Synthesis and DPPH Radical Scavenging Activity of 5-Arylidene-*N*,*N*-Dimethylbarbiturates

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Abstract: Twenty-four derivatives of *N*,*N*-dimethylbarbituric acid **1-24** were screened for their DPPH radical scavenging activity. These compounds showed an excellent antioxidant activity. A structure-activity relationship has been discussed, while all the synthetic compounds were characterized by spectroscopic techniques and elemental analysis.

Keywords: DPPH Radical scavengers, *N*,*N*-dimethylbarbiturates.

INTRODUCTION

Barbituric acid and its derivatives have been reported as antibacterials, hypotensive and tranquilizers. Furthermore, arylidene barbituric acids are widely used as precursors for the synthesis of bioactive molecules [1] while their derivatives are important intermediates in organic synthesis [2].

Traditionally barbiturates are used as tranquilizing and hypnotic agents, in schizophrenic patients, so called as "sleep cures." Thiobarbiturates are used as potential clinical drugs in intravenous anesthesia [3]. Derivatives of barbituric acids had been known for their potential use as clinical drugs, however, biologically important constituents of barbituric acid and its analogs attracted the interest of medicinal chemists as potential drugs extensively.

The interesting mechanism of action of barbital and phenobarbital against epilepsy made them attractive targets for medicinal chemists. They have also been investigated as anticancer and anti-AIDS agents [4].

We have recently reported 5-arylidene barbiturates as novel class of DPPH radical scavengers [5]. Structural similarity of *N*,*N*-dimethyl-5-arylidene barbiturates **1-24** with 5-arylidene barbiturates, prompted us to test them for DPPH radical scavenging activity. Interestingly, we found them more active than our previous work, thereby proving that our initial hypothesis as correct.

Antioxidants prevent injury to blood vessel membranes thus ensure proper blood circulation and avoid cardiovascular diseases. They provide defense against cancer-causing DNA damages. Modes of action of antioxidants are attributed to their radical scavenging activity by contributing one electron to the free radicals to convert them into harmless molecules. Antioxidants thus protect cells from the oxidative damage that leads to aging and diseases [6-8].

Proteins, nucleic acids, lipids, and other classes of molecules such as the extra cellular matrix glycosaminoglycans (*e.g.* hyaluronic acid) are found to have strong affinity for free radicals and cause different diseases. The polyunsaturated fatty acids are more vulnerable to free radical damage, causing cerebral ischemia and other CNS diseases [9].

Free radicals have also been found to contribute in the pathology of arteriosclerosis, malaria and rheumatoid arthritis, in neurodegenerative disease and aging [10, 11].

This discovery and development of effective antioxidants, capable of supplementing body's antioxidant system, is an important area of research.

RESULTS AND DISCUSSION

In recent past, we synthesized a number of lead molecules of different classes of heterocycles [12-17]. In the present study, 5-arylidene-*N*,*N*-dimethylbarbiturates **1-24** were synthesized from commercially available *N*,*N*-dimethylbarbituric acid by refluxing with different aromatic aldehydes in water in very high yields (Scheme. **1**). In a typical reaction, *N*,*N*-dimethylbarbituric acid (1.56 mmol) and corresponding aldehyde (1.56 mmol, 1 eq.) were dissolved in distilled water (10 mL) and the mixture was refluxed for 30 minutes. In all cases, solid product was formed which was filtered, washed with cold water and ether followed by drying under vacuum. The pure products were obtained as fluffy solids. The structures of compounds **1-24** were confirmed by using different spectroscopic techniques, including ^{1}H NMR and EI spectrometry. All compounds gave a satisfactory CHN analysis.

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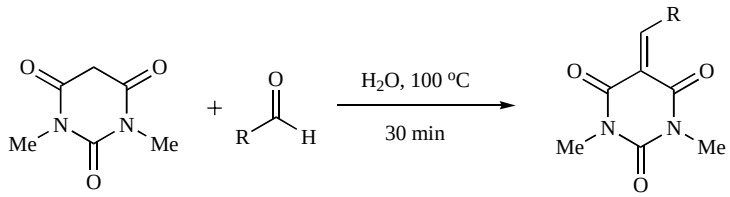

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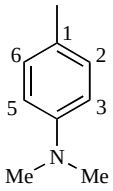
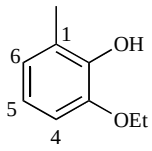
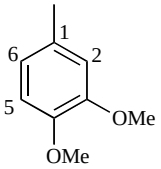
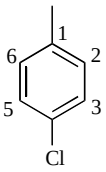
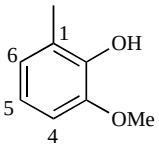
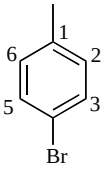
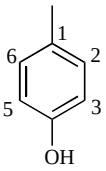
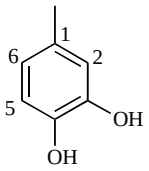
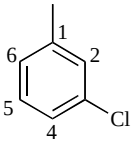
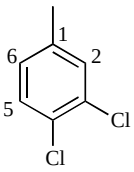
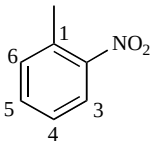
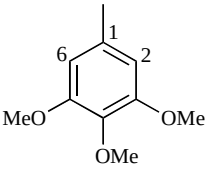
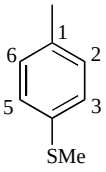
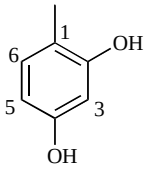
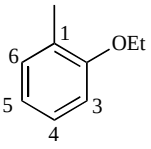
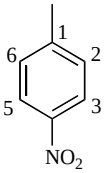
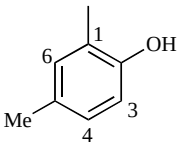
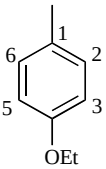
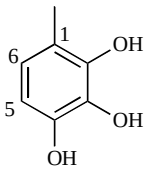
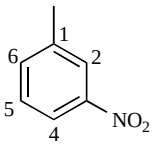
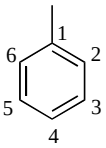
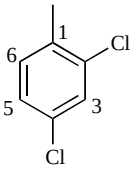
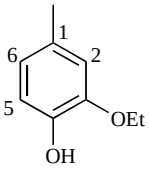
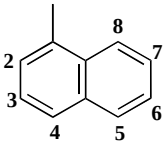
1		**9**		**17**	
2		**10**		**18**	
3		**11**		**19**	
4		**12**		**20**	
5		**13**		**21**	
6		**14**		**22**	
7		**15**		**23**	
8		**16**		**24**	

Scheme 1. 5-Arylidene-*N,N*-dimethylbarbiturates 1-24.

All the synthetic compounds **1-24** were subjected to *in vitro* free radical scavenging activity, according to literature protocol (Table. **1**) [18].

Table 1. *In Vitro* DPPH Radical Scavenging Activity of 5-arylidene-*N,N*-dimethylbarbiturates 1-24

Compound No.	IC_{50} ± SEM[a] (μM)
1.	NA[b]
2.	26.00 ± 1.02
3.	150.41 ± 1.74
4.	32.25 ± 1.56
5.	21.56 ± 2.08
6.	24.19 ± 2.58
7.	18.62 ± 2.81
8.	29.50 ± 3.12
9.	22.63 ± 2.98
10.	27.62 ± 0.98
11.	16.32 ± 2.54
12.	185.8 ± 1.21
13.	95.68 ± 1.48
14.	34.29 ± 4.01
15.	23.60 ± 2.00
16.	21.85 ± 1.47
17.	98.40 ± 3.64
18.	19.30 ± 2.50
19.	28.20 ± 3.09
20.	31.25 ± 1.89
21.	30.28 ± 1.79
22.	25.96 ± 1.56
23.	26.96 ± 1.25
24.	29.65 ± 2.56
n-propyl gallate[c]	30. 27 ± 1.6

SEM[a] is the standard error of the mean, NA[b] Not active, *n*-propyl gallate [c] standard inhibitor for DPPH radical scavenging activity

Most of the *N,N*-dimethyl barbituric acid derivatives demonstrated an excellent free radical scavenging activity. Out of twenty-four (**24**), fifteen compounds **11**, **7**, **18**, **5**, **16**, **9**, **15**, **6**, **22**, **2**, **23**, **10**, **19**, **8**, and **24** showed potent activities with IC_{50} values 16.32 ± 2.54, 18.62 ± 2.81, 19.30 ± 2.50, 21.56 ± 2.08, 21.85 ± 1.47, 22.63 ± 2.98, 23.60 ± 2.00, 24.19 ± 2.58, 25.96 ± 1.56, 26.00 ± 1.02, 26.96 ± 1.25, 27.62 ± 0.98, 28.20 ± 3.09, 29.50 ± 3.12 and 29.65 ± 2.56 μM, respectively, when compared with standard *n*-propyl gallate (IC_{50} = 30.27 ± 1.6 μM) as presented in Table **1**. Compounds **21** (IC_{50} = 30.28 ± 1.79 μM), **20** (IC_{50} = 31.25 ± 1.89 μM), **4** (IC_{50} = 32.25 ± 1.56 μM) and **14** (IC_{50} = 34.29 ± 4.01 μM) showed comparable free radical scavenging activities to standard *n*-propyl gallate. However, compounds **13** (IC_{50} = 95.68 ± 1.48 μM), **17** (IC_{50} = 98.40 ± 3.64 μM), **3** (IC_{50} = 150.41 ± 1.74 μM) and **12** (IC_{50} = 185.8 ± 1.21 μM) were found to be only moderately active. Compound **1** was found to be completely inactive.

Compounds **11** and **7** were found to be the most active among the series, with IC_{50} values of 16.32 ± 2.54 μM and 18.62 ± 2.81 μM, respectively. The free radical scavenging potential of a compound is based on its ability to stabilize the free radicals. Compound **11** possesses two vicinal hydroxyl moieties, while compound **7** contains three hydroxyl groups on the benzene ring which upon abstraction of hydrogen by DPPH lead to the formation of stable phenoxide radical on aromatic nucleus. Extended conjugation may help in their stabilization. This ability of compounds to stabilize the free radicals actually determines their free radical scavenging strength.

4-Bromo- (**18**) and 4-methylthio- (**5**) analogs exhibited a potent activity with IC_{50} values of 19.30 ± 2.50 and 21.56 ± 2.08 μM, respectively. It is predicted that a free radical is formed at electron rich centers such as at bromine or sulfur atoms.

Compounds **16**, a 3-ethoxy-4-hydroxy- and **9**, a 3-ethoxy-2-hydroxy- analog of *N,N*-dimethyl-5-arylidene barbiturates also showed a good inhibitory effect with IC_{50} values 21.85 ± 1.47 and 22.63 ± 2.98 μM against the DPPH, respectively. A small difference in these values might be due to the position of hydroxyl group.

A general trend of increase in activity was observed in compounds **22** (IC_{50} = 25.96 ± 1.56 μM), **10** (27.62 ± 0.98 μM), **24** (29.65 ± 2.56 μM), **21** (30.28 ± 1.79 μM), **20** (31.25 ± 1.89 μM) and **14** (34.29 ± 4.01 μM) as all of them possess electron donating groups.

The nitro-substituted arylidenes **15** (*meta*-derivative), **6** (*para*-substituted) and **12** (an *ortho*-analog) have the IC_{50} values of 23.60 ± 2.0 μM, 24.19 ± 2.58 and 185.8 ± 1.21 μM, respectively. Nitro-group being an inductively and electron withdrawing group mesomerrically offers more stabilization to the free radicals when it resides at aromatic nucleus [5]. In these cases, radicals are formed at benzylic carbon atoms. The case of weak antioxidant potential of *ortho*-substituted nitro analog **12** is somewhat unusual, as compared to *meta*- and *para*-analogs **15** and **6**. This noteworthy difference may be attributed sterically more demanding *ortho*-nitro group.

Para- and *meta*-chloro- substituted derivatives **2** (IC_{50} = 26.0 ± 1.02 μM) and **19** (IC_{50} = 28.2 ± 3.09 μM), were found to have good DPPH radical scavenging activities. However, dichloro substituted 5-arylidene barbiturates **8** (2,4-dichloro-) with IC_{50} = 29.50 ± 3.12 μM and **4** (3,4-dichloro-) with 32.25 ± 1.56 μM exhibited a slight lower activity, as compared to their mono chloro analogs **2** and **19**. This demonstrated that the addition of chloro group at aromatic ring reduces the antioxidant potential.

CONCLUSION

In conclusion, it has been found that the newly synthesized *N,N*-dimethyl-5-arylidene barbiturates **1-24** exhibited

far better antioxidant potential than previously reported 5-arylidene barbiturates [5]. Among the new series fifteen compounds demonstrated higher radical scavenging activity, than the standard *n*-propyl gallate. These compounds, therefore, may serve as viable lead molecules in the existing plethora of antioxidants.

MATERIALS AND METHODS

Experimental

EI Mass spectra were recorded with various MAT 711 (70 eV) spectrometers and data are tabulated as m/z. 1H-NMR spectra were recorded in DMSO-d6 using Bruker AC300 (300 MHz) spectrophotometers, respectively. Splitting patterns were as follows; s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. Chemical shifts are reported in δ (ppm) and coupling constants are given in Hz. The progress of all reactions was monitored by TLC which was performed on 2.0 x 5.0 cm aluminum sheets pre-coated with silica gel 60F254 to a thickness of 0.25 mm (Merck). The chromatograms were visualized under ultraviolet light (254-366 nm) or iodine vapors. The title compounds were synthesized and characterized satisfactorily.

DPPH (1,1-Diphenyl-2-Picryl Hydrazyl) Free Radical Scavenging Assay (*In vitro*)

The hydrogen donating activity of compounds was measured by 1,1-diphenyl-2-picrylhydrazil (DPPH) by using literature protocol [18]. Reaction mixture contains 5 μL of test sample (1 mM in DMSO) and 95 μL of DPPH (Sigma, 300 μM) in ethanol. The reaction mixture was taken into a 96-well microtiter plate and incubated at 37° C for 30 min. The absorbance was measured at 515 nm on microtiter plate reader (Molecular Devices, USA). Radical scavenging activity was determined by comparing with a DMSO containing control (Table-1), all assays were conducted in triplicate and in dark. IC_{50} values represent the concentration of compounds to scavenge 50% of DPPH radicals. *n*-Propyl gallate was used as a positive control. All the chemicals used were of analytical grade (Sigma, USA).

Synthesis and Characterization of New 5-Arylidene Barbiturates 1-24

N,N-Dimethyl barbituric acid derivatives (1.56 mmol) and corresponding aldehyde (1.56 mmol, 1 eq.) were dissolved in 10 mL of distilled water and the mixture was refluxed for 30 minutes. In all cases, solid product were formed which were filtered off and washed with cold water and ether followed by drying under vacuum. The pure compounds **1-24** were obtained as fluffy solids having satisfactory physical and spectroscopic data.

5-[4-(Dimethylamino)Benzylidene]-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (1)

Yield: 0.25 g (87%); ^{1}H-NMR (DMSO-d_6): δ 8.41 (2H, d, J = 9.3 Hz), 8.22 (1H, s), 6.80 (2H, d, J= 9.3 Hz), 3.28 (6H, s), 3.21 (6H,s); MS: *m/z* (rel. abund. %), 287 (M^+, 100), 172 (14), 144 (26), 129 (10); Anal. calcd. for $C_{15}H_{17}N_3O_3$ (287.31): C, 62.71; H, 5.96; N, 14.63; O, 16.71; Found: C, 62.70; H, 5.98; N, 14.62.

5-(4-Chlorobenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (2)

Yield: 0.235g (84%); ^{1}H-NMR (DMSO-d_6): 8.32 (s, 1H, *vin*. H), 8.02 (d, 2H, J = 8.4 Hz), 7.53 (d, 2H, J = 8.4 Hz), 3.22 (s, 3H, N-CH_3), 3.16 (s, 3H); MS: *m/z* (rel. abund. %), 278 (M^+, 70), 277 (100), 136 (58), 101 (37); Anal. calcd. for $C_{13}H_{11}ClN_2O_3$ (278.69): C, 56.03; H, 3.98; Cl, 12.72; N, 10.05; O, 17.22; Found: C, 56.05; H, 3.98; N, 10.02.

5-(4-Hydroxybenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (3)

Yield: 0.23 g (88%); ^{1}H-NMR (DMSO-d_6): 10.79 (br. s, 1H), 8.30 (d, 2H, J = 8.7 Hz), 8.27 (s, 1H), 6.88 (d, 2H, J = 8.7 Hz), 3.21 (s, 6H); MS: *m/z* (rel. abund. %), 260 (M^+, 100), 202 (34), 146 (62), 118 (51), 89 (37); Anal. calcd. for $C_{13}H_{12}N_2O_4$ (260.25): C, 60.00; H, 4.65; N, 10.76; O, 24.59; Found: C, 60.01; H, 4.64; N, 10.76.

5-(3,4-Dichlorobenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (4)

Yield: 0.26 g (83%); ^{1}H-NMR (DMSO-d_6): 8.28 (s, 1H), 8.27 (d, 1H, J = 2.1 Hz), 7.87 (dd, 1H, J= 2.1, 8.4 Hz), 7.30 (d, 1H, J = 8.4 Hz), 3.22 (s, 3H), 3.16 (s, 3H); MS: *m/z* (rel. abund. %), 313 (M^+, 77), 311(100), 198 (43), 170 (50), 135 (27); Anal. calcd. for $C_{13}H_{10}C_{l2}N_2O_3$ (313.14): C, 49.86; H, 3.22; Cl, 22.64; N, 8.95; O, 15.33; Found: C, 49.85; H, 3.23; N, 8.93.

1,3-Dimethyl-5-[4-(methylsulfanyl)benzylidene]-2,4,6(1H,3H,5H)-pyrimidinetrione (5)

Yield: 0.25 g (86%); ^{1}H-NMR (DMSO-d_6): 8.29 (s, 1H), 8.14 (d, 2H, J = 8.4 Hz), 7.34 (d, 2H, J = 8.4 Hz), 3.22 (s, 3H), 3.19 (s, 3H), 2.55 (s, 3H); MS: *m/z* (rel. abund. %), 290 (M^+, 100), 232(17), 176 (15), 133 (11); Anal. calcd. for $C_{14}H_{14}N_2O_3S$ (290.34): C, 57.92; H, 4.86; N, 9.65; O, 16.53; S, 11.04; Found: C, 57.90; H, 4.87; N, 9.66.

1,3-Dimethyl-5-(4-Nitrobenzylidene)-2,4,6(1H,3H,5H)-Pyrimidinetrione (6)

Yield: 0.24 g (83%); ^{1}H-NMR (DMSO-d_6): 8.41 (s, 1H), 8.25 (d, 2H, J = 9.0 Hz), 7.96 (d, 2H, J = 9.0 Hz), 3.35 (s, 6H); MS: *m/z* (rel. abund. %), 289 (M^+, 100), 242 (64), 175 (42), 101 (56); Anal. calcd. for $C_{13}H_{11}N_3O_5$ (289.24): C, 53.98; H, 3.83; N, 14.53; O, 27.66; Found: C, 53.97; H, 3.82; N, 14.52.

1,3-Dimethyl-5-(2,3,4-Trihydroxybenzylidene)-2,4,6(1H,3H,5H)-Pyrimidinetrione (7)

Yield: 0.23 g (79%); ^{1}H-NMR (DMSO-d_6): 8.86 (s, 1H), 8.25 (d, 1H, J= 9.3 Hz), 6.40 (d, 1H, J = 9.3 Hz), 3.19 (s, 6H); MS: *m/z* (rel. abund. %), 292 (M^+, 100), 275 (63), 205 (73), 150 (38); Anal. calcd. for $C_{13}H_{12}N_2O_6$ (292.24): C, 53.43; H, 4.14; N, 9.59; O, 32.85; Found: C, 53.45; H, 4.13; N, 9.57.

5-(2,4-Dichlorobenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (8)

Yield: 0.26 g (83%); ^{1}H-NMR (DMSO-d_6): δ 8.28 (s, 1H), 7.75 (d, 1H, J = 2.1 Hz), 7.69 (d, 1H, J = 8.7 Hz), 7.48 (dd, 1H, J = 2.1, 8.7 Hz), 3.22 (s, 3H), 3.11 (s, 3H,); MS: *m/z* (rel. abund. %), 313 (M^+, 10), 277 (100), 220 (73), 170 (15);

Anal. calcd. for $C_{13}H_{10}Cl_2N_2O_3$ (313.14): C, 49.86; H, 3.22; Cl, 22.64; N, 8.95; O, 15.33; Found: C, 49.87; H, 3.21; N, 8.93.

5-(3-Ethoxy-2-Hydroxybenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (9)

Yield: 0.25 g (82%); ^{1}H-NMR (DMSO-d_6): 9.57 (s, 1H), 8.66 (s, 1H), 7.62 (d, 1H, *J* = 8.1 Hz), 7.11 (d, 1H, *J* = 8.1 Hz), 6.31 (t, 1H, *J* = 8.1 Hz), 4.07 (q, 2H, *J* = 6.9 Hz), 3.21 (s, 3H), 3.16 (s, 3H), 1.35 (t, 3H, *J* = 7.2 Hz); MS: *m/z* (rel. abund. %), 304 (M^+, 100), 287 (94), 259 (76), 162 (48); Anal. calcd. for $C_{15}H_{16}N_2O_5$ (304.30): C, 59.21; H, 5.30; N, 9.21; O, 26.29; Found: C, 59.22; H, 5.31; N, 9.20.

5-(2-Hydroxy-3-Methoxybenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (10)

Yield: 0.23g (79%); ^{1}H-NMR (DMSO-d_6): 9.79 (s, 1H), 8.66 (s, 1H), 7.63 (d, 1H, *J* = 8.1 Hz), 7.11 (dd, 1H, *J* = 0.9, 8.1 Hz), 6.31 (t, 1H, *J* = 8.1 Hz), 3.83 (s, 3H), 3.22 (s, 3H), 3.15 (s, 3H); MS: *m/z* (rel. abund. %), 290 (M^+, 100), 273 (97), 203 (45), 156 (22); Anal. calcd. for $C_{14}H_{14}N_2O_5$ (290.27): C, 57.93; H, 4.86; N, 9.65; O, 27.56; Found: C, 57.91; H, 4.87; N, 9.66.

5-(3,4-Dihydroxybenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (11)

Yield: 0.22 g (79%); ^{1}H-NMR (DMSO-d_6): 8.18 (s, 1H), 8.17 (s, 1H), 7.87 (dd, 1H, *J* = 2.1, 8.4 Hz), 7.85 (d, 1H, *J* = 8.4 Hz), 3.21 (s, 6H); MS: *m/z* (rel. abund. %), 276 (M^+, 100), 218 (23), 162 (22), 134 (11); Anal. calcd. for $C_{13}H_{12}N_2O_5$ (276.24): C, 56.52; H, 4.38; N, 10.14; O, 28.96; Found: C, 56.54; H, 4.35; N, 10.14.

1,3-Dimethyl-5-(2-Nitrobenzylidene)-2,4,6(1H,3H,5H)-Pyrimidinetrione (12)

Yield: 0.23 g (80%); ^{1}H-NMR (DMSO-d_6): 8.69 (s, 1H), 8.24 (dd, 1H, *J* = 0.9, 8.4 Hz), 7.79 (dt, 1H, *J* = 0.9, 7.5 Hz), 6.31 (t, 1H, *J* = 7.5 Hz), 7.51 (d, 1H, *J* = 7.5 Hz), 3.30 (s, 3H), 3.24 (s, 3H); MS: *m/z* (rel. abund. %), 289 (M^+, 00.0), 243 (100), 186 (82); Anal. calcd. for $C_{13}H_{11}N_3O_5$ (289.24): C, 53.98; H, 3.83; N, 14.53; O, 27.66; Found: C, 53.97; H, 3.84; N, 14.53.

5-(2,4-Dihydroxybenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (13)

Yield: 0.20 g (72%); ^{1}H-NMR (DMSO-d_6): 10.81 (br. s, 1H,), 10.74 (br. s, 1H), 8.81 (s, 1H), 8.64 (d, 1H, *J* = 9.0 Hz,), 6.88 (d, 1H, *J* = 2.4 Hz), 6.31 (dd, 1H, *J* = 2.4, 9.0 Hz), 3.18 (s, 6H); MS: *m/z* (rel. abund. %), 276 (M^+, 100), 259 (100), 202 (48), 189 (66), 145 (27); Anal. calcd. for $C_{13}H_{12}N_2O_5$ (276.24): C, 56.52; H, 4.38; N, 10.14; O, 28.96; Found: C, 56.53; H, 4.36; N, 10.15.

5-(2-Hydroxy-5-Methylbenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (14)

Yield: 0.24 g (87%); ^{1}H-NMR (DMSO-d_6): 10.36 (s, 1H), 8.65 (s, 1H), 7.94 (s, 1H), 7.20 (dd, 1H, *J* = 2.1, 8.4 Hz), 6.83 (d, 1H, *J* = 8.4 Hz), 3.21 (s, 3H), 3.18 (s, 3H), 2.20 (s, 3H); MS: *m/z* (rel. abund. %), 274 (M^+, 81), 257 (100), 217 (59), 187 (82), 160 (57); Anal. calcd. for $C_{14}H_{14}N_2O_4$ (274.27): C, 61.31; H, 5.14; N, 10.21; O, 23.33; Found: C, 61.32; H, 5.13; N, 10.20.

1,3-Dimethyl-5-(3-Nitrobenzylidene)-2,4,6(1H,3H,5H)-Pyrimidinetrione (15)

Yield: 0.25 g (86%); ^{1}H-NMR (DMSO-d_6): 8.82 (s, 1H), 8.42 (s, 1H), 8.31 (dd, 1H, *J* =2.1, 8.1 Hz), 8.20 (d, 1H, *J* = 8.1 Hz), 6.31 (t, 1H, *J* = 8.1 Hz), 3.16 (s, 3H), 3.13 (s, 3H); MS: *m/z* (rel. abund. %), 289 (M^+, 100), 242 (59), 129 (27), 101 (35); Anal. calcd. for $C_{13}H_{11}N_3O_5$ (289.24): C, 53.98; H, 3.83; N, 14.53; O, 27.66; Found: C, 53.99; H, 3.82; N, 14.52.

5-(3-Ethoxy-4-Hydroxybenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (16)

Yield: 0.27 g (89%); ^{1}H-NMR (DMSO-d_6): 10.47 (s, 1H), 8.34 (d, 1H, *J* = 1.8 Hz), 8.27 (s, 1H), 7.80 (dd, 1H, *J* = 1.8, 8.4 Hz), 6.90 (d, 1H, *J* = 8.4 Hz), 4.08 (s, 2H,), 3.21 (s, 6H), 1.37 (t, 3H, *J* = 6.9 Hz); MS: *m/z* (rel. abund. %), 304 (M^+, 23), 166 (100), 137 (100), 109 (49); Anal. calcd. for $C_{15}H_{16}N_2O_5$ (304.30): C, 59.21; H, 5.30; N, 9.21; O, 26.29; Found: C, 59.20; H, 5.31; N, 9.22.

5-(3,4-Dimethoxybenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (17)

Yield: 0.26 g (85%); ^{1}H-NMR (DMSO-d_6): 8.30 (s, 1H), 8.28 (d, 1H, *J* = 2.1 Hz), 7.91 (dd, 1H, *J* = 2.1, 8.7 Hz), 6.31 (d, 1H, *J* = 8.7 Hz), 3.87 (s, 3H), 3.81 (s, 3H), 3.22 (s, 3H), 3.21 (s, 3H); MS: *m/z* (rel. abund. %), 304 (M^+, 100), 246 (21), 204 (13); Anal. calcd. for $C_{15}H_{16}N_2O_5$ (304.30): C, 59.21; H, 5.30; N, 9.21; O, 26.29; Found: C, 59.20; H, 5.31; N, 9.21.

5-(4-Bromobenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (18)

Yield: 0.29 g (90%); ^{1}H-NMR (DMSO-d_6): 8.28 (s, 1H), 7.93 (d, 2H, *J* = 8.4 Hz), 7.66 (d, 2H, *J* = 8.4 Hz), 3.22 (s, 3H), 3.16 (s, 3H); MS: *m/z* (rel. abund. %), 323 (M^+, 100), 264 (21), 243 (19), 101 (21); Anal. calcd. for $C_{13}H_{11}BrN_2O_3$ (323.14): C, 48.32; H, 3.43; Br, 24.73; N, 8.67; O, 14.85; Found: C, 48.30; H, 3.44; N, 8.66.

5-(3-Chlorobenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (19)

Yield: 0.23 g (82%); ^{1}H-NMR (DMSO-d_6): 8.30 (s, 1H), 8.01 (s, 1H), 7.82 (d, 1H, *J* = 7.5 Hz), 7.56 (d, 1H, *J* = 7.5 Hz), 7.48 (t, 1H, *J* = 7.8 Hz), 3.22 (s, 3H), 3.16 (s, 3H); MS: *m/z* (rel. abund. %), 278 (M^+, 89), 277 (100), 243 (14), 164 (37), 136 (52), 101 (33); Anal. calcd. for $C_{13}H_{11}ClN_2O_3$ (278.69): C, 56.03; H, 3.98; Cl, 12.72; N, 10.05; O, 17.22; Found: C, 56.04; H, 3.99; N, 10.04.

1,3-Dimethyl-5-(3,4,5-Trimethoxybenzylidene)-2,4,6(1H,3H,5H)-Pyrimidinetrione (20)

Yield: 0.28 g (84%); ^{1}H-NMR (DMSO-d_6): 9.80 (s, 1H), 7.24 (s, 2H), 3.85 (s, 9H), 3.22 (s, 3H), 3.16 (s, 3H); : *m/z* (rel. abund. %), 334 (M^+, 97), 319 (34), 196 (100), 181 (53); Anal. calcd. for $C_{16}H_{18}N_2O_6$ (334.32): C, 57.48; H, 5.43; N, 8.38; O, 28.71; Found: C, 57.50; H, 5.42; N, 8.38.

5-(2-Ethoxybenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (21)

Yield: 0.22 g (78%); ^{1}H-NMR (DMSO-d_6): 8.56 (s, 1H), 7.63 (d, 1H, J = 1.2, 7.8 Hz), 7.48 (td, 1H, J = 1.8, 8.7 Hz), 7.1 (d, 1H, J = 8.4 Hz), 6.96 (t, 1H, J = 7.5 Hz), 4.13 (q, 2H, J = 6.9 Hz), 3.21 (s, 3H), 3.15 (s, 3H), 1.34 (t, 3H, J = 6.9 Hz); MS: *m/z* (rel. abund. %), 288 (M^+, 12), 243 (100), 186 (32), 118 (34); Anal. calcd. for $C_{15}H_{16}N_2O_4$ (288.30): C, 62.49; H, 5.59; N, 9.72; O, 22.20; Found: C, 62.48; H, 5.59; N, 9.74.

5-(4-Ethoxybenzylidene)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (22)

Yield: 0.23 g (80%); ^{1}H-NMR (DMSO-d_6):, 8.32 (d, 2H, J = 8.4 Hz), 8.30 (s, 1H), 7.04 (d, 2H, J = 8.4 Hz), 4.15 (q, 2H, J = 7.2 Hz), 3.21 (s, 3H), 3.00 (s, 3H), 1.34 (t, 3H, J = 6.9 Hz); MS: *m/z* (rel. abund. %), 288 (M^+, 100), 249 (78), 202 (15), 146 (16); Anal. calcd. for $C_{15}H_{16}N_2O_4$ (288.30): C, 62.49; H, 5.59; N, 9.72; O, 22.20; Found: C, 62.51; H, 5.58; N, 9.73.

5-Benzylidene-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (23)

Yield: 0.20 g (82%); ^{1}H-NMR (DMSO-d_6): 8.35 (s, 1H), 8.00 (d, 2H, J = 8.4 Hz), 7.50 (m, 3H), 3.22 (s, 3H), 3.17 (s, 3H); MS: *m/z* (rel. abund. %), 244 (M^+, 68), 243 (100), 186 (38), 130 (33), 102 (56); Anal. calcd. for $C_{13}H_{12}N_2O_3$ (244.25): C, 63.93; H, 4.95; N, 11.47; O, 19.65; Found: C, 63.95; H, 4.94; N, 11.47.

1,3-Dimethyl-5-(1-Naphthylmethylene)-2,4,6(1H,3H,5H)-Pyrimidinetrione (24)

Yield: 0.25 g (85%); ^{1}H-NMR (DMSO-d_6): 8.86 (s, 1H), 8.01 (m, 2H), 7.81 (m, 2H), 7.56 (m, 3H), 3.27 (s, 3H), 3.08 (s, 3H); MS: *m/z* (rel. abund. %); 294 (M^+, 100), 243 (80), 180 (81), 152 (100); Anal. calcd. for $C_{17}H_{14}N_2O_3$ (294.30): C, 69.38; H, 4.79; N, 9.52; O, 16.31; Found: C, 69.39; H, 4.78; N, 9.51.

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