Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 24 Feb 2009.

To cite this article: Hashem Sharghi & Mahboubeh Jokar (2009): $Al_2O_3/MeSO_3H$: A Novel and Recyclable Catalyst for One-Pot Synthesis of 3,4-Dihydropyrimidinones or Their Sulfur Derivatives in Biginelli Condensation, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:6, 958-979

To link to this article: http://dx.doi.org/10.1080/00397910802444258

Synthetic Communications®, 39: 958–979, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802444258

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Al_2O_3/$MeSO_3H$: A Novel and Recyclable Catalyst for One-Pot Synthesis of 3,4-Dihydropyrimidinones or Their Sulfur Derivatives in Biginelli Condensation

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Abstract: Al_2O_3/CH_3SO_3H (AMA) is an efficient catalyst for the three-component condensation reaction of aldehyde, 1,3-dicarbonyl compound, and urea or thiourea to afford the corresponding 3,4-dihydropyrimidin-2-(1H)-ones in high isolated yield via this procedure, which works very effectively regardless of the electronic nature of the substituent on the ring, although electron-donating groups precipitate the rate of reaction. The catalyst is recyclable and stable at room temperature, and the reaction protocol is simple, is cost-effective, and gives good isolated yield with high purity.

Keywords: AMA, Biginelli, dihydropyrimidinones, methansulfonic acid, recyclable catalysis

INTRODUCTION

Multicomponent reactions (MCRs) occupy an outstanding position in organic and medicinal chemistry for their high degree of atom economy, applications in combinatorial chemistry, and diversity-oriented synthesis.[1] The Biginelli reaction,[2] one of the most useful multicomponent reactions, offers an efficient way to access multifunctionalized 3,4-dihydropyrimidin-2-(1H)-ones (DHPMs) and related heterocyclic compounds.[3] Such

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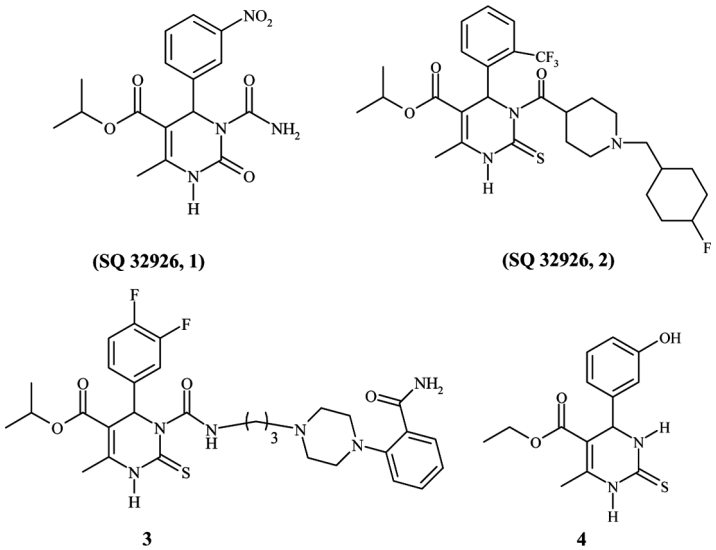
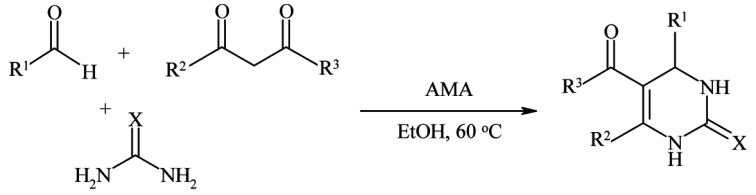
heterocycles (Scheme 1) show a wide scope of pharmacological properties including antiviral, antitumor, antibacterial, and anti-inflammatory activities.[4] Recently, appropriately functionalized DHPM analogs have emerged as orally active antihypertensive agents (**1**,**2**)[5] and α_{1a} adrenoceptor-selective antagonists (**3**).[6] Another highlight in this context has been the identification of the structurally rather simple DHPM monastrol (**4**) as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells, causing cell cycle arrest.[7]

Thus the synthesis of these heterocyclic compounds is of much current importance. The search for more suitable preparation of dihydropyrimidinones continues today. The first protocol to prepare the compounds of this type was presented by Biginelli in 1893 and involved a three-component, one-pot condensation.[2] A major drawback to Biginelli's original reactions, however, was poor to moderate yields.[8] Recently, many improved procedures have been reported using $InBr_3$,[9] $InCl_3$,[10] $LiClO_4$,[11] $FeCl_3 \cdot 6H_2O$ or $NiCl_2 \cdot 6H_2O$,[12] p-TsOH,[13] $LaCl_3 \cdot 7H_2O$,[14] $Bi(OTf)_3$,[15] $La(OTf)_3$,[16] $BF_3 \cdot OEt_2$,[17] ionic liquids ($BMIm \cdot PF_6$ and $BMIm \cdot BF_4$),[18] natural HEU type zeolite, [19] I_2,[20] N-bromosuccinimide (NBS),[21] polyaniline–bismoclite complex [22] and other Lewis acids,[23] heteropoly acid,[24] sulfated zirconia,[25] $Sr(NO_3)_2$,[26] and covalently anchored sulfonic acid onto silica.[27] However, some of the newer reported methods also suffer from drawbacks such as unsatisfactory



Scheme 1. Four of these related heterocyclic compounds 3,4-dihydropyrimidin-2-(1H)-ones (DHPMs) that have pharmacological properties are illustrated above.



Scheme 2. One-pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones and thiones using Al_2O_3/CH_3SO_3H (AMA).

yields, cumbersome product isolation procedures, and environmental pollution.[9,10,14,16,17] Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the workup procedure and cannot be recovered or reused. Therefore, still there is need for versatile, simple, and environmentally friendly processes whereby DHPMs may be formed under milder and practical conditions.

Solid-supported reagents are unique acid catalysts that have become popular over the past two decades. The activity and selectivity of a reagent dispersed on the surface of a support are improved as the effective surface area of the reagent is increased significantly, and hence they are expected to perform more effectively than the individual reagents.[28]

Low toxicity, air tolerance, low prices, and moisture resistance are other common features that cause the use of solid-supported reagents to be more attractive than alternatives of conventional Lewis acids or metal triflates.

In our last work, it was reported that a mixture of Al_2O_3/CH_3SO_3H (AMA) is an inexpensive and effective reagent for Fries rearrangement,[29] Beckmann rearrangements,[30] direct conversions of aromatic aldehydes to the corresponding glycol monoesters,[31] hydration of nitriles into amides,[32] syntheses of macrocyclic polyether-diesters,[33] syntheses of new hydroxythioxanthone derivatives,[34] direct sulfonyltion of phenloes with p-toluensulfonic acid,[35] and synthesis of coumarin derivatives,[36] in excellent yields and with high selectivity. Here we report the ability of this reagent as reusable catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones and thiones in high yields (Scheme 2).

RESULTS AND DISCUSSION

To exploit simple and suitable conditions for synthesis of 3,4-dihydropyrimidin-2-(1H)-ones, the reaction of benzaldehyde **5a**, urea **6a**, and

ethyl acetoacetate **7a** was chosen as a model to afford the DHPM **8a** ($R^1 = Ph$, $R^2 = Me$, $R^3 = OEt$, $X = O$), and its behavior was studied under a variety of conditions via thin-layer chromatography (TLC) and ^1H NMR and ^{13}C NMR spectroscopy (Table 1).

A summary of obtained results is provided in Table 1. At room temperature, the reaction rate was found to be slow and was increased with increase in temperature. At 60 °C, the reaction rate was found to be maximal, and further increase in temperature did not show any enhancement (Table 1, entries 6 and 7). Entries 1–6 show the effect of various solvents on the yield of reaction. Although toluene, acetonitrile, and dimethyl formamide afforded the product in high yields, we chose ethanol for its low cost and environmental acceptability. Our results show that the reaction does not proceed if no catalyst is employed (Table 1, entry 8), whereas the yield of Biginelli product is increased to 98% with the addition of AMA (0.1 g, equal to 0.5 mmol H^+). Entry 6 described the yields of five consecutive condensations leading to **8a**. In these experiments, the product was isolated by filtration and washing the solid residues with ethyl acetate. Thus the remaining catalyst, which always works the same, begins reloading with fresh reagents for further runs. We did not observe any large decrease in the yield, demonstrating the efficiency of alumina methansulfonic acid (AMA) as a catalyst in Biginelli

Table 1. Reaction of benzaldehyde **5a** (1 mmol), ethyl acetoacetate **7a** (1 mmol), and urea **6a** (1.2 mmol) under various reaction conditions

Entry	Conditions	Catalyst[a]	Time (h)	Yield (%)[b]
1	CH_2Cl_2/Refluxed	AMA	10	45
2	CH_3CN/60 °C	AMA	10	90
3	THF/60 °C	AMA	10	70
4	Toluene/60 °C	AMA	10	75
5	DMF/60 °C	AMA	10	80
6	C_2H_5OH/60 °C	AMA	1	98, 97, 96, 95, 95[c]
7	C_2H_5OH/rt	AMA	3	53
8	C_2 H_5 OH/Refluxed	None	24	25
9	C_2H_5OH/60 °C	Al_2O_3	10	0

[a]0.1 g, equal to 0.5 mmol H^+.
[b]Isolated yield.
[c]The same catalyst was used for each of five runs.

condensations. Therefore, the solid insoluble $MeSO_3H/Al_2O_3$ is a truly heterogeneous efficient catalyst for this transformation.

The previously mentioned results show the advantages of this method as a new and more suitable way to DHPM synthesis.

Results of the Biginelli reaction catalyzed by AMA are presented in Table 2. Alumina methansulfonic acid (AMA) works for the condensation of a series of aldehydes, 1,3-dicarbonyl compounds, and urea or thiourea. It is an environmentally, friendly catalyst that works at 60 °deg;C in short reaction times (20 min-3 h). This catalyst works regardless of structural variations in the aldehydes or β-ketoesters.

Besides, the β-ketoester, β-diketone (Table 2, entries 14, 15, 16, and 21) can also be employed without any decrease in yields. Under these conditions, the yields were significantly better in comparison with classical Biginelli procedure. Thus, several pharmacologically relevant substituent patterns could be introduced with high efficiency under the present conditions.

A variety of heterocyclic, aliphatic, and aromatic aldehydes were reacted with urea and β-dicarbonyl compound to afford 3,4-dihydropyrimidin-2-(1H)-ones in high yields using catalytic amounts of AMA (0.1 g, equal to 0.5 mmol H^+) under similar reaction conditions.

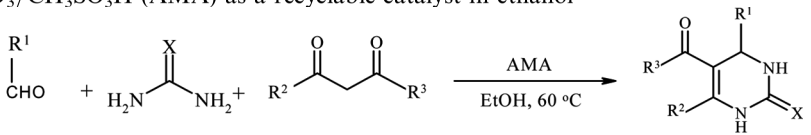
Various types of substituted benzaldehydes containing either electron-withdrawing or electron-donating substitutions successfully afforded the Biginelli products in high yields (Table 2, entries 1–28). An important feature of this procedure is the survival of a variety of functional groups such as ethers, nitro, hydroxyl, halides, cyanide, etc. under the reaction conditions. Acid-sensitive substrates such as 4-cyano benzaldehyde are also reacted in high yields without the formation of any side products (Table 2, entry 11).

Although aromatic aldehydes having either electron-donating or electron-withdrawing substituents reacted efficiently to afford excellent yields of 3,4-dihydropyrimidin-2-(1H)-ones, the aliphatic aldehydes, which are known to be less reactive under conventional Biginelli reaction conditions, also reacted smoothly to afford very high yields (Table 2, entries 26 and 27).

Thiourea was used as one of the substrates to provide the corresponding DHPMs in reasonable yields (Table 2, entries 21–24, 27, and 28). Most important, many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced without any interruption in efficiency.

To access the feasibility of applying this method in a preparative scale, we carried out the one-pot, three-component Biginelli condensation of benzaldehyde with ethyl acetoacetate and urea on a 100-mmol scale (Table 2, entry 29). As expected, the reaction proceeded similarly to the

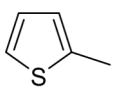
Table 2. Synthesis of dihydropyrimidin-ones and -thiones (DHPMs) by the condensation of aldehydes, β-dicarbonyls, and urea or thiourea catalyzed by Al_2O_3/CH_3SO_3H (AMA) as a recyclable catalyst in ethanol



5a-q **6a-b** **7a-d** **8a-8a'**

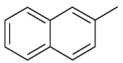
R^1= Aryl, Alkyl **R^2=Me, CH_2Cl** **R^3=OEt, OCH_2Ph, Me**

X= O, S

Entry	DHPM[a]	R^1	R^2/R^3	X	Yield (%)[b]	Time (min)	Mp (°C) Found	Mp (°C) Reported
1	**8a**	C_6H_5 (**5a**)	Me/OEt (**7a**)	O	98	25	204–206	202–204[37]
2	**8b**	4-O_2N-C_6H_4 (**5b**)	Me/OEt (**7a**)	O	91	35	209–211	208–211[37]
3	**8c**	4-Cl-C_6H_4 (**5c**)	Me/OEt (**7a**)	O	95	30	212–214	213–215[37]
4	**8d**	4-CH_3O-C_6H_4 (**5d**)	Me/OEt (**7a**)	O	96	35	203–205	201–203[37]
5	**8e**	3-Cl-C_6H_4 (**5e**)	Me/OEt (**7a**)	O	90	40	190–192	190–193[38]
6	**8f**	3-O_2N-C_6H_4 (**5f**)	Me/OEt (**7a**)	O	92	35	227–229	226–227[37]
7	**8g**	2-Cl-C_6H_4 (**5g**)	Me/OEt (**7a**)	O	88	60	216–217	215–218[9]
8	**8h**	 **(5h)**	Me/OEt (**7a**)	O	95	25	209–210	209–210[39]
9	**8i**	4-CH_3-C_6H_4 (**5i**)	Me/OEt (**7a**)	O	96	20	169–171	169–171[11]
10	**8j**	2,4-CH_3O-C_6H_3 (**5j**)	Me/OEt (**7a**)	O	95	35	157–159	158–160[40]
11	**8k**	4-CN-C_6H_4 (**5k**)	Me/OEt (**7a**)	O	85	60	219–221	219–222[38]

(*Continued*)

Table 2. Continued

Entry	DHPM[a]	R^1	R^2/R^3	X	Yield (%)[b]	Time (min)	Mp (°C) Found	Mp (°C) Reported
12	**8l**	2,6-Cl-C_6H_3 (**5l**)	Me/OEt (**7a**)	O	88	100	280–283	—
13	**8m**	4-iPr-C_6H_4 (**5m**)	Me/OEt (**7a**)	O	90	20	140–142	—
14	**8n**	4-CH_3-C_6H_4 (**5i**)	Me/Me (**7b**)	O	93	40	204–206	—
15	**8o**	3-Cl-C_6H_4 (**5e**)	Me/Me (**7b**)	O	86	55	280–281	284–285[41]
16	**8p**	C_6H_5 (**5a**)	Me/Me (**7b**)	O	89	30	229–230	233–236[16]
17	**8q**	4-CH_3-C_6H_4 (**5i**)	$ClCH_2$//OEt (**7c**)	O	90	110	164–166	—
18	**8r**	3-O_2N-C_6H_4 (**5f**)	$ClCH_2$//OEt (**7b**)	O	87	130	162–164	—
19	**8s**	C_6H_5 (**5a**)	$ClCH_2$//OEt (**7b**)	O	84	90	174–176	—
20	**8t**	 (**5n**)	Me/OEt (**7a**)	O	91	50	196–198	—
21	**8u**	C_6H_5 (**5a**)	Me/Me (**7c**)	S	89	180	183(dec)	185(dec)[42]
22	**8v**	C_6H_5 (**5a**)	Me/OEt (**7a**)	S	85	130	209–211	208–210[9]
23	**8w**	3-NO_2-C_6H_4 (**5f**)	Me/OEt (**7a**)	S	88	150	206–208	—
24	**8x**	3-OH-C_6H_4 (**5o**)	Me/OEt (**7a**)	S	87	52	183–184	184–186[43]
25	**8y**	3-OH-C_6H_4 (**5o**)	Me/OEt (**7a**)	O	94	100	163–165	163–166[9]
26	**8z**	n-C_5H_{11} (**5p**)	Me/OEt (**7a**)	O	85	120	151–154	—
27	**8a′**	n-C_4H_9 (**5q**)	Me/OEt (**7a**)	S	83	180	138–140	—
28	**8b′**	C_6H_5 (**5a**)	Me/$OCCH_2Ph$ (**7d**)	S	89	165	157–159	—
29	**8a**	C_6H_5 (**5a**)	Me/OEt (**7a**)	O	98[c]	25	204–206	202–204[37]

[a]Products were characterized by comparison of their spectroscopic data (^{1}H NMR, ^{13}C NMR, and IR) and melting points with those reported in the literature.

[b]Isolated yield.

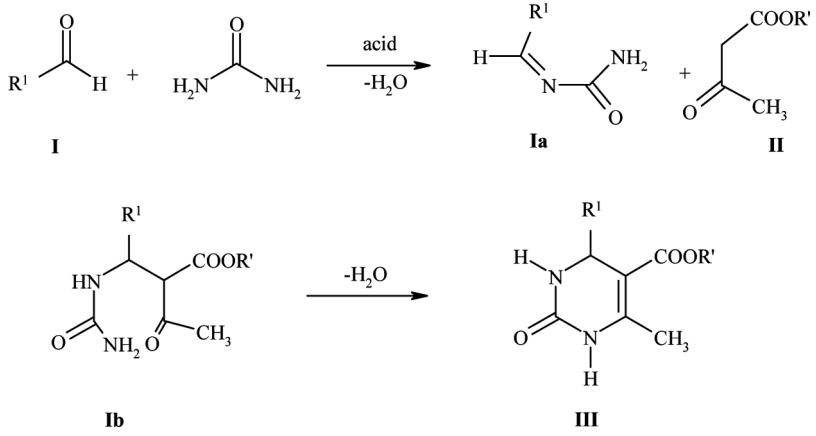
[c]The reaction was carried out on a 100-mmol scale.

case in a smallerly scale (Table 2, entry 1), and the desired 3,4-dihydropyrimidinone was obtained in 98% isolated yield in 25 min.

The merits of the present method are reflected from the fact that it provides better yields of various substituted 3,4-dihydropyrimidinones in shorter reaction times as compared to the recently known methods using heterogeneous catalysts.

The generally accepted Biginelli reaction mechanism[17,44,45a] (Scheme 3) involves the formation of C=N bond from the parent aldehyde (I) and urea followed by (protic or Lewis) acid-catalyzed addition of acetoacetate ester (II) to the aryl (or alkyl)idene–urea (Ia) and cyclodehydration (via Ib), yielding dihydropyrimidinones (III). AMA might promote the reaction by accelerating the formation C=N bond in the rate-determining step.[45b]

In conclusion, the present procedure provides an efficient and improved modification of Biginelli reactions. Mild reaction condition, ease of workup, high yields, stability and recyclability of the catalyst, large-scale synthesis, and simple procedure are features of this new procedure. Moreover, this method has the ability to tolerate a wide variety of substituents in all three components. When we compare our results (time, yield, reaction conditions) with some results obtained by other groups, as can be seen, our method is simpler, is more efficient, and uses no toxic solvents, and the catalyst could be readily recovered and reused for the one-pot formation of DHPMs. Hence, we believe that this method will find wide application in organic synthesis as well as industry.



Scheme 3. Suggested Biginelli reaction mechanism.

EXPERIMENTAL

General Information

NMR spectra were recorded on a Bruker Avance DPX-250 (^{1}H NMR 250 MHz and ^{13}C NMR 62.9 MHz) spectrometer in pure deuterated solvents with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (*J*) are in hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. IR spectra were obtained using a Shimadzu Fourier transform infrared (FT-IR) 8300 spectrophotometer. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instrument at 70 or 20 ev. Melting points were determined in open capillary tubes in a Büchi-535 circulating-oil melting-point apparatus. The purity determination of the substrates and reaction monitoring were accomplished by thin-layer chromatography (TLC) on silica-gel Poly-Gram SILG/UV 254 plates. Chemical materials were purchased from Fluka, Aldrich and Merck companies. Acidic alumina (Al_2O_3) type 540 C was purchased from Fluka.

Preparation of AMA

Methansulfonic acid (16.52 mL, 255 mmol) was added dropwise over a period of 90 min at 40 °C to a mixture of alumina (51 g, 510 mmol) in dichloromethane (30 mL). After the addition was complete, the mixture was stirred for 2 h, and then the solvent was evaporated under reduced pressure. After removal of CH_2Cl_2 in a rotary evaporator, the solid powder was kept at 120 °C for 72 h. A white solid of 68.0 g was obtained.

General Procedure for Synthesis of DHPMs

A mixture of the aldehyde (1 mmol), β-dicarbonyl compound (1 mmol), urea or thiourea (1.2 mmol), and alumina-methansulfonic acid (0.1 g, equal to 0.5 mmol H^+) in ethanol (5 mL) was heated at 60 °C for the appropriate time (Table 2). After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature and was filtered through a sinter funnel. The solid residue was washed with 20 mL hot ethanol (50 °C). The remaining catalyst was reloaded with fresh reagents for further runs. The filtrate was concentrated, and the

solid product was recrystallized from ethyl acetate/n-hexane (1/3) or ethanol.

All produced DHPMs were characterized in detailed structural data by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis as given next.

Data

Unknown compounds or compounds for which incomplete physical data were reported in the literature were characterized by FTIR, NMR (^{1}H, ^{13}C), and elemental analysis.

Ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-5-pyrimidine-carboxylate (**8a**)

Compound **8a** was obtained in 98% yield. Mp 204–206 °C (lit. 202–204 °C)[37]; ^{1}H NMR (250 MHz, $CDCl_3$): 1.19 (t, $J = 7.1$ Hz, 3H), 2.33 (s, 3H), 4.01 (q, $J = 7.2$ Hz, 2H), 5.31 (s, 1H), 5.90 (s, 1H), 7.10–7.35 (m, 5H), 8.30 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.1, 18.6, 55.7, 60.0, 101.3, 126.5, 127.0, 128.0, 143.0, 146.2.

Ethyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8b**)

Compound **8b** was obtained in 91% yield. Mp 209–211 °C, (lit. 209–211 °C) [37]; ^{1}H NMR (250 MHz, DMSO): 1.04 (t, $J = 7.0$ Hz, 3H), 2.24 (s, 3H), 3.86 (q, $J = 7.0$ Hz, 2H), 5.25 (s, 1H), 7.50 (d, $J = 7.3$ Hz, 2H), 7.85 (s, 1H), 8.20 (d, $J = 7.2$ Hz, 2H), 8.54 (s, 1H); ^{13}C NMR (62.9 MHz, DMSO): 13.9, 17.8, 53.6, 59.3, 98.1, 123.7, 127.6, 146.6, 149.3, 151.7, 151.9, 165.0.

Ethyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8c**)

Compound **8c** was obtained in 95% yield. Mp 212–214 °C, (lit. 213–215 °C)[37]; ^{1}H NMR (250 MHz, $CDCl_3$): 1.18 (t, $J = 7.2$ Hz, 3H), 2.31 (s, 3H), 4.06 (q, $J = 7.2$ Hz, 2H), 5.35 (s, 1H), 6.80 (s, 1H), 7.22–7.28 (m, 4H), 8.37 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.1, 18.6, 55.0, 60.1, 101.1, 127.9, 128.8, 133.7, 142.2, 146.5, 153.6, 165.4.

Ethyl-4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8d**)

Compound **8d** was obtained in 96% yield. Mp 203–205 °C, (lit. 201–203 °C)[37]; ^{1}H NMR (250 MHz, DMSO): 1.10 (t, $J = 7.0$ Hz, 3H), 2.23 (s, 3H), 3.70 (s, 3H), 3.96 (q, $J = 7.0$ Hz, 2H), 5.10 (s, 1H), 6.88 (d, $J = 8.8$ Hz, 2H), 7.15 (d, $J = 8.6$ Hz, 2H), 7.65 (s, 1H), 9.14 (s, 1H); ^{13}C NMR (62.9 MHz, DMSO): 14.5, 18.1, 53.7, 55.4, 59.5, 100.1, 114.1, 127.8, 137.4, 148.4, 152.6, 158.8, 165.8.

Ethyl-4-(3-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8e**)

Compound **8e** was obtained in 90% yield. Mp 190–192 °C, (lit. 190–193 °C)[38]; ^{1}H NMR (250 MHz, $CDCl_3$): 1.20 (t, $J = 7.2$ Hz, 3H), 2.34 (s, 3H), 4.06 (q, $J = 7.2$ Hz, 2H), 5.37 (s, 1H), 6.15 (s, 1H), 7.16–7.40 (m, 4H), 8.37 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.11, 18.61, 55.25, 60.19, 100.0, 124.0, 126.0, 128.0, 130.0, 134.0, 145.0, 146.0, 153.0, 165.0.

Ethyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8f**)

Compound 8f was obtained in 92% yield. Mp 227–229 °C, (lit. 226–227 °C)[37]; ^{1}H NMR (250 MHz, DMSO): 1.07 (t, $J = 7.2$ Hz, 3H), 2.25 (s, 3H), 3.96 (q, $J = 7.2$ Hz, 2H), 7.61–7.70 (m, 2H), 7.87 (s, 1H), 8.07–8.36 (m, 2H), 9.34 (s, 1H); ^{13}C NMR (62.9 MHz, DMSO): 13.9, 17.8, 53.6, 59.3, 98.3, 120.9, 122.3, 130.1, 132.9, 146.9, 147.7, 149.4, 151.7, 164.0.

Ethyl-4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8g**)

Compound **8g** was obtained in 88% yield. Mp = 216–217 °C, (lit. 215–218 °C)[9]; ^{1}H NMR (250 MHz, $CDCl_3$): 1.13 (t, $J = 7.2$ Hz, 3H), 2.41 (s, 3H), 3.90 (q, $J = 7.0$ Hz, 2H), 5.77 (s, 1H), 5.87 (s, 1H), 7.05–7.26 (m, 3H), 7.34–7.51 (m, 1H), 8.69 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 13.9, 18.3, 55.1, 59.9, 98.8, 127.5, 128.0, 129.3, 129.8, 132.6, 139.5, 148.4, 153.1, 165.3.

Ethyl-6-methyl-2-oxo-4-(2-thienyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8h**)

Compound **8h** was obtained in 95% yield. Mp = 209–210 °C, (lit. 209–210 °C)[39]; ^{1}H NMR (250 MHz, $CDCl_3$): 1.29 (t, $J = 7.0$ Hz, 3H), 2.27 (s, 3H), 4.13 (q, $J = 7.2$ Hz, 2H), 5.68 (s, 1H), 6.35 (s, 1H), 6.87–6.95 (m, 2H), 7.17 (d, $J = 5.0$ Hz, 1H), 8.51 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.2, 18.5, 50.6, 60.2, 101.6, 123.9, 124.8, 126.7, 146.8, 147.3, 153.9, 165.4.

Ethyl-6-methyl-4-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8i**)

Compound **8i** was obtained in 96% yield. Mp 169–171 °C, (lit. 169–171 °C)[11]; ^{1}H NMR (250 MHz, $CDCl_3$): 1.10 (t, $J = 7.2$ Hz, 3H), 2.31 (s, 6H), 4.06 (q, $J = 7.2$ Hz, 2H), 5.34 (s, 1H), 5.86 (s, 1H), 7.02–7.42 (4H, m), 8.25 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.1, 18.6, 21.0, 55.3, 59.9, 101.5, 126.5, 129.3, 137.6, 140.8, 146.2, 153.5, 165.7.

Ethyl-4-(2,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8j**)

Compound **8j** was obtained in 95% yield. Mp = 157–159 °C, (lit. 158–160 °C)[40]; ^{1}H NMR (250 MHz, $CDCl_3$): 1.10 (t, $J = 7.0$ Hz, 3H), 2.26 (s, 3H), 3.71 (s, 3H), 3.76 (s, 3H), 4.04 (q, $J = 7.0$ Hz, 2H), 5.67 (s, 1H), 5.84 (s, 1H), 6.75 (d, $J = 2.7$ Hz, 1H), 6.70–6.88 (m, 2H), 8.59 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.2, 18.5, 49.9, 55.6, 55.7, 59.9, 98.1, 111.2, 112.1, 113.8, 130.9, 148.5, 150.9, 153.5, 153.7, 165.7.

Ethyl-4-(4-cyanophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8k**)

Compound **8k** was obtained in 85% yield. Mp 219–221 °C, (lit. 219–222 °C)[38]; ^{1}H NMR (250 MHz, $CDCl_3$): 1.14 (t, $J = 7.0$ Hz, 3H), 2.33 (s, 3H), 4.01 (q, $J = 7.2$ Hz, 2H), 5.45 (s, 1H), 6.11 (s, 1H), 7.37 (d, $J = 8.2$ Hz, 2H), 7.62 (d, $J = 8.1$ Hz, 2H), 8.52 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.2, 18.8, 55.3, 60.3, 100.4, 111.9, 118.5, 127.4, 132.6, 147.1, 148.5, 153.2, 165.2.

Ethyl-4-(2,6-dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8l**)

Compound **8l** was obtained in 88% yield. Mp = 280–283 °C, (lit. 226°C)[23e]; ^{1}H NMR (250 MHz, DMSO): 0.87 (t, $J = 7.1$ Hz, 3H), 2.15 (s, 3H), 3.80 (q, $J = 7.2$ Hz, 2H), 6.1 (s, 1H), 7.25 (t, $J = 8.67$ Hz, 1H), 7.35 (d, $J = 7.7$ Hz, 2H), 7.69 (s, 1H), 9.25 (s, 1H); ^{13}C NMR (62.9 MHz, DMSO): 13.6, 17.8, 52.1, 58.7, 94.0, 129.3, 135.1, 137.5, 149.7, 150.5, 164.8.

Ethyl-4-(4-isopropylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8m**)

Compound **8m** was obtained in 90% yield. Mp 140–142 °C; IR (KBr), υ (cm^{-1}): 3247, 3120, 2962, 2931, 1705, 1651, 1288, 1096, 775, 663; ^{1}H NMR (250 MHz, $CDCl_3$) 1.08–1.21 (m, 9H), 2.29 (s, 3H), 2.73 (m, 1H), 3.98 (q, $J = 7.2$ Hz, 2H), 5.28 (s, 1H), 6.00 (s, 1H), 7.06 (d, $J = 8.2$ Hz, 2H), 7.15 (d, $J = 8.2$ Hz, 2H), 8.64 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.1, 18.5, 23.9, 33.7, 55.2, 59.9, 101.4, 126.5, 126.7, 129.8, 141.2, 146.4, 148.4, 153.9, 165.8. $C_{17}H_{22}N_2O_3$ (302.371): calc. C, 67.53%; H, 7.33%; N, 9.26%, found C, 67.59%; H, 7.26%, N, 9.20%.

5-Acetyl-6-methyl-4-(4-methylphenyl)-3,4-dihydro-2(1H)-pyrimidinone (**8n**)

Compound **8n** was obtained in 93% yield. Mp 204–206 °C; IR (KBr), υ (cm^{-1}): 3288, 3120, 2920, 1699, 1616, 1236, 1139, 765, 561; ^{1}H NMR (250 MHz, $CDCl_3$) 2.07 (s, 3H), 2.30 (s, 6H), 5.42 (s, 1H), 6.29 (s, 1H), 7.01–7.22 (m, 4H), 8.59 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 19.5, 21.1, 30.8, 55.9, 110.5, 126.5, 129.7, 137.9, 139.9, 146.1, 153.5, 195.4. $C_{14}H_{16}N_2O_2$ (244.292): calc. C, 68.83%; H, 6.60%; N 1.47%, found C, 68.89%; H, 6.50%, N 1.51%.

5-Acetyl-4-(3-chlorophenyl)-6-methyl-3,4-dihydro-2(1H)-pyrimidinone (**8o**)

Compound **8o** was obtained in 86% yield. Mp 280–281 °C; IR (KBr), υ (cm^{-1}): 3290, 3105, 3915, 1706, 1676, 1614, 1362, 1234, 1190, 917, 763, 628; ^{1}H NMR (250 MHz, DMSO): 2.1 (s, 3H), 2.28 (s, 1H), 5.25 (s, 1H), 7.16–7.45 (m, 4H), 7.87 (s, 1H), 9.24 (s,1H); ^{13} C NMR (62.9 MHz, DMSO): 18.9, 30.4, 53.1, 109.3, 124.9, 126.8, 127.2, 130.4,

133.0, 146.6, 148.7, 152.0, 194.0 $C_{13}H_{13}ClN_2O_2$ (264.710): calc. C, 58.99%; H, 4.95%; N, 10.56%, found C, 58.89%, H, 5.00%; N, 10. 61%.

5-Acetyl-6-methyl-4-phenyl-3,4-dihydro-2(1H)-pyrimidinone (**8p**)

Compound **8p** was obtained in 89% yield. Mp = 229–230 °C, (lit. 233–236 °C)[16]; ^{1}H NMR (250 MHz, DMSO): 2.16 (s, 1H), 2.27 (s, 1H), 5.24 (s, 1H), 7.25–7.35 (m, 5H), 7.80 (s, 1H), 9.16 (s,1H); ^{13}C NMR (62.9 MHz, DMSO): 18.8, 30.3, 53.7, 109.5, 126.4, 127.5, 128.17, 144.2, 148.1, 152.1, 194.2.

Ethyl-6-(chloromethyl)-4-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8q**)

Compound **8q** was obtained in 90% yield. Mp 164–166 °C; IR (KBr), υ (cm^{-1}): 3363, 3232, 3124, 2927, 2866, 1704, 1654, 1434, 1099, 1018, 771. ^{1}H NMR (250 MHz, $CDCl_3$): 1.20 (t, $J = 7.0$ Hz, 3H), 2.29 (s. 3H), 4.08 (q, $J = 7.0$ Hz, 2H), 4.75 (d, $J = 13.0$ Hz, 1H), 4.83 (d, $J = 13.0$ Hz, 2H), 5.39 (s, 1H), 6.56 (s, 1H), 7.09–7.026 (m, 4H), 8.01 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.0, 21.1, 55.1, 60.6, 103.5, 126.5, 129.1, 129.4, 129.9, 137.8, 140.1, 143.8, 153.9, 164.6. $C_{16}H_{17}ClN_2O_3$ (308.736): calc. C, 58.35%; H, 5.55%, 9.07%, found C, 58.40%; H 5.45%, N, 9.00%.

Ethyl-6-(chloromethyl)-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8r**)

Compound **8r** was obtained in 87% yield. Mp 162–164 °C; IR (KBr), υ (cm^{-1}): 3355, 3232, 3132, 2869, 1704, 1635, 1099, 1022, 914, 732, 455; ^{1}H NMR (250 MHz, DMSO): 1.06 (t, $J = 7.0$ Hz, 3H), 4.01 (q, $J = 7.2$ Hz, 2H), 4.57 (dd, $J_1 = 10.7$ Hz $J_2 = 3.2$ Hz, 1H), 4.61 (dd, $J_1 = 10.2$ Hz, $J_2 = 3.5$ Hz, 1H), 5.35 (s, 1H), 7.60–7.71 (m, 2H), 8.0–8.12 (m, 3H), 9.68 (s, 1H); ^{13}C NMR (62.9 MHz, DMSO): 13.6, 53.3, 60.1, 100.8, 121.1, 122.5, 130.2, 132.9, 145.9, 146.5, 146.9, 147.7, 151.9, 163.8. $C_{14}H_{14}ClN_3O_5$ (339.733): calc. C, 49.50%, H, 4.15%; N, 12.37%, found C, 49.60%; H 4.10%, N 12.0%.

Ethyl-6-(chloromethyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8s**)

Compound **8s** was obtained in 87% yield. Mp 174–176 °C; IR (KBr), υ (cm^{-1}): 3355, 3228, 3124, 2974, 1693, 1647, 1307, 1230, 1099, 1022,

756, 694; ^{1}H NMR (250 MHz, $CDCl_3$): 1.13 (t, $J = 7.0$ Hz, 3H), 4.03 (q, $J = 7.0$ Hz, 2H), 4.71 (d, $J = 13.2$ Hz, 1H), 4.84 (d, $J = 13.1$ Hz, 1H), 5.35 (s, 1H), 5.78 (s, 1H), 7.14–7.81 (m, 5H), 7.98 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.0, 39.7, 55.8, 60.7, 67.9, 126.6, 127.8, 128.3, 128.9, 142.7, 143.1, 147.0, 148.9, 164. $C_{14}H_{15}ClN_2O_3$ (294.736): calc. C, 57.05%: H, 5.13%; N, 9.50%, found C, 57.15%; H, 5.10%; N, 9.45%.

Ethyl-6-methyl-4-(2-naphthyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidine-carboxylate (**8t**)

Compound **8t** was obtained in 91% yield. Mp 196–198 °C; IR (KBr), υ (cm^{-1}): 3222, 3095, 2929, 1703, 1651, 1429, 1284, 1085, 1020, 779, 682, 478; ^{1}H NMR (250 MHz, $CDCl_3$): 1.14 (t, $J = 7.2$ Hz, 3H), 2.33 (s, 3H), 4.05 (q, $J = 7.2$ Hz, 2H), 5.52 (s, 1H), 6.24 (s, 1H), 7.35–7.48 (m, 3H), 7.62 (s, 1H), 7.70–7.80 (m, 3H), 8.64 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.0, 18.3, 52.1, 60.0, 98.8, 127.1, 127.9, 129.3, 129.8, 132.6, 139.5, 148.4, 153.1, 165.3. $C_{18}H_{18}N_2O_3$ (310.351): calc. C, 69.66%; H, 5.85%; N, 9.03%; found C, 69.78%; H, 5.80%; N, 9.10%.

1-(6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinyl) ethanone (**8u**)

Compound **8u** was obtained in 89% yield. Mp 183°C (decomposed) (lit. 185°C decomposed)[42]; ^{1}H NMR (250 MHz, DMSO): 2.16 (s, 3H), 2.37 (s, 3H), 5.28 (s, 1H), 7.26–7.59 (m, 5H), 9.89 (s, 1H), 10.37 (s, 1H); ^{13}C NMR (62.9 MHz, DMSO): 18.2, 30.4, 53.7, 110.4, 126.5, 127.46, 128.6, 142.8, 144.5, 168.0, 174.0, 194.7.

Ethyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecar-boxylate (**8v**)

Compound **8v** was obtained in 85% yield. Mp 209–211 °C (lit. 208–211 °C)[9]; ^{1}H NMR (250 MHz, $CDCl_3$): 1.19 (t, $J = 7.1$ Hz, 3H), 2.35 (s, 3H), 4.10 (q, $J = 7.1$ Hz, 2H), 5.38 (s, 1H), 7.20–7.35 (m, 5H), 7.48 (s, 1H), 8.12 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.1, 18.3, 56.2, 60.4, 102.9, 126.8, 128.4, 128.9, 142.3, 142.7, 165.2, 174.5.

Ethyl-4-(3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8w**)

Compound **8w** was obtained in 88% yield. Mp 206–208 °C (lit. 206–207 °C)[23a]; ^{1}H NMR (250 MHz, $CDCl_3$): 1.08 (t, $J = 7.2$ Hz, 3H), 2.29 (s, 3H), 4.05 (q, $J = 7.2$ Hz, 2H), 5.30 (s, 1H), 7.63–7.67 (m, 2H), 8.04 (s, 1H), 8.14 (dd, $J_1 = 6.2$ Hz, $J_2 = 2.2$ Hz, 1H), 9.74 (s, 1H), 10.48 (s, 1H); ^{13}C NMR (62.9 MHz, DMSO): 13.9, 17.8, 53.4, 59.7, 99.8, 121.1, 122.7, 130.4, 133.0, 145.4, 145.9, 147.7, 164.8, 174.4.

Ethyl-4-(3-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8x**)

Compound **8x** was obtained in 87% yield. Mp 183–184 °C (lit. 184–186 °C)[43]; ^{1}H NMR (250 MHz, DMSO): 1.06 (t, $J = 7.2$ Hz, 3H), 2.26 (s, 3H), 4.01 (q, $J = 7.0$ Hz, 2H), 5.08 (s, 1H), 7.63 (m, 3H), 7.20 (t, $J = 8.7$ Hz, 1H), 9.40 (s, 1H), 9.56 (s, 1H), 10.41 (s, 1H); ^{13}C NMR (62.9 MHz, DMSO): 13.9, 17.1, 53.9, 59.5, 100.7, 113.2, 114.5, 116.9, 129.4, 144.7, 144.8, 157.4, 165.1, 174.1.

Ethyl-4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8y**)

Compound **8y** was obtained in 94% yield. Mp 163–164°C (lit. 163–165 °C)[9]; ^{1}H NMR (250 MHz, DMSO):1.10 (t, $J = 7.0$ Hz, 3H), 2.22 (s, 3H), 4.05 (q, $J = 7.0$ Hz, 2H), 5.04 (s, 1H), 6.58–6.66 (m, 3H), 7.07 (t, $J = 8.1$ Hz, 1H), 7.66 (s, 1H), 9.32 (s, 1H), 9.34 (s, 1H); ^{13}C NMR (62.9 MHz, DMSO): 14.0, 17.7, 53.7, 59.1, 99.3, 113.0, 114.1, 116.8, 129.2, 146.1, 148.0, 152.0, 157.3, 165.3.

Ethyl-6-methyl-2-oxo-4-pentyl-1,2,3,4-tetrahydro-5-pyrimidine-carboxylate (**8z**)

Compound **8z** was obtained in 85% yield. Mp 151–154 °C; IR (KBr), υ (cm^{-1}): 3263, 3101, 2939, 3862, 1728, 1651, 1465, 1226, 1087, 1026, 779; ^{1}H NMR (250 MHz, DMSO): 0.80 (t, $J = 6.5$ Hz, 3H), 1.08–120 (m, 11H), 1.92 (s, 3H), 4.80 (q, $J = 6.7$ Hz, 2H), 8.09 (s, 1H), 8.19 (s, 1H); ^{13}C NMR (62.9 MHz, DMSO): 13.7, 14.1, 18.0, 21.9, 23.3, 30.9, 36.6, 49.9, 58.9, 99.8, 148.2, 152.4, 165.4; $C_{13}H_{22}N_2O_3$ (254.325): calc. C, 61.39%, H, 8.72%, N, 11.01%, found C, 61.45%, H, 8.67%, N, 11.10%.

Ethyl-4-butyl-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8a′**)

Compound **8a′** was obtained in 83% yield. Mp 138–140 °C; IR (KBr), υ (cm^{-1}): 3186, 2927, 2856, 1710, 1651, 1596, 1434, 1184, 1095, 752, 644, 528; ^{1}H NMR (250 MHz, DMSO): 0.81 (t, $J = 6.5$ Hz, 3H), 1.1–1.2 (m, 9H), 2.18 (s, 3H), 3.98–4.18 (m, 3H), 9.34 (s, 1H), 10.24 (s, 1H); ^{13}C NMR (62.9 MHz, DMSO): 13.6, 14.1, 17.0, 21.8, 25.5, 35.8, 50.3, 59.4, 100.6, 145.1, 165.1, 174.9; $C_{12}H_{20}N_2O_2S$ (256.365): calc. C 56.22%; H, 7.86%; N, 10.93%; S, 12.51%, found C, 56.31%; H, 7.81%; N, 10.87%; S, 12.59%.

Benzyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (**8b′**)

Compound **8b′** was obtained in 83% yield. Mp 157–159 °C (lit.156–157 °C)[46]; ^{1}H NMR (250 MHz, DMSO): 2.30 (s, 3H), 4.99 (d, $J = 12.7$ Hz, 1H), 5.10 (d, $J = 12.7$ Hz, 1H), 5.19 (s, 1H), 7.10–7.31 (m, 10H), 9.66 (s, 1H), 10.38 (s, 1H); ^{13}C NMR (62.9 MHz, DMSO): 17.2, 54.0, 65.1, 100.1, 126.4, 127.5, 127.7, 127.7, 128.2, 128.5, 136.2, 143.2, 145.8, 164.8, 174.1.

ACKNOWLEDGMENT

We gratefully acknowledge the support of this work by the Shiraz University Research Council and Shiraz Faculty of Pharmacy. We are also grateful to Mr. H. Sajedian Fard for helpful cooperation.

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