Archive for
Organic Chemistry

The Free Internet Journal
for Organic Chemistry

Paper

Arkivoc **2019**, part v, 0-0

A simple route for synthesis of 5-(furan-3-yl)barbiturate/thiobarbiturate derivatives *via* a multi-component reaction between arylglyoxals, acetylacetone and barbituric/thiobarbituric acid

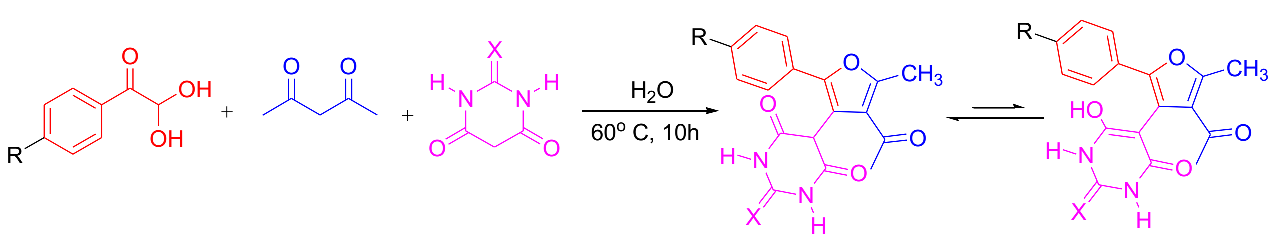
Fatemeh Dehghanzadeh, Fereshteh Shahrokhabadi, and Mohammad Anary-Abbasinejad*

Department of Chemistry, Faculty of Science, Vali-e-Asr University of Rafsanjan, Rafsanjan 77176, Iran
E-mail: m.anary@vru.ac.ir

Received 12-05-2018 **Accepted** 02-10-2019 **Published on line** 03-03-2019

Abstract

An effective protocol for the synthesis of 5-(furan-3-yl)barbiturate and 5-(furan-3-yl)thiobarbiturate derivatives through a one-pot three-component reaction of readily available starting materials arylglyoxals, barbituric acid or thiobarbituric acid and acetylacetone in water as solvent is reported.



Keywords: Multi-component reactions, arylglyoxal, acetylacetone, barbituric acid, thiobarbituric acid, furan

Introduction

Barbituric and 2-thiobarbituric acids are well-known classes of organic compounds with a wide variety of pharmacological activities which have found applications as the main skeleton for a series of barbiturate / thiobarbiturate drugs used as antioxidants, hypnotics, anticonvulsants, sedatives, anaesthetics, antifungal, and central nervous system depressants.[1–3] Combination of barbituric/thiobarbituric acid moieties with other pharmacophoric moieties may result in new types of scaffold with potential biological activities. Many efforts have been made in fusing barbiturates and thiobarbiturates with other molecular skeletons such as 1,3-diketones,[4,5] isatins,[6–8] Meldrum's acid,[9] 4-hydroxycoumarin[10] and pyrroles.[11] Barbiturates have also been widely used in the manufacturing of plastics,[12] textiles,[13] and polymers.[14]

Furan moieties are important substructures that have been found in numerous natural products, such as kailolides[15] and combranolides.[16] These heterocycles are also found in a variety of commercial products such as pharmaceuticals, fragrances, and dyes.[17]

Multi-component reactions (MCRs), especially those conducted in water, offer significant advantages over conventional linear-type syntheses, because the reaction components combine with each other in a single step to generate new products. On the other hand, the low cost, and the lack of inflammability, explosive, and carcinogenic properties of water are some of the economic and environmental benefits of using water as solvent.[18,19]

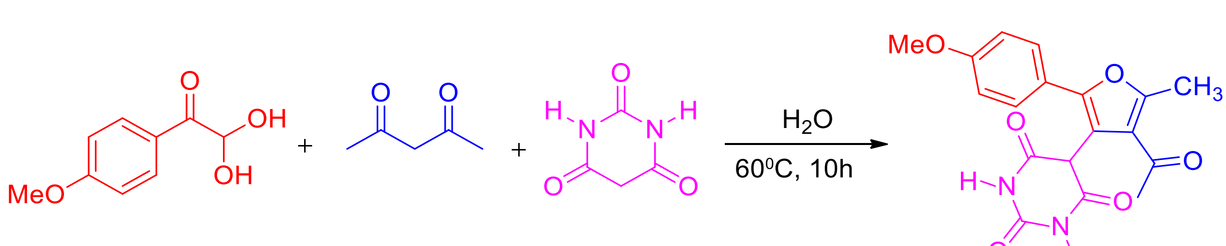
Arylglyoxals with a carbonyl group adjacent to the aldehyde functionality, are reactive and versatile species which have been widely used for the synthesis of various heterocyclic and carbocyclic compounds. Arylglyoxals have been recently reported as the key component in several multi-component reactions for connecting reaction components to each other to make the main skeleton of the product.[20-22]

We have recently focused our attention on developing new multi-component reactions of arylglyoxals for the synthesis of new heterocyclic compounds.[23-25] In continuation of these works, here we report a new three-component reaction of arylglyoxals with acetylacetone and barbituric or thiobarbituric acid for the synthesis of a series of new polyfunctionalized 5-(furan-3-yl)barbiturates and 5-(furan-3-yl)thiobarbiturates.

Results and Discussion

In order to investigate the three-component reaction of arylglyoxals, acetylacetone and barbituric acid, at first we studied the reaction between 4-methoxyphenylglyoxal monohydrate **1a**, acetylacetone **2** and barbituric acid **3a** in water as solvent (Scheme 1). A mixture of 4-methoxyphenylglyoxal monohydrate **1a** and acetylacetone **2** was stirred in water at 60 °C. After thirty minutes barbituric acid was added and the mixture was heated at 60 °C for 10 hours more. TLC analysis of the reaction mixture showed the presence of only one product. Silica-gel chromatography afforded 5-[4-acetyl-2-(4-methoxyphenyl)-5-methylfuran-3-yl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **4a** in 90% yield.

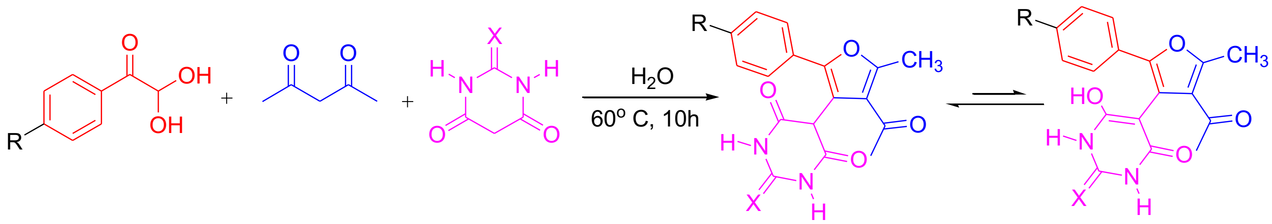
To investigate the scope of the reaction, different arylglyoxals were treated with acetylacetone and barbituric acid and the corresponding 5-furyl-3-barbiturates **4a-g** were obtained in good yields (Table 1). Next, reactions were carried out between acetylacetone, arylglyoxals and thiobarbituric acid in water at similar conditions and the corresponding 5-(furan-3-yl)thiobarbiturates **4h-m** were obtained in good yields.



1a **2** **3a** **4a**

Scheme 1. Synthesis of 5-[4-acetyl-2-(4-methoxyphenyl)-5-methylfuran-3-yl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **4a** by three-component reaction between 4-methoxyphenylglyoxal monohydrate, acetylacetone and barbituric acid.

Table 1. Three-component reaction between arylglyoxals, barbituric acid or thiobarbituric acid and acetylacetone for synthesis of 5-(furan-3-yl)barbiturate/thiobarbiturate derivatives



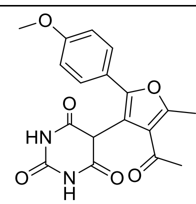
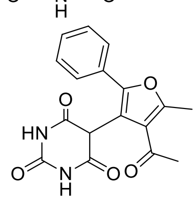
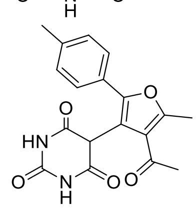
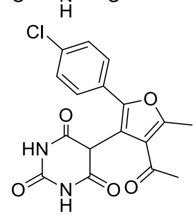
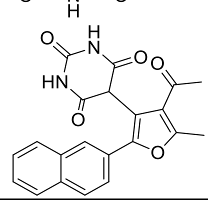
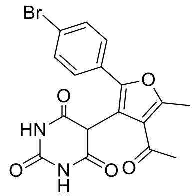
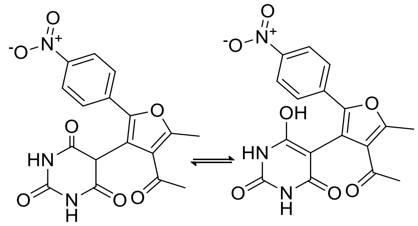
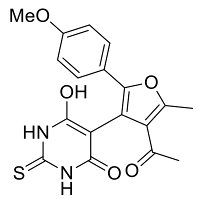
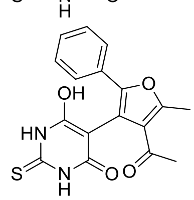
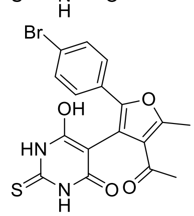
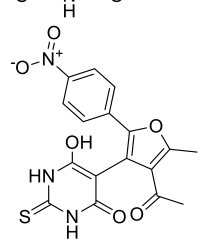
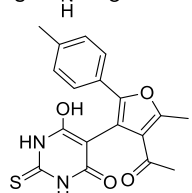
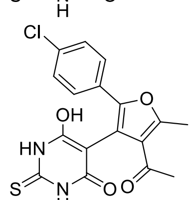
4, 4′	R	X	Product	mp ºC	Yield %
a	OMe	O		300-303	90
b	H	O		309-311	78
c	Me	O		274-276	86
d	Cl	O		298-300	90
e	C_4H_4	O		279-281	94

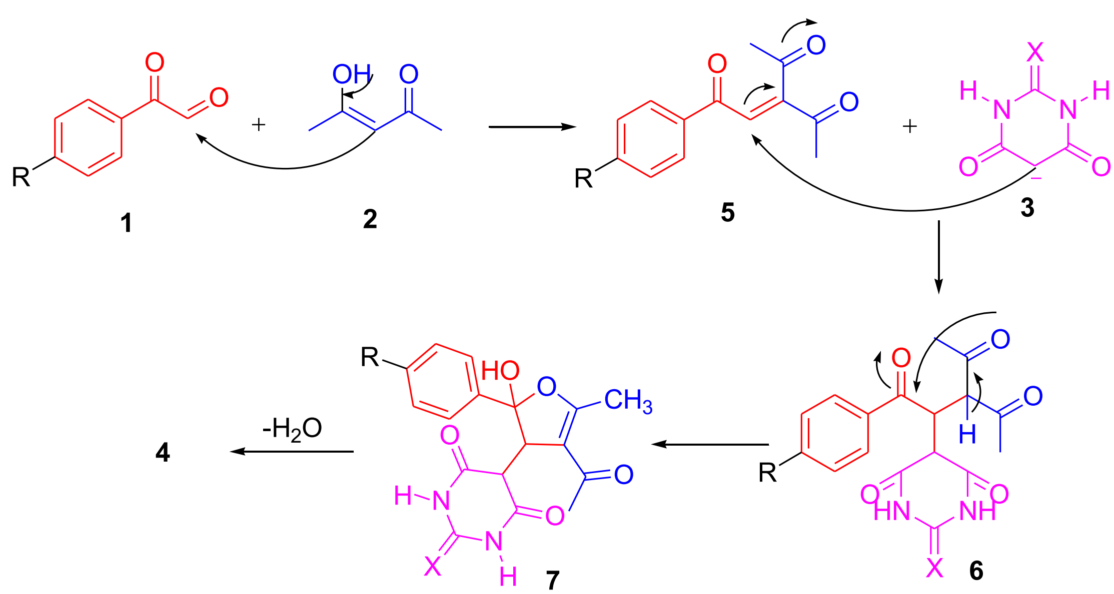
Table 1. Continued

4, 4′	R	X	Product	mp °C	Yield %
f	Br	O		297-299	88
g	NO_2	O		280-282	90
h	OMe	S		275-277	90
i	H	S		279-281	95
j	Br	S		264-266	78
k	NO_2	S		229-231	80
l	Me	S		273-275	90
m	Cl	S		261-263	85

The structures of compounds **4a–m** were inferred from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data. Compounds **4a-m** may exist as two tautomers **4** or **4**' (Table 1). The tautomerism of barbituric acid and thiobarbituric acid derivatives has been extensively studied. These studies showed that

5-substituted barbiturates usually exist as the keto form in polar solvents such as DMSO in contrast to 5-substituted thiobarbiturates which exist mainly as the enol form in polar solvents.[26,27] The NMR spectra of compounds **4a-4f** showed that those compounds which include the barbiturate moiety in their structures existed mainly as keto tautomer **4** in DMSO-d_6 solution. In contrast, compounds **4h-4m** with a thiobarbiturate moiety in their structure existed as the enol tautomer **4′**. The NMR spectra of compound **4g** with nitrophenyl and barbiturate moieties showed the presence of two isomers in nearly equal amounts. The 500-MHz ^{1}H NMR spectrum of **4a** exhibited three sharp signals at δ 2.19, 2.47, 3.72, ppm for two methyl groups and one methoxy. The CH proton of the barbiturate moiety resonated as a singlet signal at 4.93 ppm. This signal was not observed at the ^{1}H NMR spectrum of thiobarbiturate derivative **4h**, which showed that this compound exists as the enol form. The aromatic protons of **4a** resonated as two doublet signals at 6.88 and 7.54 ppm. Two NH protons were observed at 9.22 ppm as a broad signal. The ^{13}C NMR spectrum of compound **4a** showed fifteen distinct signals in agreement with the proposed structure. The CH carbon of the barbiturate moiety resonated at 40.89 ppm. In derivatives that are in the enol form, such as **4h**, this carbon was observed at about 90 ppm. The structural assignments made on the basis of the NMR spectra of compound **4a** were supported by its IR spectrum. The amide carbonyl groups exhibited a strong absorption band at about 1666 cm^{-1}. The ketone carbonyl was observed at 1701 cm^{-1} as a strong absorption band.

The suggested mechanism for formation of furanyl barbiturate/thiobarbiturate derivatives **4a-m** by the reaction between arylglyoxals, acetylacetone and barbituric/thiobarbituric acids is shown in Scheme 2. The Michael addition of barbituric/thiobarbituric acid to the Intermediate obtained from Knoevenagel condensation of arylglyoxals with acetylacetone afforded reactive 1,4-diketone **6**. The Paal-Knorr cyclization of this intermediate afforded product **4**.



Scheme 2. Suggested mechanism for formation of 5-(furan-3-yl)barbiturate/thiobarbiturate derivatives **4a-m**

Conclusions

In conclusion, we report a simple three-component reaction between arylglyoxal monohydrates, acetylacetone and barbituric or thiobarbituric acid for the synthesis of polyfunctionalized 5-(furan-3-

yl)barbiturates and 5-(furan-3-yl)thiobarbiturate derivatives in good yields. The method employs readily available starting materials, neutral reaction conditions and water as an environmentally green solvent.

Experimental Section

General. All solvents and chemicals except arylglyoxals were purchased from commercial sources and used without further purification. The utilized arylglyoxals were prepared by the SeO_2-oxidation of the related aryl methylketones on the basis of the reported procedure, and used as their monohydrates.[28] Melting points were determined on a Melt-Tem II melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-470 spectrometer. All of the NMR spectra were recorded on a Varian model UNITY Inova 500 MHz (^{1}H: 500 ^{13}C: 125 MHz) NMR spectrometer. Chemical shifts of ^{1}H, ^{13}C NMR are reported in parts per million (ppm) from tetramethylsilane (TMS) as an internal standard in DMSO-d_6 as a solvent.

General procedure. A mixture of arylglyoxal (1 mmol) and acetylacetone (1 mmol) in water (15 mL) was stirred at 60 °C for 20 min. Then, barbituric or thiobarbituric acid (1 mmol) was added to this mixture. The reaction mixture was then stirred at 60 °C for 10 h more. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica-gel, using EtOAc-EtOH mixture (7:1) as eluent.

5-[4-Acetyl-2-(4-methoxyphenyl)-5-methylfuran-3-yl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4a**). Dark yellow powder, mp 300-303 °C (Yield: 90%). IR (KBr) ν_{max}/cm^{-1}: 1666, 1701 (C=O), 3424 (NH). ^{1}H-NMR (500 MHz DMSO-d_6): δ (ppm): 2.19 (3H, s, CH_3), 2.47 (3H, s, CH_3), 3.72 (3H, s, OCH_3), 4.93 (H, s, CH), 6.88 (2H, d, $^3J_{HH}$ 8.8 Hz, 2CH, Ar), 7.55(2H, d, $^3J_{HH}$ 8.8 Hz, 2CH, Ar), 9.22(2H, s, 2NH). ^{13}C-NMR (125 MHz DMSO-d_6): δ (ppm): 14.7, 28.9, 40.9, 55.5, 114.0, 115.8, 125.0, 126.0, 126.7, 147.9, 152.7, 154.8, 158.3, 164.3, 196.5. Calcd. for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86%. Found: C, 60.55; H, 4.67; N, 7.93%.

5-[4-Acetyl-5-methyl-2-phenylfuran-3-yl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4b**). Light orange powder, mp 309-311 °C (Yield: 78%). IR (KBr) ν_{max}/cm^{-1}: 1654 (C=O), 1694 (C=O), 3199 (NH). ^{1}H-NMR (500 MHz DMSO-d_6): δ (ppm): 2.41 (3H, s, CH_3), 2.72 (3H, s, CH_3), 5.12 (H, s, CH), 7.43-7.56 (5H, m, HAr), 11.21 (2H, s, 2NH). ^{13}C-NMR (125 MHz DMSO-d_6): δ (ppm): 15.8, 30.3, 47.5, 113.4, 121.4, 125.1, 127.3, 129.0, 129.5, 151.7, 152.4, 159.1, 169.1, 194.8. Calcd. for $C_{34}H_{28}N_4O_{10}$: C, 62.57; H, 4.32; N, 8.59%. Found: C, 62.55; H, 4.37; N, 8.53%.

5-[4-Acetyl-5-methyl-2-(*p*-tolyl)furan-3-yl]pyrimidine-2,4,6(1*H*,3*H*,5*H*) (**4c**). Light pink powder, mp 274-276 °C (Yield: 86%). IR (KBr) ν_{max}/cm^{-1}: 1645, 1718 (C=O), 3218 (NH). ^{1}H-NMR (500 MHz DMSO-d_6): δ (ppm): 2.34 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.71 (3H, s, CH_3), 5.07 (H, s, CH), 7.29 (2H, d, $^3J_{HH}$ 8.2 Hz, 2CH, HAr), 7.44 (2H, d, ^3J_H 8.2 Hz, 2CH, HAr), 11.21(2H, s, 2NH). ^{13}C-NMR (125 MHz DMSO-d_6): δ (ppm): 15.8, 21.3, 30.3, 47.5, 112.8, 121.4, 127.2, 129.7, 130.0, 139.0, 151.7, 152.5, 158.8, 169.1, 194.8. Calcd. for ($C_{18}H_{16}N_2O_5$): C, 63.52; H, 4.74; N, 8.23%. Found: C, 63.45; H, 4.87; N, 8.27%.

5-[4-Acetyl-2-(4-chlorophenyl)-5-methylfuran-3-yl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4d**). Light yellow powder, mp 298-300 °C (Yield: 87%). IR (KBr) ν_{max}/cm^{-1}: 1650, 1708 (C=O), 3202(NH). ^{1}H-NMR (500 MHz DMSO-d_6): δ (ppm): 2.41 (3H, s, CH_3), 2.72 (3H, s, CH_3), 5.13 (H, s, CH), 7.48 (2H, d, $^3J_{HH}$ 8.5 Hz, 2CH, HAr), 7.52 (2H, d, $^3J_{HH}$ 8.5 Hz, 2CH, HAr), 11.26 (2H, s, 2NH). ^{13}C-NMR (125 MHz DMSO-d_6): δ (ppm): 15.8, 30.3, 47.5, 114.0, 126.7, 127.8, 129.0, 129.5, 134.1, 151.2, 151.7, 159.4, 168.9, 194.8. Calcd. for ($C_{17}H_{13}ClN_2O_5$): C, 56.60; H, 3.63; N, 7.77%. Found: C, 56.45; H, 3.75; N, 7.56%.

5-[4-Acetyl-5-methyl-2-(naphthalen-2-yl)furan-3-yl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4e**). Light brown powder, mp 279-281 °C Yield: 94%. IR (KBr) ν_{max}/cm^{-1}: 1643, 1715 (C=O), 3622 (NH). ^{1}H-NMR (500 MHz DMSO-d_6): δ (ppm): 2.43 (3H, s, CH_3), 2.76 (3H, s, CH_3), 5.31 (H, s, CH), 7.50-7.52 (H, m, HAr), 7.55-7.57 (H, m, HAr), 7.69-7.71 (H, m, HAr), 7.55-7.86 (2H, d, $^3J_{HH}$ 7.5, HAr), 7.95-7.97 (H, m, HAr), 8.02 (H, d, $^3J_{HH}$ 8.5, HAr), 8.09 (H, s, HAr), 11.26 (2H, s, 2NH). ^{13}C-NMR (125 MHz DMSO-d_6): δ (ppm): 15.9, 30.319, 47.7, 113.9, 121.6, 124.8, 126.2, 126.5, 127.2, 127.3, 128.1, 128.8, 129.1, 133.1, 133.2, 151.8, 152.3, 159.4, 169.1, 194.8. Calcd. for ($C_{21}H_{16}ClN_2O_5$): C, 67.02; H, 4.28; N, 7.44%. Found: C, 67.25; H, 3.95; N, 7.56%.

5-[4-Acetyl-2-(4-bromophenyl)-5-methylfuran-3-yl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4f**). Light pink powder, mp 297-299 °C (Yield: 92%). IR (KBr) ν_{max}/cm^{-1}: 1706, 1768 (C=O), 3273 (NH). ^{1}H-NMR (500 MHz DMSO-d_6): δ (ppm): 2.40 (3H, s, CH_3), 2.71 (3H, s, CH_3), 5.12 (H, s, CH), 7.49 (H, $^3J_{HH}$ 8.5 Hz, HAr), 7.69 (H, $^3J_{HH}$ 8.5 Hz, HAr), 11.25 (2H, s, 2NH). ^{13}C-NMR (125 MHz DMSO-d_6): δ (ppm): 15.8, 30.3, 47.5, 114.1, 121.5, 122.7, 129.2, 132.2, 132.5, 151.3, 151.7, 159.4, 168.9, 194.8. Calcd. for ($C_{17}H_{13}BrN_2O_5$): C, 50.39; H, 3.23; N, 6.91%. Found: C, 50.45; H, 3.32; N, 6.95%

5-[4-Acetyl-5-methyl-2-(4-nitrophenyl)furan-3-yl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione and 5-[4-acetyl-5-methyl-2-(4-nitrophenyl)furan-3-yl]-6-hydroxypyrimidine-2,4(1*H*,3*H*)-dione (**4g**). Orange powder, mp 280-282 °C (Yield: 90%). IR (KBr) ν_{max}/cm^{-1}: 1663, 1697 (C=O), 3233 (NH), 3481 (OH). ^{1}H-NMR (500 MHz DMSO-d_6): δ (ppm): 2.23 (3H, s, CH_3), 2.43 (3H, s, CH_3), 2.62 (3H, s, CH_3), 2.76 (3H, s, CH_3), 5.28 (H, s, CH), 7.27 (H, $^3J_{HH}$ 9.0 Hz, HAr), 7.82 (H, $^3J_{HH}$ 8.9 Hz, HAr), 8.27 (H, $^3J_{HH}$ 9.0 Hz, HAr), 8.32 (H, $^3J_{HH}$ 8.9 Hz, HAr), 10.90 (H, s, NH), 11.30 (2H, s, 2NH). ^{13}C-NMR (125 MHz DMSO-d_6): δ (ppm): 15.1, 15.8, 29.8, 29.3, 47.5, 83.4, 115.3, 116.6, 121.8, 124.7, 125.5, 125.8, 127.9, 134.9, 136.7, 146.3, 147.0, 147.5, 150.1, 150.7, , 151.6, 158.8, 160.6, 168.6, 194.5, 194.8. Calcd. for ($C_{17}H_{13}N_3O_7$): C, 54.99; H, 3.53; N, 11.32%. Found: C, 54.95; H, 3.52; N, 11.49%.

5-[4-Acetyl-2-(4-methoxyphenyl)-5-methylfuran-3-yl]-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**4h**). Brown powder, mp 275-277 °C (Yield: 90%). IR (KBr) ν_{max}/cm^{-1}: 1703, 1741 (C=O), 3423 (OH, NH). ^{1}H-NMR (500 MHz DMSO-d_6): δ (ppm): 2.22 (3H, s, CH_3), 2.59 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 6.98 (H, d, $^3J_{HH}$ 8.8 Hz, HAr), 7.41 (H, d, $^3J_{HH}$ 8.8 Hz, HAr), 12.28 (1H, bs, NH), 12.31 (1H, s, NH). ^{13}C-NMR (125 MHz DMSO-d_6): δ (ppm): 15.1, 30.0, 55.6, 89.4, 108.4, 114.7, 123.1, 124.8, 126.8, 128.8, 149.4, 156.8, 159.4, 160.6, 174.4, 194.3. Calcd. for ($C_{18}H_{16}N_2O_5S$): C, 58.05; H, 4.33; N, 7.52; S, 8.61%. Found: C, 58.19; H, 4.14; N, 7.56; S, 8.71%.

5-(4-Acetyl-5-methyl-2-phenylfuran-3-yl)-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**4i**). Light pink powder, mp 279-281 °C (Yield: 95%). IR (KBr) ν_{max}/cm^{-1}: 1709, 1744 (C=O), 3138 (OH, NH). ^{1}H-NMR (500 MHz DMSO-d_6): δ (ppm): 2.23 (3H, s, CH_3), 2.61 (3H, s, CH_3), 7.30 (H, d,$^3J_{HH}$ 7.7 Hz, HAr), 7.40 (H, t,$^3J_{HH}$ 7.7 Hz, HAr), 7.49 (2H, d,$^3J_{HH}$ 7.7 Hz, 2CH, HAr), 12.29 (2H, s, 2NH). ^{13}C-NMR (125 MHz DMSO-d_6): δ (ppm): 15.1, 30.0, 89.1, 110.3, 124.9, 125.2, 128.3, 129.2,129.4, 130.5, 149.1, 157.3, 160.6, 174.4, 194.3. Calcd. for ($C_{17}H_{14}N_2O_4S$): C, 59.64; H, 4.12; N, 8.18; S, 9.37%. Found: C, 59.45; H, 4.27; N, 8.03; S, 9.44%.

5-[4-Acetyl-2-(4-bromophenyl)-5-methylfuran-3-yl]-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**4j**). Orange powder, mp 264-266 °C (Yield: 78%). IR (KBr) ν_{max}/cm^{-1}: 1645 (C=O), 3201 (OH, NH). ^{1}H-NMR (500 MHz DMSO-d_6): δ (ppm): 2.25 (3H, s, CH_3), 2.60 (3H, s, CH_3), 5.16 (1H, bs, OH), 7.44 (2H, d, $^3J_{HH}$ 8.1 Hz, HAr), 7.60 (2H, d, $^3J_{HH}$ 8.1 Hz, HAr), 11.68 (H, s, NH), 12.35 (H, s, NH). ^{13}C-NMR (125 MHz DMSO-d_6): δ (ppm): 15.1, 30.0, 88.9, 111.1, 121.4, 125.0, 127.1, 129.7, 132.2, 132.4, 148.1, 157.7, 160.7, 174.4, 194.3. Calcd. for ($C_{17}H_{13}BrN_2O_4S$): C, 48.47; H, 3.11; N, 6.65; S, 7.61%. Found: C, 48.25; H, 3.17; N, 6.73; S, 7.54%.

5-[4-Acetyl-5-methyl-2-(4-nitrophenyl)furan-3-yl]-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**4k**). Yellow powder, mp 229-231 °C (Yield: 80%). IR (KBr) ν_{max}/cm^{-1}: 1695, 1744 (C=O), 3473 (OH, NH). ^{1}H-NMR (500 MHz DMSO-d_6): δ (ppm): 2.25 (3H, s, CH_3), 2.63 (3H, s, CH_3), 5.01 (1H, bs, OH), 7.76 (2H, d, $^3J_{HH}$ 8.8 Hz, HAr), 8.27 (2H, d, $^3J_{HH}$ 8.8, HAr), 12.16 (2H, s, 2NH). ^{13}C-NMR (125 MHz DMSO-d_6): δ (ppm): 15.1, 30.0, 88.0, 112.7, 120.9, 124.7, 125.6, 127.4, 136.6, 146.3, 146.8, 158.7, 160.6, 174.5, 194.4. Calcd. for ($C_{17}H_{13}N_3O_6S$): C, 52.71; H, 3.38; N, 10.85; S, 8.28%. Found: C, 52.45; H, 3.34; N, 10.83; S, 8.10%.

5-[4-Acetyl-5-methyl-2-(*p*-tolyl)furan-3-yl]-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**4l**). Light orange powder, mp 273-275 °C (Yield: 90%). IR (KBr) ν_{max}/cm^{-1}: 1706, 1742 (C=O), 3411 (OH, NH). ^{1}H-NMR

(500 MHz DMSO-d_6): δ (ppm): 2.23 (3H, s, CH_3), 2.28 (3H, s, CH_3), 2.60 (3H, s, CH_3), 7.21 (2H, d, $^3J_{HH}$ 8.0 Hz, HAr), 7.37(2H, d, $^3J_{HH}$ 8.0 Hz, HAr), 12.26 (2H, s, 2NH). ^{13}C-NMR (125 MHz DMSO-d_6): δ (ppm): 15.1, 21.3, 30.0, 89.2, 109.5, 124.9, 125.2, 127.1, 127.8, 129.7, 137.8, 149.4, 157.1, 160.6, 174.4, 194.3. Calcd.for ($C_{18}H_{16}N_2O_4S$): C, 60.66; H, 4.53; N, 7.86; S, 9.00%. Found: C, 60.44; H, 4.54; N, 7.93; S, 8.79%.

5-[4-Acetyl-2-(4-chlorophenyl)-5-methylfuran-3-yl]-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**4m**). Light pink powder, mp 261-263 °C (Yield: 85%). IR (KBr) ν_{max}/cm^{-1}: 1713, 1748 (C=O), 3144 (OH, NH). ^{1}H-NMR (500 MHz DMSO-d_6): δ (ppm): 2.23 (3H, s, CH_3), 2.61 (3H, s, CH_3), 7.47-7.51 (4H, m, HAr), 12.30 (H, s, NH), 12.34 (H, s, NH). ^{13}C-NMR (125 MHz DMSO-d_6): δ (ppm): 15.1, 30.0, 88.76, 111.1, 125.0, 126.8, 129.31, 129.3, 129.5, 132.8, 148.0, 157.6, 160.6, 174.4, 194.2. Calcd.for ($C_{17}H_{13}ClN_2O_4S$): C, 54.19; H, 3.48; N, 7.43; S, 8.51. Found: C, 54.16; H, 3.44; N, 7.47; S, 8.55%.

Acknowledgements

We gratefully acknowledge financial support from the Vail-e-Asr University of Rafsanjan Faculty Research Grant.

Supplementary Material

The ^{1}H NMR and ^{13}C NMR data for compounds **4a-m** associated with this article can be found in the online version.

References

1. Rathee, P.; Tonk, R. K.; Dalal, A.; Ruhil, M. K.; Kumar, A. *Org. Cell. Mol. Biol.* **2016**, *62*, 5.
2. Mobinikhaledi, A.; Kalhor, M. *Int. J. Drug Dev. Res*. **2010**, *2*, 268.
3. Mohamed, N. R.; El-Saidi, M. M. T.; Ali, Y. M.; Elnagdi, M. H. *Bioorg. Med. Chem*. **2007**, *15*, 6227. https://doi.org/10.1016/j.bmc.2007.06.023
4. Li, J.; Shi, W.; Yang, W.; Kang, Z.; Zhang, M.; Song, L. *RSC Adv*. **2014**, *4*, 29549. https://doi.org/10.1039/C4RA03199G
5. Khalafi-Nezhad, A.; Panahi, F. *Synthesis* **2011**, *6*, 984. https://doi.org/10.1055/s-0030-1258446
6. Soleimani, E.; Ghorbani, S.; Ghasempour, H. R. *Tetrahedron* **2013**, *69*, 8511. https://doi.org/10.1016/j.tet.2013.06.080
7. Safaei, H. R.; Shekouhy, M.; Rahmanpur, S.; Shirinfeshan, A. *Green Chem*. **2012**, *14*, 1696. https://doi.org/10.1039/c2gc35135h
8. Deng, J.; Mo, L. P.; Zhao, F. Y.; Zhang, Z. H. *ACS Comb. Sci*. **2012**, *14*, 335. https://doi.org/10.1021/co3000264
9. Azzam, S. H. S.; Pasha, M. A. *Tetrahedron Lett.* **2012**, *53*, 7056. https://doi.org/10.1016/j.tetlet.2012.10.056
10. Kazemi-Rad, R.; Azizian, J.; Kefayati, H. *Tetrahedron Lett.* **2014**, *55*, 6887. https://doi.org/10.1016/j.tetlet.2014.10.099

11. Dommaraju, Y.; Prajapati, D. *Mol. Divers*. **2015**, *19*, 173.
https://doi.org/10.1007/s11030-014-9547-1
12. Bartzatt, R. *J. Pharm. Biomed. Anal.* **2002**, *29*, 909.
https://doi.org/10.1016/S0731-7085(02)00168-1
13. McClenaghan, N. D.; Absalon, C.; Bassani, D. M. *J. Am. Chem. Soc*. **2003**, *125*, 13004.
https://doi.org/10.1021/ja0372098
14. Look, S. A.; Burch, M. T.; Fenical, W.; Qi-tai, Z.; Clardy, J. *J. Org. Chem*. **1985**, *50*, 5741.
https://doi.org/10.1021/jo00350a061
15. Fenical, W.; Okeeda, R. K.; Basnadurraga, M. M.; Culver, P.; Jacobs, R. S. *Science* **1981**, *212*, 1512.
https://doi.org/10.1126/science.6112796
16. Hou, X. L.; Cheung, H. Y.; Hon, T. U.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, 54, 1955 and references cited therein.
https://doi.org/10.1016/S0040-4020(97)10303-9
17. Candeias, N. R.; Cal, P. M.; André, V.; Duarte, M. T.;Veiros, L. F.; Gois, P. M.*Tetrahedron* **2010**, *66*, 2736.
https://doi.org/10.1016/j.tet.2010.01.084
18. Pirrung, M. C.; Sarma. K. D. *J. Am. Chem. Soc*. **2004**, *126*, 444.
https://doi.org/10.1021/ja038583a
19. Jiang, B.; Li, Q. Y.; Zhang, H.; Tu, S. J.; Pindi, S.; Li, G. *Org, Lett*. **2012**, *14*, 700.
https://doi.org/10.1021/ol203166c
20. Jiang, B.; Yi, M. S.; Shi, F.; Tu, S. J.; Pindi, S.; Mc Dowell, P.; Li, G. *Chem. Commun*. **2012**, *48*, 808.
https://doi.org/10.1039/C1CC15913E
21. Eftekhari-Sis, B.; Zirak, M.; Akbari, A. *Chem. Rev*. **2013**, *113*, 2958.
https://doi.org/10.1021/cr300176g
22. Anary-Abbasinejad, M ; Talebizadeh, M. *J. Iran. Chem. Soc*. **2014**, *11*, 963.
https://doi.org/10.1007/s13738-013-0362-x
23. Mousavizadeh, F.; Talebizadeh, M.; Anary-Abbasinejad, M. *Tetrahedron Lett.* **2018**, 59, 2970.
https://doi.org/10.1016/j.tetlet.2018.06.043
24. Masoudi, M.; Anary-Abbasinejad, M. *TetrahedronLett*. **2016**, *57*, 103.
https://doi.org/10.1016/j.tetlet.2015.11.075
25. Oguz, S. F.; Dogan I. *Spect. Lett*. **2004**, *37*, 607.
https://doi.org/10.1081/SL-200037606
26. Bojarski, J. T.; Mokrosz. J. L.; Barton, H. J.; Paluchowska, M. H. *Adv. Heterocycl. Chem.* **1985**, *38*, 229.
https://doi.org/10.1016/S0065-2725(08)60921-6
27. Riley, H. A.; Gray, A. R. *Org. Synth.* **1943**, *2*, 509.

