SYNTHESIS AND CHARACTERIZATION OF NOVEL PYRIMIDINE DERIVATIVES FROM 2,3-FURANDIONES

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Abstract: Various novel pyrimidine-2(*1H*)-one and pyrimidine-2(*1H*)-thione derivatives **3a-m** have been synthesized efficiently in good yields by the treatment of 4-*p*-methylbenzoyl-5-*p*-methylphenyl-2,3-furandione (**1a**) and 4-(3,4-dimethoxybenzoyl)-5-(3,4-dimethoxyphenyl)-2,3-furandione (**1b**) with some ureas and thioureas **2**. Structures of these compounds **3** were established on the basis of elemental analysis, IR, ^{1}H- and ^{13}C-NMR spectral studies.

Keywords: 2,3-Furandione, pyrimidine-2(*1H*)-one, pyrimidine-2(*1H*)-thione, nucleophilic cycloaddition.

Introduction

Pyrimidine bases are an integral part of nucleic acids and natural products. They serve as building blocks for numerous pharmaceuticals and occupy a unigue place in heterocyclic and medicinal chemistry[1]. These compounds display anticonvulsant, anti-inflammatory, antibacterial, antimycotic, antifungal, antiviral, insecticidal and miticidal activities[2-8]. In addition fused pyrimidines are selective inhibitors for multidrug resistance (MDR)[9]. Folate metabolism has long been recognized as an attractive target for cancer chemotherapy because of indispensable role of fuse pyrimidine antifolates as antitumor agents[10].

There are published report about synthesis of some 1*H*-pyrimidine derivatives from 2,3-furandiones[11-13]. Also conformational analysis and quantum chemical calculations were carried out by means of MMP2, CNDO, MNDO and AM1 approximation methods for the series of compounds being functionalised 1*H*-pyrimidines[14-16]. In this study, the reactions of 4-*p*-methylbenzoyl-5-*p*-methylphenyl-2,3-furandione (**1a**) and 4-(3,4-dimethoxybenzoyl)-5-(3,4-dimethoxyphenyl)-2,3-furandione (**1b**) with some monosubstituted ureas and thioureas **2** were investigated. The reactions afforded the 1*H*-pyrimidine derivatives **3a-m** which are potential drug compounds and all the compounds synthesized are original to this study.

Scheme-1

Experimental

Melting points were performed on an Electrothermal 9200 apparatus: They were uncorrected. The IR spectra measured on a Jasco Plus Model 460 FT-IR spectrometer, as KBr pellets. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker instruments with $CDCl_3$ solvents at 300 and 75 MHz, respectively. Elemental analysis were carried out using LECO

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932 CHNS-O analyzer. All experiments followed by TLC using DC Alufolien 60 F254 Merck and Camag TLC lamp (254/366 nm). Solvents and other chemical reagents were purchased from Merck, Fluka, Sigma and Aldrich. The compounds **1** were prepared according to published method[17].

Synthesis of 1*H*-Pyrimidines **3a-m**.

General Prodecure.

Equimolar amounts of 2,3-furandiones and the corresponding urea or thiourea in benzene (30 mL) were heated, under reflux, for 1-6 h. The reaction mixture was concentrated under vacuum. The oily residue was treated with diethyl ether for 2-5 h at room temperature. The obtained solid product was filtered off and recrystallized from proper solvents.

1-Methyl-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(*1H*)-one (**3a**).

From 0.50 g (1.63 mmol) **1a** and 0.12 g methylurea, 0.31 g (60%) **3a** was obtained after 5 h reaction time. Mp: 198 °C (1-butanol). IR (KBr, cm^{-1}): ν = 3064-2862 (aromatic and aliphatic C-H stretching), 1667, 1656 (C=O groups), 1604-1480 (C=C and C=N aromatic rings). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.02 (s, 1H, C-6), 7.54-6.97 (four d, 8H, aromatic), 3.63 (s, 3H, N-CH_3), 2.30 (s, 3H, Ar-CH_3), 2.22 (s, 3H, Ar-CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 192.02 (Ar-C=O), 172.75, 155.52, 151.42 (C-4, C-6 and C-2 atoms of pyrimidine ring, respectively), 144.39-128.94 (aromatic carbons), 116.95 (C-5), 39.03 (N-CH_3), 21.66, 21.41 (2xAr-CH_3). Elemental analysis: Calculated for $C_{20}H_{18}N_2O_2$ (318.14): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.56; H, 5.73; N, 8.76.

1-Ethyl-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(*1H*)-one (**3b**).

From 0.50 g **1a** and 0.14 g ethylurea, 0.29 g (51%) **3b** was obtained after 6 h reaction time. Mp: 156 °C (ethanol). IR (KBr, cm^{-1}): ν = 3092-2878 (aromatic and aliphatic C-H stretching), 1661 (broad, C=O groups), 1605-1480 (C=C and C=N aromatic rings). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.99 (s, 1H, C-6), 7.54-6.97 (four d, 8H, aromatic), 4.07-4.00 (q, 2H, N-CH_2), 2.29 (s, 3H, Ar-CH_3), 2.22 (s, 3H, Ar-CH_3), 1.46-1.41 (t, 3H, aliphatic $\underline{CH_3}$-CH_2). Elemental analysis: Calculated for $C_{21}H_{20}N_2O_2$ (332.15): C, 75.88; H, 6.06; N, 8.43. Found: C, 76.16; H, 6.34; N, 8.63.

1-Allyl-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(*1H*)-one (**3c**).

From 0.50 g **1a** and 0.17 g allylurea, 0.21 g (38%) **3c** was obtained after 4 h reaction time. Mp: 149 °C (2-propanol). IR (KBr, cm^{-1}): ν = 3087-2857 (aromatic and aliphatic C-H stretching), 1656 (broad, C=O groups), 1604-1481 (C=C and C=N aromatic rings). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.96 (s, 1H, C-6), 7.54-6.97 (four d, 8H, aromatic), 6.06-5.92 (m, 1H, =CH-), 5.37-5.31 (t, 2H, =CH_2), 4.60-4.58 (d, 2H, N-CH_2), 2.29 (s, 3H, Ar-CH_3), 2.22 (s, 3H, Ar-CH_3). Elemental analysis: Calculated for $C_{22}H_{20}N_2O_2$ (344.41): C, 76.72; H, 5.85; N, 8.13. Found: C, 76.91; H, 5.76; N, 8.14.

1-Butyl-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(*1H*)-one (**3d**).

From 0.50 g **1a** and 0.19 g butylurea, 0.30 g (51%) **3d** was obtained after 4 h reaction time. Mp: 153 °C (ethanol). IR (KBr, cm^{-1}): ν = 3053-2872 (aromatic and aliphatic C-H stretching), 1653 (broad, C=O groups), 1615-1482 (C=C and C=N aromatic rings). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.96 (s, 1H, C-6), 7.58-7.00 (four d, 8H, aromatic), 4.02-3.97 (t, 2H, N-CH_2), 2.33 (s, 3H, Ar-CH_3), 2.25 (s, 3H, Ar-CH_3), 1.89-1.74 (m, 2H, CH_2-$\underline{CH_2}$-CH_2), 1.48-1.35 (m, 2H, CH_2-$\underline{CH_2}$-CH_3), 1.00-0.95 (t, 3H, CH_2-$\underline{CH_3}$). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 192.10 (Ar-C=O), 172.47, 154.97, 150.64 (C-4, C-6 and C-2 atoms of pyrimidine ring, respectively), 144.39-128.93 (aromatic carbons), 116.81 (C-5), 51.55 (N-CH_2), 30.87 (CH_2-$\underline{CH_2}$-CH_2), 21.66 (Ar-CH_3), 21.41(Ar-CH_3), 19.86 (CH_2-$\underline{CH_2}$-CH_3), 13.65 (CH_2-$\underline{CH_3}$). Elemental analysis: Calculated for $C_{23}H_{24}N_2O_2$ (360.18): C, 76.64; H, 6.71; N, 7.77. Found: C, 76.61; H, 6.88; N, 7.86.

1-Benzyl-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(*1H*)-one (**3e**).
From 0.50 g **1a** and 0.25 g benzylurea, 0.37 g (58%) **3e** was obtained after 3 h reaction time. Mp: 174 °C (2-propanol). IR (KBr, cm^{-1}): ν = 3066-2857 (aromatic and aliphatic C-H stretching), 1670, 1658 (C=O groups), 1618-1435 (C=C and C=N aromatic rings). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.97 (s, 1H, C-6), 7.49-6.95 (m, 13H, aromatic), 5.14 (s, 2H, N-CH_2), 2.26 (s, 3H, Ar-CH_3), 2.20 (s, 3H, Ar-CH_3). Elemental analysis: Calculated for $C_{26}H_{22}N_2O_2$ (394.17): C, 79.16; H, 5.62; N, 7.10. Found: C, 78.73; H, 5.69; N, 7.02.

1-Methyl-5-(3,4-dimethoxybenzoyl)-4-(3,4-dimethoxyphenyl)pyrimidine-2(*1H*)-one (**3f**).
From 0.50 g **1b** and 0.10 g methylurea, 0.38 g (74%) **3f** was obtained after 5.5 h reaction time. Mp: 236 °C (1-butanol). IR (KBr, cm^{-1}): ν = 3064-2842 (aromatic and aliphatic C-H stretching), 1668, 1643 s (C=O groups), 1625-1493 (C=C and C=N aromatic rings), 1273 (broad, C-O-C). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.48 (s, 1H, C-6), 7.45-6.87 (m, 6H, aromatic), 3.88 (s, 3H, N-CH_3), 3.74-3.51 (four s, 12H, Ar-OCH_3). Elemental analysis: Calculated for $C_{22}H_{22}N_2O_6$ (410.42): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.15; H, 5.46; N, 6.86.

1-Allyl-5-(3,4-dimethoxybenzoyl)-4-(3,4-dimethoxyphenyl)pyrimidine-2(*1H*)-one (**3g**).
From 0.50 g **1b** and 0.13 g allylurea, 0.43 g (79%) **3g** was obtained after 6 h reaction time. Mp: 229 °C (1-butanol). IR (KBr, cm^{-1}): ν = 3063-2840 (aromatic and aliphatic C-H strecthing), 1672, 1644 (C=O groups), 1623-1486 (C=C and C=N aromatic rings), 1279, 1267 (C-O-C). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.95 (s, 1H, C-6), 7.31-6.66 (m, 6H, aromatic), 6.07-6.00 (m, 1H, =CH-), 5.42-5.37 (t, 2H, $=CH_2$), 4.65-4.63 (d, 2H, N-CH_2), 3.98-3.80 (four s, 12H, Ar-OCH_3). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 191.18 (Ar-C=O), 171.33, 154.95, 153.70 (C-4, C-6 and C-2 atoms of pyrimidine ring, respectively), 149.37-110.00 (aromatic and olefinic carbons), 121.02 (C-5), 56.06-55.86 (4xAr-OCH_3), 52.78 (N-CH_2). Elemental analysis: Calculated for $C_{24}H_{24}N_2O_6$ (436.46): C, 66.04; H, 5.54; N, 6.42. Found: C, 65.81; H, 5.86; N, 6.25.

1-Butyl-5-(3,4-dimethoxybenzoyl)-4-(3,4-dimethoxyphenyl)pyrimidine-2(*1H*)-one (**3h**)
From 0.50 g **1b** and 0.15 g butylurea, 0.33 g (58%) **3h** was obtained after 5 h reaction time. Mp: 201 °C (ethanol). IR (KBr, cm^{-1}): ν = 3076-2837 (aromatic and aliphatic C-H stretching), 1671, 1643 (broad, C=O groups), 1623-1487 (C=C and C=N aromatic rings), 1266 (broad, C-O-C). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.47 (s, 1H, C-6), 7.45-6.87 (m, 6H, aromatic), 3.98-3.91 (t, 2H, N-CH_2), 3.81-3.64 (s, 12H, Ar-OCH_3), 1.72-1.65 (m, 2H, CH_2-$\underline{CH_2}$-CH_2), 1.36-1.27 (m, 2H, CH_2-$\underline{CH_2}$-CH_3), 0.92-0.88 (t, 3H, CH_2-$\underline{CH_3}$). Elemental analysis: Calculated for $C_{25}H_{28}N_2O_6$ (452.50): C, 66.36; H, 6.24; N, 6.19. Found: C, 66.24; H, 6.32; N, 6.45.

1-Benzyl-5-(3,4-dimethoxybenzoyl)-4-(3,4-dimethoxyphenyl)pyrimidine-2(*1H*)-one (**3i**).
From 0.50 g **1b** and 0.12 g benzylurea, 0.28 g (76%) **3i** was obtained after 3.5 h reaction time. Mp: 233 °C (1-propanol). IR (KBr, cm^{-1}): ν = 3061-2837 (aromatic and aliphatic C-H stretching), 1677, 1644 (C=O groups), 1622-1437 (C=C and C=N aromatic rings), 1274, 1264 (C-O-C). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.92 (s, 1H, C-6), 7.40-6.60 (m, 11H, aromatic), 5.20 (s, 2H, N-CH_2), 3.93-3.81 (four s, 12H, Ar-OCH_3). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ= 191.05 (Ar-C=O), 171.29, 155.23, 153.68 (C-4, C-6 and C-2 atoms of pyrimidine ring, respectively), 151.86-109.98 (aromatic carbons), 117.13 (C-5), 56.06-55.85 (4xAr-OCH_3), 53.79 (N-CH_2). Elemental analysis: Calculated for $C_{28}H_{26}N_2O_6$ (486.50): C, 69.12; H, 5.39; N, 5.76. Found: C, 68.78; H, 5.57; N, 6.04.

1-Ethyl-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(*1H*)-thione (**3j**).
From 0.50 g **1a** and 0.17 g ethylthiourea, 0.34 g (60%) **3j** was obtained after 4 h reaction time. Mp: 195 °C (ethanol). IR (KBr, cm^{-1}): ν = 3060-2857 (aromatic and aliphatic C-H stretching), 1654 (C=O), 1607-1480 (C=C and C=N aromatic

rings), 1183 (C=S). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.12 (s, 1H, C-6), 7.53-6.96 (four d, 8H, aromatic), 4.55-4.48 (q, 2H, N-CH_2), 2.29 (s, 3H, Ar-CH_3), 2.21 (s, 3H, Ar-CH_3), 1.54-1.50 (t, 3H, aliphatic $\underline{CH_3}$-CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 191.82 (Ar-C=O), 181.20 (C=S), 164.58, 149.24 (C-4 and C-6 atoms of pyrimidine ring, respectively), 144.85-129.09 (aromatic carbons), 121.01 (C-5), 52.76 (N-CH_2), 21.72, 21.47 (2xAr-CH_3), 13.65 ($\underline{CH_3}$-CH_2). Elemental analysis: Calculated for $C_{21}H_{20}N_2OS$ (348.13): C, 72.38; H, 5.79; N, 8.04; S, 9.20. Found: C, 72.22; H, 5.69; N, 7.89; S, 9.10.

1-Phenyl-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(*1H*)-one (**3k**).
From 0.50 g **1a** and 0.25g phenylthiourea, 0.21 g (33%) **3k** was obtained after 1 h reaction time. Mp: 249 °C (methanol). IR (KBr, cm^{-1}): ν = 3031-2857 (aromatic and aliphatic C-H stretching), 1657 (C=O), 1604-1463 (C=C and C=N aromatic rings), 1178 (C=S). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.09 (s, 1H, C-6), 7.66-7.06 (m, 13H, aromatic), 2.34, 2.24 (two s, 6H, Ar-CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 191.61 (Ar-C=O), 182.50 (C=S), 165.63, 149.99 (C-4 and C-6 atoms of pyrimidine ring, respectively), 145.02-126.48 (aromatic carbons), 120.33 (C-5), 21.76, 21.58 (2xAr-CH_3). Elemental analysis: Calculated for $C_{25}H_{20}N_2OS$ (396.13): C, 75.73; H, 5.08; N, 7.07; S, 8.09. Found: C, 75.97; H, 5.37; N, 6.94; S, 8.30.

1-Ethyl-5-(3,4-dimethoxybenzoyl)-4-(3,4-dimethoxyphenyl)pyrimidine-2(*1H*)-thione (**3l**).
From 0.5o g **1b** and 0.13 g ethylthiourea, 0.40 g (72%) **3l** was obtained after 6 h reaction time. Mp: 138 °C, (ethanol). IR (KBr, cm^{-1}): ν = 3067-2836 (aromatic and aliphatic C-H stretching), 1648 (C=O), 1610-1483 (C=C and C=N aromatic rings), 1264 (C-O-C), 1179 (C=S). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.06 (s, 1H, C-6), 7.36-6.65 (m, 6H, aromatic), 4.59-4.50 (q, 2H, N-CH_2), 3.89-3.78 (four s, 12H, Ar-OCH_3), 1.63-1.56 (t, 3H, aliphatic $\underline{CH_3}$-CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 190.90 (Ar-C=O), 180.96 (C=S), 163.53, 153.99 (C-4 and C-6 atoms of pyrimidine ring, respectively), 152.17-110.04 (aromatic carbons), 56.10-55.89 (Ar-OCH_3), 52.71 (N-CH_2), 13.64 ($\underline{CH_3}$-CH_2). Elemental analysis: Calculated for $C_{23}H_{24}N_2O_5S$ (440.51): C, 62.71; H, 5.49; N, 6.36; S, 7.28. Found: C, 63.03; H, 5.71; N, 6.61; S, 7.06.

1-Allyl-5-(3,4-dimethoxybenzoyl)-4-(3,4-dimethoxyphenyl)pyrimidine-2(*1H*)-thione (**3m**).
From 0.50 g **1b** and 0.15 g allylthiourea, 0.46 g (81%) **3m** was obtained after 4.5 h reaction time. Mp: 190 °C (2-propanol). IR (KBr, cm^{-1}): ν = 3063-2834 (aromatic and aliphatic C-H stretching), 1655 (C=O), 1610-1479 (C=C and C=N aromatic rings and allyl group), 1267, 1248 (C-O-C), 1176 (C=S). ^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.60 (s, 1H, C-6), 7.71-6.82 (m, 6H, aromatic), 6.14-6.04 (m, 1H, =CH-), 5.51-5.29 (t, 2H, $=CH_2$), 5.16-5.10 (d, 2H, N-CH_2), 3.82-3.63 (four s, 12H, Ar-OCH_3). Elemental analysis: Calculated for $C_{24}H_{24}N_2O_5S$ (452.52): C, 63.70; H, 5.35; N, 6.19; S, 7.09. Found: C, 63.38; H, 5.51; N, 5.90; S, 6.77.

Results and Discussion

The reactions of 2,3-furandiones (**1a,b**) with the corresponding ureas or thioureas proceed smoothly in benzene under reflux for 1-6 h to produce 1*H*-pyrimidine derivatives **3a-m** in 33-81% yields (see Scheme-1).

The structure of new compounds **3a-m** were deduced from their elemental analysis, ^{1}H- and ^{13}C-NMR spectra. The ^{1}H-NMR spectrum of **3a** exhibited one singlet readily recognized as arising from C-H proton of C_6 atom (δ 8.02 ppm) at pyrimidine ring and four dublets for the other aromatic protons (δ 7.54-6.97 ppm). The signals of the methyl groups observed as a singlet at δ 3.63, 2.30 and 2.22 ppm. The proton decoupled ^{13}C-NMR spectrum of **3a** showed 16 distinct resonances. The ^{13}C-NMR spectrum of **3a** exhibited aroyl carbonyl resonance at δ = 192.02 ppm. The chemical shift for C_4, C_6, C_2 at pyrimidine ring appeared at δ 172.75, 155.52 and 151.42 ppm, respectively. Also, methyl groups observed

at δ 39.03 ppm for N-$\underline{C}H_3$ and 21.66, 21.41 ppm for Ar-$\underline{C}H_3$. In the IR spectrum of compound **3a**, the (C=O) absorption bands observed at 1667 and 1656 cm^{-1}. The spectral data of other synthesized compounds are in good agreement with the proposed structure.

Previously, the mechanism of formation of 1*H*-pyrimidine derivatives from the 2,3-furandione with the ureas or semicarbazones was reported[12-15]. The reaction mechanism is similar to published methods. It is outlined in Scheme-2. The structure of those previously studied compounds had already been determined by X-ray examination[11,18-21].

Scheme-2

The formation of compounds **3** may be initiated by Micheal-type addition, via nucleophilic attack at C-5 of the furan ring in **1** by the $-NH_2$ group of urea or thiourea as the nucleophile and during this interaction ring opened to give 2-oxo-3-butenoic acid derivatived intermediate forms. The following steps progressed closing ring and subsequent elimination of CO_2 and H_2O to give 1*H*-pyrimidine derivatives **3**.

Nucleophilicity of $-NH_2$ group at thiourea is higher than corresponding urea. So, The yields of pyrimidine-2(*1H*)-thiones are higher except for **3k**, because of steric hindrance and resonance effect of phenyl group at phenylthiourea.

In conclusion, the compounds synthesized are significant preliminary compounds due to the fact that original 1*H*-pyrimidine derivatives include 4-methylphenyl or 3,4-dimethoxyphenyl groups in their structures. We think about that these compounds may be important from a medicinal point of view as well as their widespread biological significance.

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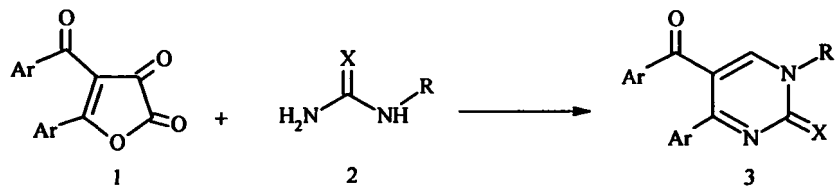
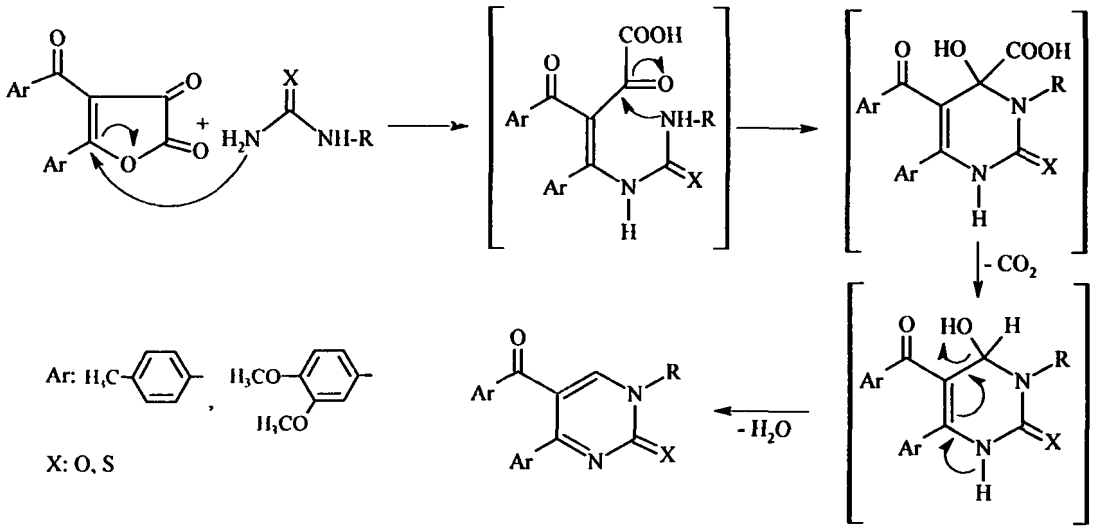
Schemes and Captions



1 2 3

3	Ar	R	X	m.p. (°C)	Yield (%)
a	H_3C-Ph-	$-CH_3$	O	198	60
b	H_3C-Ph-	$-C_2H_5$	O	156	51
c	H_3C-Ph-	$-CH_2-CH=CH_2$	O	149	38
d	H_3C-Ph-	$-C_4H_9$	O	153	51
e	H_3C-Ph-	$-CH_2-Ph$	O	174	58
f	H_3CO, H_3CO-Ph-	$-CH_3$	O	236	74
g	H_3CO, H_3CO-Ph-	$-CH_2-CH=CH_2$	O	229	79
h	H_3CO, H_3CO-Ph-	$-C_4H_9$	O	201	58
i	H_3CO, H_3CO-Ph-	$-CH_2-Ph$	O	233	76
j	H_3C-Ph-	$-C_2H_5$	S	195	60
k	H_3C-Ph-	$-Ph$	S	249	33
l	H_3CO, H_3CO-Ph-	$-C_2H_5$	S	138	72
m	H_3CO, H_3CO-Ph-	$-CH_2-CH=CH_2$	S	190	81

Scheme-1



Scheme-2