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Research Article

Enaminonitrile as Building Block in Heterocyclic Synthesis: Synthesis of Novel *4H*-Furo[2,3-*d*][1,3]oxazin-4-one and Furo[2,3-*d*]pyrimidin-4*(3H)*-one Derivatives

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2-Amino-4,5-diphenylfuran-3-carbonitrile **1** was utilized as building block for the construction of new furo[2,3-*d*]pyrimidin-4*(3H)*-one derivative **2** and *4H*-furo[2,3-*d*][1,3]oxazin-4-one derivative **3** via treatment with acetic anhydride and benzoyl chloride, respectively. The *4H*-furo[2,3-*d*][1,3]oxazin-4-one derivative **3** was transformed into novel furo[2,3-*d*]pyrimidin-4*(3H)*-ones **4**–**8**, tetrazolylfuran derivative **10**, and furo[3,2-*d*]imadazolone derivative **11** via reaction with various nitrogen nucleophiles. The structure features of the synthesized compounds were established from their spectral and elemental analyses.

1. Introduction

Substituted and fused furans are one of the most important scaffolds in medicinal chemistry due to owning various biological activities including antimicrobial, antitumor, antiviral, antidepressant, and antihistaminic effects [1]. On the other hand, pyrimidines and fused pyrimidines represent an important class of heterocyclic compounds due to their biological activities [2–7]. Among the fused pyrimidines, the furopyrimidines attract the attention of the chemists due to possessing broad scope of pharmaceutical activities such as anticancer [8, 9], antiviral [10, 11], and antimicrobial [12] activities. There are great numbers of synthetic strategies for the preparation of furo[2,3-*d*]pyrimidines [10, 13–20]. Substituted 2-aminofuran-3-carbonitriles are known as easily obtainable starting material for synthesis of furo[2,3-*d*]pyrimidines using different reagents [13–16]. In the context of our sustained efforts to construct fused oxazine systems [21–23] and other heterocycles with potent antimicrobial activities [24–27], herein we reported the utility of 2-amino-4,5-diphenylfuran-3-carbonitrile [28] in synthesis of furo[2,3-*d*][1,3]oxazin-4-one and its transformation into different furo[2,3-*d*]pyrimidines and other heterocyclic systems via reactions with different nitrogen nucleophiles.

2. Experimental

Melting points were recorded on a Gallenkamp melting point apparatus. The FTIR spectra were run on a Pye Unicam SP 3-300 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL ECA-500 (300 MHz) spectrometer; chemical shifts were expressed in part per million δ (ppm) against TMS as an internal standard. ^{13}C-NMR spectra were run at 75.46 MHz. The MS spectra were measured on Agilent 5977A/MSD mass spectrometers (Agilent Technologies, USA) at 70 eV. Elemental analysis was performed by Vario EL-III elemental analysis.

*2.1. 2,5,6-Triphenylfuro[2,3-d]pyrimidin-4(3H)-one **2**.* A mixture of amino carbonitrile **1** (3 g, 10 mmol) and benzoyl chloride (30 mL) was refluxed for 24 hrs. The excess solvent was distilled off and the remaining solid was crystallized from

benzene to give **2** as brown crystals, m.p. 122–124°C, yield 49%. Anal. Calcd. for $C_{24}H_{16}N_2O_2$ (364.388): C, 79.11; H, 4.42; N, 7.69. Found: C, 79.07; H, 4.45; N, 7.65. IR (KBr, ν cm^{-1}): 3169 (NH), 1687 (CO). ^{1}H-NMR (DMSO-d_6) δ (ppm): 12.93 (s, 1H NH, exchangeable by D_2O), 7.92–7.44 (m, 15H, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 167.87, 133.50, 130.99, 129.78, 129.12. MS *m/z* (%): 364 ($M^{+\bullet}$, 100), 345 (10), 204 (9), 128 (15), 122 (18), 105 (42), 77 (40).

2.2. 2-Methyl-5,6-diphenyl-4H-furo[2,3-d][1,3]oxazin-4-one ***3***. A solution of amino carbonitrile **1** (3 g, 10 mmol) and freshly distilled acetic anhydride (30 mL) was heated under reflux for 24 hrs. The excess of acetic anhydride was removed and the remaining solid was crystallized from benzene to give **3** as gray crystals, m.p. 196–198°C, yield 55%. Anal. Calcd. for $C_{19}H_{13}NO_3$ (303.303): C, 75.24; H, 4.32; N, 4.62. Found: C, 75.20; H, 4.30; N, 4.65. IR (KBr, ν cm^{-1}): 1773 (CO). ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.70–7.00 (m, 10H, Ar-H), 2.4 (s, 3H, CH_3); ^{13}C- NMR (DMSO-d_6) δ (ppm): 167.68, 163.56, 156.18, 146.88, 145.68, 130.27, 129.44, 129.26, 129.16, 129.03, 128.83, 126.82, 21.90. MS *m/z* (%): 303 ($M^{+\bullet}$, 100), 261 (96), 204 (18), 178 (14), 128 (28), 105 (31), 77 (33).

2.3. 3-Amino-2-methyl-5,6-diphenylfuro[2,3-d]pyrimidin-4-one ***4***. A mixture of furo[2,3-*d*][1,3]oxazinone **3** (1.5 g, 5 mmol) and hydrazine hydrate (0.25 mL, 5 mmol) was stirred at room temperature in absolute ethanol (30 mL) for 30 min. The solid produced was filtered off, dried, and then crystallized from dioxane to afford **4** as pale yellow crystals, m.p. 212–214°C, yield 87%. Anal. Calcd. for $C_{19}H_{15}N_3O_2$ (317.330): C, 71.92; H, 4.76; N, 13.24. Found: C, 71.95; H, 4.80; N, 13.27. IR (KBr, ν cm^{-1}): 3308, 3256 (NH_2), 1691 (CO). ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.75–7.30 (m, 10H, Ar-H), 5.79 (s, 2H, NH_2, exchangeable by D_2O), 2.4 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) δ (ppm): 161.76, 157.64, 157.48, 146.27, 131.10, 130.50, 129.50, 129.31, 128.92, 128.66, 126.72, 104.95, 22.45. MS *m/z* (%): 317 ($M^{+\bullet}$, 100), 260 (9), 184 (15), 178 (4), 128 (4), 105 (13), 77 (12).

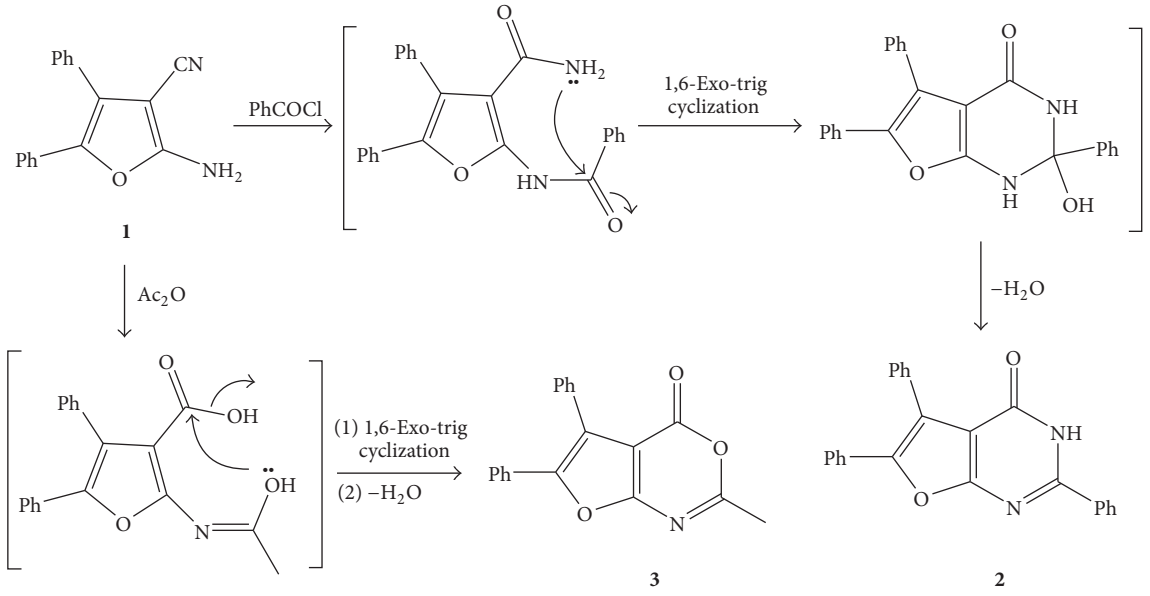
2.4. 2-Methyl-5,6-diphenylfuro[2,3-d]pyrimidin-4-one ***5***. A mixture of furo[2,3-*d*][1,3]oxazinone **3** (1.5 g, 5 mmol) in formamide (15 mL) was refluxed for 3 hrs. The reaction mixture, after cooling, was poured into ice/cold water and the separated solid was filtered off, dried, and crystallized from benzene to give **5**, as pale yellow crystals, m.p. 225-226°C, yield 75%. Anal. Calcd. for $C_{19}H_{14}N_2O_2$ (302.317): C, 75.53; H, 4.67; N, 9.27. Found: C, 75.51; H, 4.64; N, 9.30. IR (KBr, ν cm^{-1}): 3474, (NH), 1676 (CO). ^{1}H-NMR (DMSO-d_6) δ (ppm): 12.63 (s, 1H, NH, exchangeable by D_2O), 7.50–7.29 (m, 10H, Ar-H), 2.4 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6) δ (ppm): 161.40, 151.96, 148.31, 129.95, 129.43, 129.25, 128.86, 74.51, 22.45. MS *m/z* (%): 302 ($M^{+\bullet}$, 3), 288 (9), 271 (100), 256 (14), 216 (9), 189 (13), 105 (3), 77 (6).

2.5. 3-Hydroxy-2-methyl-5,6-diphenylfuro[2,3-d]pyrimidin-4-one ***6***. A solution of furo[2,3-*d*][1,3]oxazin-4-one **3** (1.5 g, 5 mmol) and hydroxylamine hydrochloride (0.34 g, 5 mmol) in pyridine (10 mL) was heated under reflux for 3 hrs. The reaction mixture was allowed to cool and then poured into ice/HCl. The obtained solid was filtered off, dried, and crystallized from benzene to give **6** as pale yellow crystals, m.p. 70–72°C, yield 77%. Anal. Calcd. for $C_{19}H_{14}N_2O_3$ (318.316): C, 71.69; H, 4.43; N, 8.80. Found: C, 71.65; H, 4.40; N, 8.83. IR (KBr, ν cm^{-1}): 3412, (br, OH), 1670 (CO). ^{1}H-NMR (DMSO-d_6) δ (ppm): 8.02–7.20 (m, 10H, Ar-H), 7.36 (s, 1H, OH, exchangeable by D_2O), 2.46 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6) δ (ppm): 167.19, 137.99, 134.21, 129.74, 129.40, 129.25, 128.54, 128.27, 49.91, 22.40. MS *m/z* (%): 318 ($M^{+\bullet}$, 3), 317 (13), 286 (19), 271 (21), 236 (38), 231 (20), 189 (11), 105 (100), 77 (51).

2.6. 1-(2-Methyl-4-oxo-5,6-diphenylfuro[2,3-d]pyrimidin-3(4H)-yl)thiourea ***7***. A mixture of furo[2,3-*d*][1,3]oxazinone **3** (1.5 g, 5 mmol), thiosemicarbazide (0.45 g, 5 mmol), and acetic acid (15 mL) was heated under reflux for 4 hrs. The reaction mixture was concentrated and poured into ice/cold water. The formed solid was filtered off, washed with water, dried, and then crystallized from toluene to give **7** as violet crystals, m.p. 168–170°C, yield 50%. Anal. Calcd. for $C_{20}H_{16}N_4O_2S$ (376.420): C, 63.82; H, 4.28; N, 14.88; S, 8.52. Found: C, 63.78; H, 4.32; N, 14.85; S, 8.55. IR (KBr, ν cm^{-1}): 3377, 3360, 3290 (NH, NH_2), 1672 (CO), 1179 (C=S). ^{1}H-NMR (DMSO-d_6) δ (ppm): 10.63 (s, 1H, NH, exchangeable by D_2O), 9.50 (s, 2H, NH_2, exchangeable by D_2O), 7.60–7.29 (m, 10H, Ar-H), 2.25 (s, 3H, CH_3). MS *m/z* (%): 376 ($M^{+\bullet}$, 1), 304 (22), 303 (100), 261 (94), 204 (16), 178 (14), 128 (27), 105 (44), 77 (39).

2.7. 2-Methyl-5,6-diphenyl-3-p-tolylfuro[2,3-d]pyrimidin-4(3H)-one ***8***. A mixture of furo[2,3-*d*][1,3]oxazinone **3** (1.5 g, 5 mmol), *p*-toluidine (0.53 g, 10 mmol), and n-butanol (15 mL) was heated under reflux for 3 hrs. The reaction mixture was concentrated and the solid formed after cooling was filtered off, dried, and then crystallized from ethanol to afford **8** as brown crystals, m.p. 160–162°C, yield 50%. Anal. Calcd. for $C_{26}H_{20}N_2O_2$ (392.436): C, 79.58; H, 5.13; N, 7.14. Found: C, 79.53; H, 5.16; N, 7.14. IR (KBr, ν cm^{-1}): 1698 (CO). ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.67–7.04 (m, 14H, Ar-H), 2.46 (s, 3H, CH_3). MS *m/z* (%): 392 ($M^{+\bullet}$, 8), 373 (12), 368 (22), 337 (21), 302 (100), 261 (30), 206 (14), 178 (15), 128, (27), 105 (71), 77 (47).

2.8. 2-Acetamido-N-(4-aminophenyl)-4,5-diphenylfuran-3-carboxamide ***9***. A mixture of furo[2,3-*d*][1,3]oxazinone **3** (1.5 g, 5 mmol), *p*-phenylenediamine (0.54 g, 5 mmol), and dioxane (15 mL) was heated under reflux for 3 hrs. The reaction mixture was concentrated and the solid formed after cooling was filtered off, dried, and then crystallized from ethanol to afford **9** as yellow crystals, m.p. 200–202°C, yield 60%. Anal. Calcd. for $C_{25}H_{21}N_3O_3$ (411.437): C, 72.98; H, 5.14; N, 10.21. Found: C, 73.02; H, 5.16; N, 10.17. IR (KBr, ν cm^{-1}): 3401, 3324 (2NH), 1699 (br, CO). ^{1}H-NMR (DMSO-d_6) δ (ppm): 12.07 (s, 1H, NH, exchangeable by D_2O), 9.77 (s, 1H, NH, exchangeable by D_2O), 7.33–7.14 (m, 14H, Ar-H), 5.09 (s, 2H, NH_2 exchangeable by D_2O), 2.46 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) δ (ppm): 163.55, 159.53, 146.92, 141.72, 133.84, 130.60, 130.46, 128.97, 128.66, 127.89, 127.32, 125.10, 124.65, 123.23, 114.36, 101.78, 66.89, 21.28. MS *m/z* (%): 411



Scheme 1

($M^{+\bullet}$, 2), 337 (14), 302 (100), 261 (10), 189 (13), 178 (10), 128, (21), 105 (74), 77 (42).

*2.9. Procedure for Preparation of **10** and **11**.* A mixture of furo[2,3-*d*][1,3]oxazinone **3** (1.5 g, 5 mmol) and sodium azide (0.65 g, 5 mmol) in glacial acetic acid (15 mL) was heated under reflux for 3 hrs. The reaction mixture was allowed to cool and then poured onto ice/cold water and the separated solid was filtered, washed with water, and dried. Fractional crystallization from ethanol gave tetrazole derivative **10** and the insoluble fraction was crystallized from dioxane to yield the imidazolone derivative **11**.

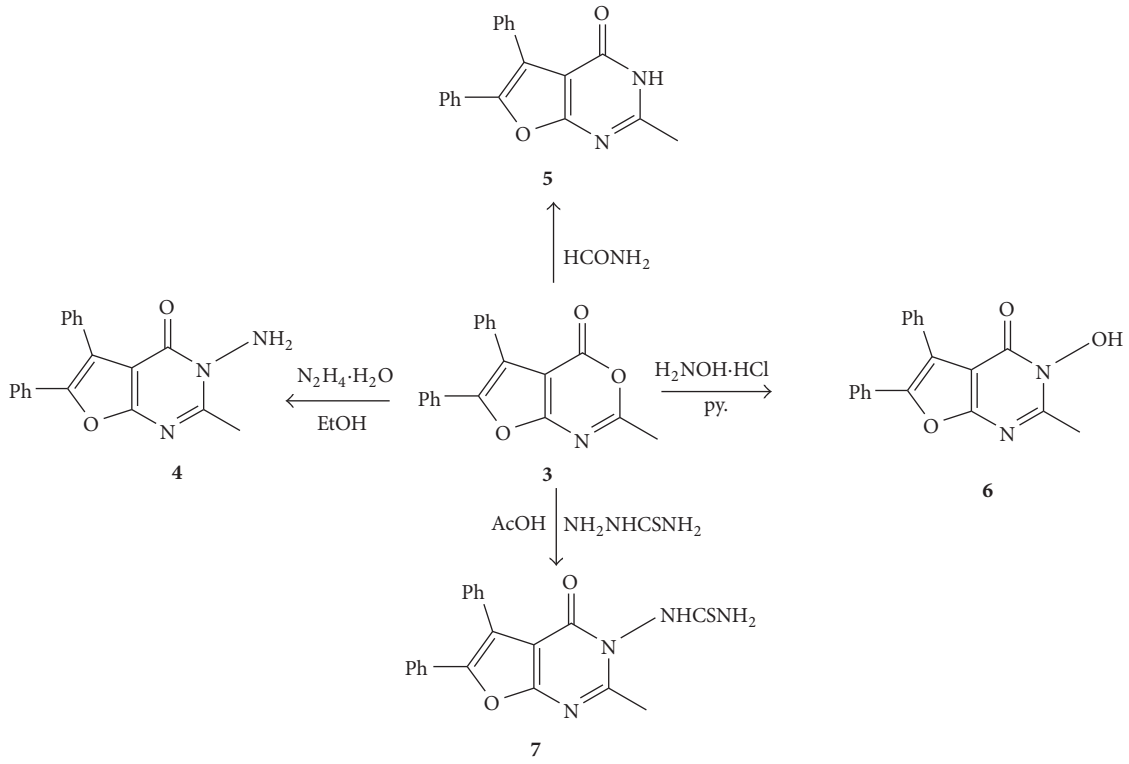
*2.9.1. 2-(5-Methyl-1H-tetrazol-1-yl)-4,5-diphenylfuran-3-carboxylic acid **10**.* White crystals; m.p. > 300°C, yield 35%. Anal. Calcd. for $C_{19}H_{14}N_4O_3$ (346.328): C, 65.89; H, 4.07; N, 16.18. Found: C, 65.92; H, 4.05; N, 16.14. IR (KBr, ν cm^{-1}): 3431 (br, OH, acid), 1669 (CO, acid). ^{1}H NMR (DMSO-d_6) δ (ppm): 11.25 (s, 1H, COOH, exchangeable by D_2O), 8.20–7.35 (m, 10H, Ar-H), 2.14 (s, 3H, CH_3). MS *m/z* (%): 346 ($M^{+\bullet}$, 30), 301 (100), 273 (25), 128 (13), 105 (65), 77 (50).

*2.9.2. 3-Acetyl-5,6-diphenyl-1H-furo[3,2-d]imidazol-2(3H)-one **11**.* Pale yellow crystals; m.p. > 300°C, yield 65%. Anal. Calcd. for $C_{19}H_{14}N_2O_3$ (318.316): C, 71.69; H, 4.43; N, 8.80. Found: C, 71.66; H, 4.46; N, 8.84. IR (KBr, ν cm^{-1}): 3262 (NH), 1746, 1668 (2CO). ^{1}H NMR (DMSO-d_6) δ (ppm): 11.98 (s, 1H, NH, exchangeable by D_2O), 7.95–7.06 (m, 10H, Ar-H), 2.45 (s, 3H, CH_3). MS *m/z* (%): 318 ($M^{+\bullet}$, 26), 303 (70), 275 (100), 128 (30), 105 (78), 77 (45).

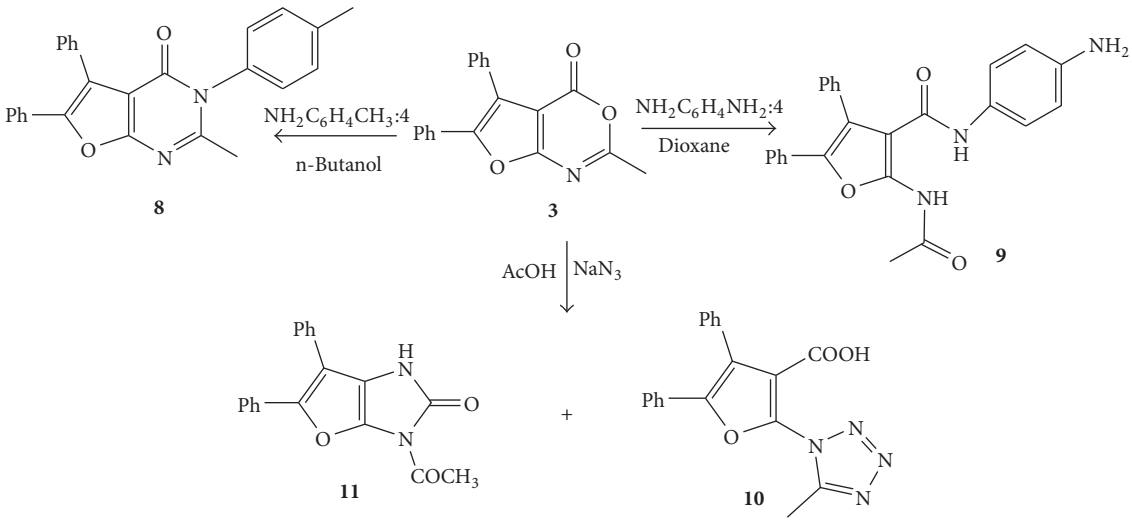
3. Results and Discussion

2-Amino-4,5-diphenylfuran-3-carbonitrile **1** [28] was used as precursor for the preparation of the target heterocyclic compounds. Thus, benzoylation of **1** using benzoyl chloride afforded 2,5,6-triphenylfuro[2,3-*d*]pyrimidin-4*(3H)*-one **2** as a sole product. The IR spectrum of **2** showed strong absorption bands at 3169 and 1687 cm^{-1} corresponding to NH and CO groups, respectively. Moreover, the ^{1}H-NMR spectrum of **2** exhibited a singlet (exchangeable by D_2O) at δ 12.93 attributed to NH group. ^{13}C-NMR spectrum of **2** displayed signals at δ of 167.87 ppm corresponding to CO of pyrimidinone ring. Formation of furo[2,3-*d*]pyrimidinone **2** is believed to proceed via benzoylation of the amino group and conversion of cyano group to the amide group, followed by 1,6-exo-trig cyclization of the amino group to the carbonyl group as formulated in Scheme 1. On the other hand, by treatment of 2-amino-4,5-diphenylfuran-3-carbonitrile **1** with freshly distilled acetic anhydride for 24 hours, the desired furo[2,3-*d*][1,3]oxazin-4-one **3** was formed via acetylation of the amino group and complete hydrolysis of cyano group to the acid group, followed by 1,6-exo-trig cyclization of enolated carbonyl group to acid group (Scheme 1). IR spectrum of **3** displayed absorption band at 1773 cm^{-1} characteristic for CO group of oxazine ring; additionally, ^{13}C-NMR spectrum of **3** showed signals at δ 167.68 and 21.90 ppm corresponding to CO of oxazine ring and CH_3, respectively.

Oxazinone ring is very reactive semiacid anhydride ring and can be transformed into pyrimidinone ring via reaction with various nitrogen nucleophiles. Thus, stirring furo[2,3-*d*][1,3]oxazin-4-one **3** with hydrazine hydrate in ethanol yielded 3-amino-2-methyl-5,6-diphenylfuro[2,3-*d*]pyrimidin-4-one **4** (Scheme 2). IR spectrum of **4** exhibited absorption bands at 3308, 3256, and 1691 cm^{-1} due to NH_2 and CO groups and ^{1}H-NMR (DMSO-d_6) showed signal at δ 5.79 ppm which disappeared by D_2O, confirming the presence of NH_2 group; also ^{13}C-NMR spectrum of **4** revealed signal at δ 161.76 ppm due to CO of pyrimidinone



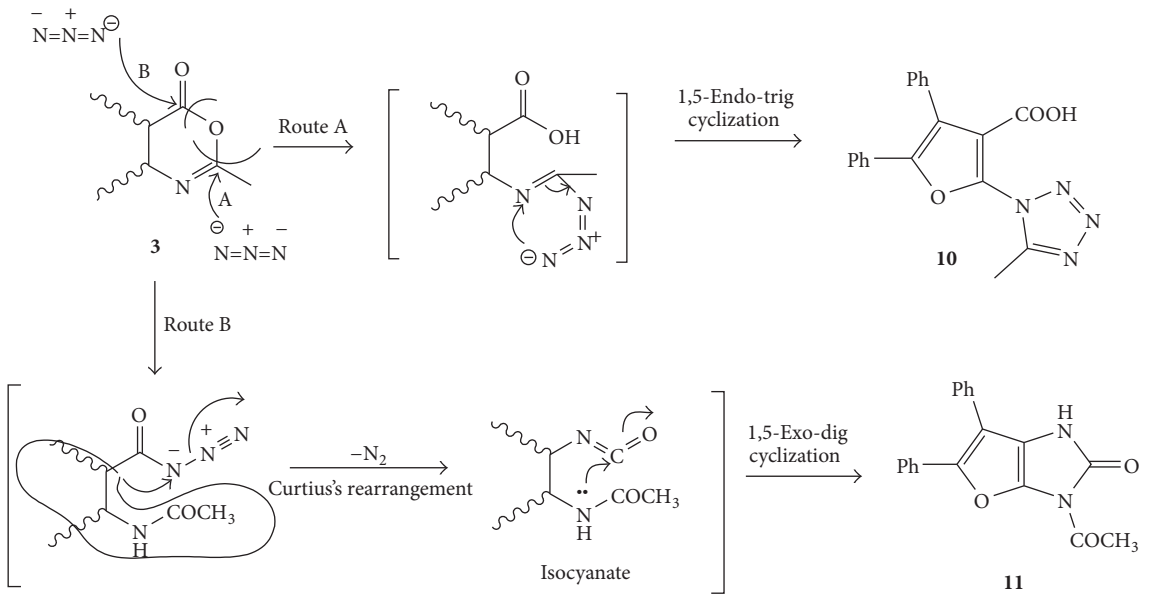
Scheme 2



Scheme 3

ring. On the other hand, boiling furo[2,3-*d*][1,3]oxazin-4-one **3** with formamide afforded furo[2,3-*d*]pyrimidin-4-one derivative **5** (Scheme 2). Furthermore, furo[2,3-*d*]pyrimidin-4-one derivative **6** was obtained on reacting hydroxylamine hydrochloride and furo[2,3-*d*][1,3]oxazin-4-one **3** (Scheme 2). Spectral data supported the proposed structure **6** as IR spectrum exhibited bands at 3412 cm^{-1} (br, OH) and 1670 cm^{-1} (CO); also ^{1}H-NMR (DMSO-d_6) showed the appearance of band at δ 7.36 ppm which disappeared by D_2O, indicating the presence of OH group. Additionally, ^{13}C-NMR spectrum of **6** exhibited signal at δ 167.19 ppm due to CO of pyrimidinone ring. Refluxing compound **3** with thiosemicarbazide in acetic acid for 4 hours yielded the thiourea derivative **7** (Scheme 2).

On the other hand, when furo[2,3-*d*][1,3]oxazin-4-one **3** was allowed to react with p-toluidine in refluxing n-butanol the corresponding furo[2,3-*d*]pyrimidin-4-one derivative **8** was produced (Scheme 3). On the contrary, the reaction of



Scheme 4

3 with *p*-phenylenediamine in boiling dioxane yielded the furancarboxamide derivative **9**, whose structure was deduced from spectral and analytical data (Scheme 3). ^{1}H-NMR spectrum revealed signals at δ 12.07 (s, 1H, NH, exchangeable by D_2O), 9.77 (s, 1H, NH, exchangeable by D_2O), 7.33–7.14 (m, 14H, Ar-H), 5.09 (s, 2H, NH_2 exchangeable by D_2O), and 2.46 (s, 3H, CH_3). Moreover, ^{13}C-NMR spectrum of **9** exhibited two signals at δ 163.55 and 159.53 ppm representing C=O of CH_3CONH and C=O of CONHAr, respectively.

Reaction of furo[2,3-*d*][1,3]oxazinone **3** with sodium azide in boiling acetic acid furnished two products separated by fractional crystallization: tetrazolylfuran derivative **10** which was crystallized from ethanol and furo[3,2-*d*]imidazolone derivative **11** which was crystallized from dioxane (Scheme 3). Anomalous heteroring opening of oxazinone by azide was supposed to occur via nucleophilic attack of azide either at C-2 of oxazinone ring followed by ring opening and addition of azido group on cyano group to yield tetrazolylfuran derivative **10** or at C-4 of oxazinone followed by Curtius's rearrangement to isocyanate intermediate and then cyclization to give furo[3,2-*d*]imidazolone derivative **11** as summarized at Scheme 4.

4. Conclusion

A new series of furo[2,3-*d*]pyrimidin-4*(3H)*-one derivatives, *4H*-furo[2,3-*d*][1,3]oxazin-4-one and heterosubstituted furan, has been synthesized and their chemical structures were confirmed by different spectral and elemental analyses. Similar to related compounds, the synthesized compounds are expected to have anticipated pharmaceutical and biological potentiality.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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