After cooling, the reaction mixture was poured over 50 ml of water. After being dried and filtered, the resulting solid was recrystallized from ethanol to create **9.**
Yield 85%; reddish crystal; mp 180–182°C (EtOH); IR (cm^{-1}) *v*: 3122, 3474 (NH_2), 3032 (CH aromatic), 2841 (CH aliphatic), 2203 (CN), 1623 (C═N); 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.73 (m, 2H, CH_2), 5.19 (m, 1H, CH), 5.50 (s, 2H, NH_2 D_2O exchangeable), 6.40–
6.53 (m, 1H, furan ring), 6.63–6.74 (d, 1H, furan ring), 7.25–8.11 (m, 7H, Ar–H + 1H, furan ring), 8.54 (s, 1H, Ar–H of the naphthalene ring); 13C-NMR (100 MHz, $CDCl_3$): δ 27.5, 34.7, 83.5, 106.7, 113.2, 117.7, 127.5 (2), 127.9, 128.6, 129.1 (2), 129.6, 130.5, 133.4, 134.4, 142.6, 152.5, 165.5, 198.4; MS: *m*/*z* (%): 313 (M^+, %), 311 (M^+-2, 59.98%).
$C_{20}H_{15}N_3O$, *Anal. calculated* (313.4): C, 76.66; H, 4.83; N, 13.41. Found: C, 76.85; H, 4.80 N, 13.50%.

Formation of 4-(furan-2-yl)-6-(naphthalen-2-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (10).
In an oil path at 170°C for 8 hours, a blend of **1** (10 mmol), ethyl cyanoacetate (10 mmol), and ammonium acetate (60 mmol) was fused. The reaction mixture was cooled and acidified with ice and water to create a solid, which was then dried and recrystallized from ethanol to produce **10**.
Yield 85%; brown crystal; mp >300°C (EtOH); IR (cm^{-1}) *v*: 3116 (NH), 3051 (CH aromatic), 2849 (CH aliphatic), 2220 (CN), 1652 (CO), 1611 (C═N); 1H-NMR (400 MHz, DMSO-*d*6) δ (ppm): 4.32 (s, 1H, NH D_2O exchangeable), 6.85 (m, 1H, of the Furan ring), 7.19 (s, 1H, Ar–H of the pyridine ring), 7.59–7.72 (m, 1H of the furan ring, 2H Ar–H of the naphthalene ring), 7.73 (d, 1H of the furan ring), 7.93–8.36 (m, 4H, Ar–H of the naphthalene ring), 8.50 (s,1H, Ar–H of the naphthalene ring), 12.68 (br. s, 1H, OH D_2O exchangeable); 13C-NMR (100 MHz, $CDCl_3$): δ 105.3, 109.5, 113.7, 115.7, 122.2, 124.7, 126.5 (2), 127.9, 128.6, 129.1, 129.7, 129.6, 131.5, 132.4, 134.4, 142.6, 149.5, 158.5, 160.4; MS: *m*/*z* (%): 311.3 (M^+-1, 88%), 312 (M^+, 16%), 313 (M^++1,100%).
$C_{20}H_{12}N_2O_2$, *Anal. calculated* (312.3): C, 76.91; H, 3.87; N, 8.97. Found: C, 76.78; H, 3.75; N, 8.95%.

Formation of 2-amino-4-(furan-2-yl)-6-(naphthalen-2-yl)-4*H-pyran-3-carbonitrile (11)*.
A fusion of **1** (10 mmol) and malononitrile (10 mmol) in ethanol (20 ml) was refluxed for 8 hours with two drops of piperidine as the catalyst. After cooling, the reaction mixture was poured over (50 ml) of water. After being dried and filtered, the resulting solid was recrystallized from ethanol to produce **11**.
Yield 76%; brown crystal; mp 180–182°C (EtOH); IR (cm^{-1}) *v*: 3121 (NH_2), 3044 (CH aromatic), 2948 (CH aliphatic), 2202 (CN), 1621 (C═N); 1H-NMR (400 MHz, DMSO-*d*6) δ (ppm): 5.32 (br. s, 2H, NH_2 D_2O exchangeable), 5.33 (d, 1H, pyran ring), 6.44 (m, 1H, pyran ring), 6.52–6.76 (m, 2H, furan ring), 7.09–7.43 (m, 2H, Ar–H + 1H of furan ring), 7.44–8.65 (m, 3H, Ar–H), 8.75 (m, 2H, Ar–H of the naphthalene ring);

13C-NMR (100 MHz, $CDCl_3$): δ 30.3, 60.5, 94.7, 107.7, 112.8, 118.7,123.4, 125.3, 126.5 (2), 127.4, 128.2, 129.1, 133.5,
134.4, 141.2, 142.6, 150.5, 155.5, 161.4; MS: *m*/*z* (%): 315 (M^++1, 8%), 155 (100%).
$C_{20}H_{14}N_2O_2$, *Anal. calculated* (314.3): C, 76.42; H, 4.49; N, 8.91. Found: C, 76.35; H, 4.54; N, 8.67%.

Formation of 4-(furan-2-yl)-6-(naphthalen-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (12).
Phosphorus pentasulfide was refluxed for two hours into a suspension of ten (10 mmol) in toluene (20 ml) and ten (10 mmol). The precipitate produced was filtered, heated, and dried before being recrystallized from ethanol to produce **12**.
Yield 56%; reddish crystal; mp >300°C (EtOH); IR (cm^{-1}) *v*: 3321 (NH), 1634 (C═N), 1476 (C═S); 1H-NMR (400 MHz, DMSO-*d6*) δ (ppm): 5.55 (s, 1H, SH D_2O exchangeable), 6.84–6.88 (m, 2H, of the furan ring), 7.21 (m, 1H, of the furan ring), 7.50 (s, 1H, Ar–H of the pyridine ring), 7.43–8.49 (m, 5H Ar–H of the naphthalene ring), 8.49 (s, 1H, Ar–H of the naphthalene ring), 8.55 (s, 1H, SH D_2O exchangeable); 13C-NMR (100 MHz, $CDCl_3$): δ 104.3, 110.5, 112.7, 116.7, 123.5, 124.2, 125.7, 126.0, 126.4, 127.9, 128.6, 128.9, 133.1, 134.7, 149.6, 150.5, 153.4, 164.4, 169.6, 170.4; MS: *m*/*z* (%): 328.4 (M^+, 11.97%), 423 (M^++2, 4.26%), 168.01 (100%).
$C_{20}H_{12}N_2OS$, *Anal. calculated* (328.4): C, 73.15; H, 3.68; N, 8.53. Found: C, 73.10; H, 3.50; N, 8.68%.

General steps for compound 13 and compound 14 development.
Anhydrous K_2CO_3 (10 mmol), active methylene, namely ethyl cyanoacetate and ethyl chloroacetate (10 mmol), and 9 (10 mmol) were added to 20 ml of dry dimethylformamide solution. After cooling and 10 hours of refluxing, the reaction mixture was dumped onto ice with hydrochloric acid. **13** and **14** were produced by filtering out the precipitate, washing it with water, drying it, and recrystallizing it from ethanol.

4-Amino-5-(furan-2-yl)-7-(naphthalen-2-yl)-2-oxo-1,2,5,6-tetrahydro-1,8-naphthyridine-3-carbonitrile (13).
Yield 79%; brown crystal; mp 152–154°C (EtOH); IR (cm^{-1}) *v*: 3306 (NH), 3043 (CH aromatic), 2923 (CH aliphatic), 2203 (CN), 1640 (CO); 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.68 (s, 2H, CH_2), 2.70–2.94 (m, 2H, CH_2), 3.69–3.74 (m, 1H, CH), 5.37 (s, 1H, NH), 6.63–6.80 (m, 2H, furan ring), 7.37–8.47 (m, 6H, Ar–H + 1H of the furan ring), 8.53 (s, 1H, Ar–H of the naphthalene ring); 13C-NMR (100 MHz, $CDCl_3$): δ 25.3, 28.5, 35.7, 90.5,
107.3, 112.2, 119.7, 125.4, 126.4, 127.3, 128.5 (2), 128.9, 129.2, 129.5, 133.5 134.4, 139.2, 142.4, 151.5, 153.2, 166.5, 168.8; MS: *m*/*z* (%): 380 (M^+, 11.36%), 134.01 (100%).
$C_{23}H_{16}N_4O_2$, *Anal. calculated* (380.4): C, 72.62; H, 4.24; N, 14.73. Found: C, 72.30; H, 4.28; N, 14.60%.

Formation of ethyl 4-amino-5-(furan-2-yl)-2-methyl-7-(naphthalen-2-yl)-1,4,5,6-tetrahydro-1,8-aphthyridine-3-carboxylate (14).
Yield 76%; brown crystal; mp 148–150°C (EtOH); IR (cm^{-1}) *v*: 3357 (NH2), 3167 (NH) 3045 (CH aromatic), 2923 (CH aliphatic), 2204 (CN), 1740 (CO), 1640 (C═N); 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.23–1.34 (t, 3H, CH_3), 1.84 (s, 1H, NH D_2O exchangeable), 2.73 (m, 2H, CH_2), 3.08 (m, 1H, CH), 3.55 (s, 3H, CH_3), 4.18 (q, 2H, CH_2), 4.22 (s, 2H, NH_2 D_2O exchangeable), 5.42 (s, 1H, CH), 6.21–6.74 (m, 2H, furan ring), 7.26–8.51 (m, 5H, Ar–H of the naphthalene ring +1H of the furan ring), 8.54–8.67 (m, 2H, Ar–H of the naphthalene ring); MS: *m*/*z* (%): 427 (M_+, 11.36%), 134.01 (100%); 13C-NMR (100 MHz, $CDCl_3$): δ 13.3, 15.5, 27.7, 35.5, 35.8, 62.3, 105.2, 108.7, 112.4, 116.4, 127.3 (2), 128.5, 129.4 (2), 129.7, 132.5 (2), 135.5, 136.4, 139.2, 142.5, 143.5, 150.2, 163.5, 168.8.
$C_{26}H_{25}N_3O_3$, *Anal. calculated* (427.5): C, 73.05; H, 5.89; N, 9.83. Found: C, 73.17; H, 5.96; N, 9.85%.

Formation of *N′*-(3-cyano-4-(furan-2-yl)-6-(naphthalen-2-yl)-4,5-dihydropyridin-2-yl)formimidamide (15).
Formamide and **(9)** were refluxed for 6 hours, chilled, and then poured onto crushed ice in a suspension. The resulting precipitate was removed, rinsed with water, dried, and recrystallized from ethanol to yield **15**.
Yield 75%; brown crystal; mp 150–152°C (EtOH); IR (cm^{-1}) *v*: 3315 (NH_2), 3045 (CH aromatic), 2923 (CH aliphatic), 2217 (CN), 1684 (CO); 1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.75–2.00 (m, 1H, of CH_2), 2.42–2.68 (m, 1H, of CH_2), 3.70 (m, 1H, CH), 5.56 (s, 2H, NH_2), 6.54–7.26 (m, 2H, furan ring), 7.37–8.23 (m, 5H, Ar–H of the naphthalene ring +1H of the furan ring) 3.70 (m, 1H, CH olefinic), 8.26–8.80 (m, 2H, Ar–

H of the naphthalene ring); 13C-NMR (100 MHz, $CDCl_3$): δ 28.1, 35.5, 105.7, 108.5, 112.8, 115, 119.3, 127.7 (2),127.9, 128.4, 129.2 (2), 129.6, 130.4, 133.3, 136.5, 142.4, 155.7, 156.5, 167.8.
$C_{21}H_{16}N_4O$, *Anal. calculated* (340.4): C, 74.10; H, 4.74; N, 16.46. Found: C, 74.05; H, 4.70; N, 16.48%.

Formation of *N*-(3-cyano-4-(furan-2-yl)-6-(naphthalen-2-yl)-4,5-dihydropyridin-2-yl)acetamide (16).
30 ml of acetic anhydride and **9** (10 mmol) were combined and refluxed for 15 minutes. The precipitate produced was removed, rinsed with water, dried, and recrystallized from ethanol to produce **16**.
Yield 78%; black crystal; mp 140–142°C (EtOH); IR (cm^{-1}) *v*: 3358 (NH), 3055 (CH aromatic), 2950 (CH aliphatic), 2217 (CN), 1710 (CO), 1591 (C═N); 1H-NMR (400 MHz, CDCl3) δ (ppm): 2.01 (s, 3H, CH3), 3.35–3.72 (m, 2H, CH2), 3.71 (m, 1H, CH), 5.41 (br. s, 1H, NH, D_2O exchangeable), 6.35–6.74 (m, 2H, furan ring), 7.32–8.60 (m, 6H, Ar–H + 1H of the furan ring), 8.66 (s, 1H, Ar–H of the naphthalene ring); 13C-NMR (100 MHz, $CDCl_3$): δ 22.1, 24.4, 34.7, 87.5, 108.8, 114, 117.7, 127.3 (2), 127.8, 128.4, 128.7, 129.2, 129.6, 130.4 (2), 134.3, 136.4, 141.4, 153.7, 164.5, 165.8; MS: *m*/*z* (%): 355 (M^+, 25.96%), 155 (100%). , $C_{22}H_{17}N_3O_2$, *Anal. calculated* (355.4): C, 74.35; H, 4.82; N, 11.82. Found: C, 74.20; H, 4.80; N, 11.92%.

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