The Arylimines of 2,4-Dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde: Synthesis and Their Application in 1,3-Dipolar Cycloaddition Reaction

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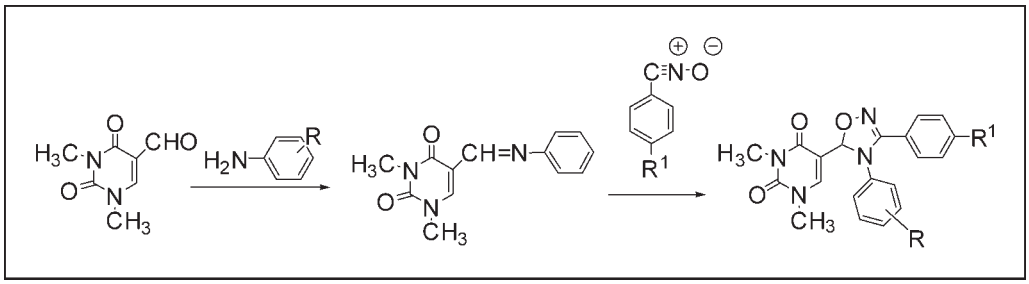

A number of aldimines have been obtained in very good yield in reaction of 5-formyl-1,3-dimethyluracil with various substituted anilines in boiling methanol. Selected aldimines were treated with nitrile oxides generated from 4-chlorobenzaldoxime or 4-methylbenzaldoxime forming the appropriate 1,3-cycloadducts in moderate yields.

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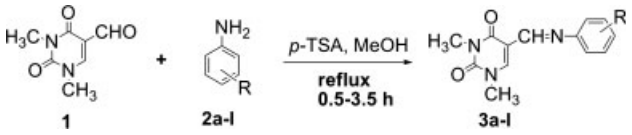
INTRODUCTION

The uracil derivatives are broadly known due to their application in bioorganic and medicinal chemistry. The 5-substituted uracils, mostly in the form of N1-glycosyl derivatives, possess biological activity, especially against viruses and neoplastic cells. 5-Fluorouracil and (*E*)-5-(2-bromovinyl)-2′-deoxyuridine belong to the best described uracil derivatives [1–3]. Similar to 5-halouridines, their analogues substituted with another heterocyclic system at C5 carbon of uracil ring, exhibit interesting biological activities. They form stable complexes with RNA [4] and inhibit thymidine kinase of HIV-1 virus [5,6]. The introduction of heteroaryl group into uracil ring can be performed using various methods. The UV irradiation of persilylated 5-iodo-2′-deoxycytidine in the presence of thiophene leads to appropriate 5-(2-thienyl)-2′-deoxycytidine in moderate yield [7]. The opposite variant of this reaction, when a mixture of 2-iodothiophene and 2-deoxycytidine was irradiated is also known [7]. Several 5-heteroaryl-2′-deoxyuridines have been obtained in palladium complexes catalyzed reaction of 5-iodo-2′-deoxyuridine with heteroaryltrialkyltin derivatives [8,9]. Other approaches based on traditional synthesis of heterocyclic rings involving 5-aminouracil as a building block in the construction of heterocyclic system have also been reported [10,11].

As a part of our research interest in the reactivity of uracil derivatives containing electron-withdrawing substituents, we have considered the molecule of 5-formyluracil (2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde) as a suitable reagent for the preparation of Schiff bases, which could be used further as dipolarophiles in 1,3-cycloaddition reaction. The chemical properties of 5-formyluracil are reported in the literature mainly in the context of its cytotoxic effect. The 5-formyl-2′-deoxyuridine formed by the oxidation of thymidine induces the damage of DNA [12–16]. Surprisingly, the syntheses involving 5-formyluracil as a reagent are rarely reported. 5-Formyl-1,3-dimethyluracil reacts with enamines giving 5-(acylvinyl)uracil derivatives. When enamines derived from 1,3-cyclohexanedione or ethyl acetate were applied, 5-(9-xanthenyl)uracil and 5-(6-cyclohexadienyl)uracil were obtained [17]. Recently, 5-formyluracil was used for the formation of nitrones, which treated with allyl alcohol as dipolarophile under harsh conditions to form isoxazolines in moderate yields [18]. Similarly, several isoxazoles, isoxazolines, and isoxazolidines have been synthesized by 1,3-dipolar cycloaddition reactions of nitrile oxides and nitrones derived from mono- and di-substituted uracil-5-carbaldehydes and 2,4-dimethoxypyrimidine-5-carbaldehyde [19].

The nickel, cobalt, and copper complexes of 5-formyluracil thiosemicarbazones were synthesized and their activity against model leukemia cells was examined [20]. Schiff bases of 5-formyluracil and chiral amino

Scheme 1. Synthesis of aldimines.



alcohols undergo highly diastereoselective 1,2- and 1,3-allylations to form homoallylic amino alcohol appended uracils [21].

RESULTS AND DISCUSSION

In our trials, which we report herein, 5-formyl-1,3-dimethyluracil (**1**) has been used as a carbonyl component in the synthesis of imines. For the preparation of **1** uracil was methylated by dimethyl sulfate followed by the Vilsmeier-Haack formylation using DMF and phosphorous trichloride [22]. Overall yield exceeded 60%. The condensation of **1** with substituted anilines **2a–l** occurs smoothly under mild condition (Scheme 1, Table 1). The desired aldimines **3a–l** were obtained by refluxing the equimolar amounts of reagents in methanol. The reaction time did not exceed 4 h in the case of less active anilines. The products **3a–l** are well soluble in hot methanol and, after cooling down to room temperature, they precipitate from the post-reaction solution in the form of crystalline solids in satisfactory yields (Table 1). The purity of the obtained imines **3a–d** was sufficient for the further synthesis as it was concluded from the NMR spectra. Other imines **3e–l** were recrystallized from methanol.

The structure of the products was assigned on the bases of NMR data and elemental analysis. The configuration of the double bond in the obtained imines was assumed as (*E*), which was confirmed by X-ray analysis of **3j** (Fig. 1) [23]. Because the synthesis of **3a–l** was performed under similar conditions (excluding time of reaction), we anticipated the same *E* configuration for all the obtained products.

For the primary trials of 1,3-dipolar cycloaddition reaction four imines **3a–d** possessing the substituent on C4 carbon of benzene ring were selected. The 1,3-dipole **4a** was generated *in situ* from 4-chlobenzaldehyde oxime using *N*-chlorosuccinimide and triethylamine as a base in chloroform solution according to the modified procedure [24]. The cycloaddition reaction of appropriate aldimine **3a–d** with 4-chlorobenzonitrile oxide **4** proceeded in refluxed $CHCl_3$ (Scheme 2). The products of reactions: 5-[3-(4-chlorophenyl)-4-(4-aryl)-4,5-dihydro-1,2,4-oxadiazole-5-yl]-1,3-dimethyl-1H-pyrimidine-2,4-dione **5a–d** were separated by column chromatography in satisfactory yields (Table 2). A same procedure was applied when 4-methylbenzonitrile oxide **4b** was used as the 1,3-dipole and cycloaddition reactions were occurred in 49–51% yields. The structure for all new compounds **5a–h** was confirmed by NMR spectroscopy and elemental analysis. As it was mentioned, the obtained aldimines have *E* configuration. The presence of single bond between C(5) of uracil ring and imine carbon atom allows for free rotation around this bond. The 1,3-cycloaddition reaction of nitrile oxide with double bond is the suprafacially concerted reaction [25]. However, when the free rotation is possible, the attack of dipole can occurs from both sides of imines and results in the formation of racemic mixture.

CONCLUSION

In summary, we have successfully carried out the condensation reaction of 1,3-dimethyl-5-formyluracil with substituted anilines. Reactions proceed under mild conditions and purity of aldimines in most of the cases was sufficient for the next step. It should be noticed that

Table 1

Synthesis of imines **3a–l** derived from 1,3-dimethyl-5-formyluracil and substituted anilines.

Product 3	R	Yield[a] (%)	Reaction time (h)	Mp (°C)
a	H	81	1.0	147–148
b	4-CH_3	91	1.5	155–156
c	4-Cl	93	0.5	183–185
d	4-Br	93	0.5	204–206
e	4-NO_2	84	1.0	282–284
f	3-CH_3	61	3.0	88–90
g	3-Cl	77	3.0	140–141
h	3-Br	75	3.5	143–144
i	3-I	79	3.0	148–149
j	2-CH_3	93	2.0	166–167
k	2-Cl	81	2.5	197–198
l	2-Br	75	2.5	195–197

[a] Isolated yield.

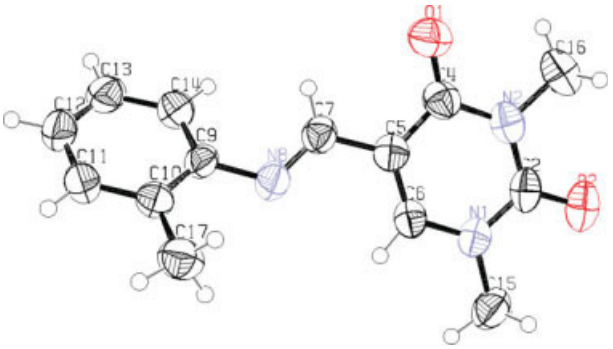


Figure 1. Crystal structure of **3j**. Displacement ellipsoids are drawn at the 50% probability level. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

the presence of neighboring carbonyl group has not influence on reactivity of 5-formyl group in uracil ring rather toward weak nucleophiles like aromatic amines. The obtained Schiff bases were applied as dipolarophiles in the 1,3-dipolar cycloaddition reactions of 4-chlorobenzonitrile oxide or 4-methylbenzonitrile oxide to produce the racemic 5-(4,5-dihydro-1,2,4-oxadiazole-5-yl)uracil derivatives in satisfactory yields. The attack of 1,3-dipole on C(5)—C(6)—double bond of uracil ring was not observed [26].

EXPERIMENTAL

NMR spectra were recorded at 300 MHz for ^{1}H NMR and 75.5 MHz for ^{13}C NMR on a Varian Inova 300 MHz in $CDCl_3$ solution; δ values are in parts per million relative to tetramethylsilane as an internal standard. Elemental analyses were obtained using a PerkinElmer 240C apparatus. 4-Chlorobenzaldoxime (mp 107–108°C, lit. mp 107–109°C) and 4-methylbenzaldoxime (mp 71–73°C, lit. mp 76–78°C) were prepared according to known procedures [27]. The other used reagents were purchased from Lancaster. TLC $60F_{254}$ plates and silica gel 60 (0.040–0.063 mm) were purchased from Merck.

General procedure for synthesis of imines (3a–l). To the solution of 1,3-dimethyl-5-formyluracil **1** (0.34 g, 2 mmol) in

Scheme 2. Synthesis of 1,3-cycloadducts.

MeOH (4 mL) containing 10 mg of *p*-TSA, appropriate aniline **2a–l** (2 mmol) was added and the reaction mixture was refluxed until the decay of substrates (0.5–3.5 h, Table 1), then cooled down to 0°C. The precipitate was filtered off, rinsed with cold methanol (2 mL), and dried in vacuum dessicator over P_2O_5. The products were sufficiently pure for the next step. If necessary the crystallization from methanol was applied and the pure compounds were obtained as light yellow crystals.

1,3-Dimethyl-5-(phenyliminomethyl)-1H,3H-pyrimidine-2,4-dione (3a). ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, CH_3), 3.51 (s, 3H, CH_3), 7.15 (d, 2H, J = 7.5 Hz, arom.), 7.22 (t, 1H, J = 7.5 Hz, arom.), 7.37 (t, 2H, J = 7.5 Hz, arom.), 8.24 (s, 1H, H-6), 8.58 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.1., 37.7, 100.2, 109.8, 121.1 (2C), 126.3, 129.3 (2C), 142.9, 151.3, 153.1, 162.5. Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.89; H, 5.01; N, 16.91.

1,3-Dimethyl-5-[(4-methylphenylimino)-methyl]-1H,3H-pyrimidine-2,4-dione (3b). ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H, CH_3, *p*-tol), 3.41 (s, 3H, CH_3), 3.55 (s, 3H, CH_3), 7.10 (d, 2H, J = 8.1 Hz, arom.), 7.17 (d, 2H, J = 8.1 Hz, arom.), 8.23 (s, 1H, H-6), 8.58 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 21.1, 28.2, 37.7, 110.0, 121.0 (2C), 129.9 (2C), 136.2, 142.7, 148.7, 151.4, 152.1, 162.5. Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.63; H, 5.47; N, 15.98.

5-[(4-chloro-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3c). ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 7.10 (d, 2H, J = 8.7 Hz, arom.), 7.33 (d, 2H, J = 8.7 Hz, arom.), 8.24 (s, 1H, H-6), 8.55 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.2, 37.8, 109.7, 122.4 (2C), 129.4 (2C), 131.9, 143.2, 149.8, 151.3, 153.5, 162.5. Anal. Calcd. for $C_{13}H_{12}ClN_3O_2$: C, 56.23; H, 4.36; N, 15.13. Found: C, 55. 96; H, 4.02; N, 14.89.

5-[(4-Bromo-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3d). ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 7.04 (dt, 2H, J = 9.3 Hz, 2.4 Hz, arom.), 7.48 (dt, 2H, J = 9.3 Hz, 2.4 Hz, arom.), 8.24 (s, 1H, H-6), 8.55 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.2, 37.8, 109.7, 119.7, 122.8 (2C), 132.4 (2C), 143.2, 150.3, 151.3, 153.5,

Table 2

The products of 1,3-dipolar cycloaddition **5a–h**.

Product 5	R	R^1	Reaction time (h)	Yield[a] (%)	Mp (°C)
a	H	Cl	1	50	114–115
b	4-CH_3	Cl	2	51	179–180
c	4-Cl	Cl	1	44	185–187
d	4-Br	Cl	1	47	212–214
e	H	CH_3	2.5	49	202–203
f	4-CH_3	CH_3	2.5	51	181–182
g	4-Cl	CH_3	2.5	44	180–181
h	4-Br	CH_3	2.5	51	184–185

[a] Isolated yield.

162.5. Anal. Calcd. for $C_{13}H_{12}BrN_3O_2$: C, 48.47; H, 3.75; N, 13.04. Found C, 48.85; H, 3.68; N, 12.75.

5-[(4-Nitro-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3e). ^{1}H NMR ($CDCl_3$): δ 3.40 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 6.63 (dt, 2H, J = 9.0 Hz, 2.6 Hz, arom.), 8.07 (m, 3H, H-6, arom.), 10.04 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.0, 38.2, 69.3, 110.4, 113.5 (2C), 126.5 (2C), 147.7, 151.1, 152.7, 162.1. Anal. Calcd. for $C_{13}H_{12}N_4O_4$: C, 54.17; H, 4.20; N, 19.44. Found: C, 53.88; H, 3.87; N, 19.06.

1,3-Dimethyl-5-[(3-methylphenyimino)-methyl]-1H,3H-pyrimidine-2,4-dione (3f). ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3, *m*-tol), 3.41 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 6.97–7.06 (m, 3H, arom.), 7.26 (t, 1H, J = 8.0 Hz, arom.), 8.32 (s, 1H, H-6), 8.61 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 21.5, 28.2, 37.8, 109.8, 118.2, 121.7, 127.3, 129.2, 139.2, 142.6, 147.6, 151.3, 153.0, 162.5. Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 64.98; H, 5.55; N, 15.98.

5-[(3-chloro-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3g). ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 7.02 (d, 1H, J = 8.0 Hz, arom.), 7.14 (m, 1H, arom.), 7.18 (d, 1H, J = 8.0 Hz, arom.), 7.29 (t, 1H, J = 8.0 Hz, arom.), 8.24 (s, 1H, H-6), 8.54 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.2, 37.8, 109.5, 119.4, 121.4, 126.2, 130.3, 134.9, 143.4, 151.3, 152.7, 154.2, 162.4. Anal. Calcd. for $C_{13}H_{12}ClN_3O_2$: C, 56.23; H, 4.36; N, 15.13. Found: C, 55.92; H, 3.98; N, 14.87.

5-[(3-Bromo-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3h). ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 7.07 (dq, 1H, J = 7.5 Hz, 1.3 Hz, arom.), 7.23 (t, 1H, J = 7.5 Hz, arom.), 7.33 (dt, 2H, J = 7.5 Hz, 1.3 Hz, arom.), 8.24 (s, 1H, H-6), 8.54 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.2, 37.8, 109.5, 120.0, 123.0, 124.2, 129.1, 130.6, 143.4, 151.3, 152.8, 154.2, 162.4. Anal. Calcd. for $C_{13}H_{12}BrN_3O_2$: C, 48.47; H, 3.75; N, 13.04. Found: C, 48.09; H, 3.46; N, 12.88.

5-[(3-Iodo-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3i). ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 7.03–7.15 (m, 2H, arom.), 7.51–7.56 (m, 2H, arom.), 8.30 (s, 1H, H-6), 8.55 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.2, 37.9, 94.6, 109.2, 120.6, 129.9, 130.7, 135.7, 143.7, 151.2, 154.2, 162.3. Anal. Calcd. for $C_{13}H_{12}IN_3O_2$: C, 42.30; H, 3.28; N, 11.38. Found: C, 42.05; H, 2.96; N, 11.03.

1,3-Dimethyl-5-[(2-methylphenylmino)-methyl]-1H,3H-pyrimidine-2,4-dione (3j). ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3, *o*-tol), 3.41 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 6.89 (d, 1H, J = 6.9 Hz, arom.), 7.09–7.21 (m, 3H, arom.), 8.23 (s, 1H, H-6), 8.46 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 18.0, 28.1, 37.8, 110.0, 118.1, 126.0, 126.9, 130.4, 131.8, 142.8, 150.6, 151.4, 152.4, 162.6. Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 64.97; H, 5.52; N, 15.98.

5-[(2-chloro-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3k). ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 7.00 (dd, 1H, J = 7.7 Hz, 1.6 Hz, arom.), 7.13 (dt, 1H, J = 7.7 Hz, 1.6 Hz, arom.), 7.24 (dq, 1H, J = 7.7 Hz, 1.6 Hz, arom.), 7.41 (dd, 1H, J = 7.7 Hz, 1.6 Hz, arom.), 8.32 (s, 1H, H-6), 8.50 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.2, 37.8, 109.6, 120.2, 126.8, 127.8, 128.2, 130.0, 143.7, 149.0, 151.4, 155.0, 162.4. Anal. Calcd. for $C_{13}H_{12}ClN_3O_2$: C, 56.23; H, 4.36; N, 15.13. Found: C, 56.56; H, 4.32; N, 14.91.

5-[(2-Bromo-phenylimino)-methyl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (3l). ^{1}H NMR ($CDCl_3$): δ 3.13 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 6.61 (dd, 1H, J = 7.9 Hz, 1.2 Hz, arom.), 6.77 (dt, 1H, J = 7.9 Hz, 1.2 Hz, arom.), 7.02 (dt, 1H, J = 7.9 Hz, 1.2 Hz, arom.), 7.31 (dd, 1H, J = 7.9 Hz, 1.2 Hz, arom.), 8.03 (s, 1H, H-6), 8.18 (s, 1H, imine). ^{13}C NMR ($CDCl_3$): δ 28.2, 37.9, 109.5, 118.5, 120.0, 127.0, 128.6, 133.1, 143.7, 150.2, 151.4, 154.7, 162.4. Anal. Calcd. for $C_{13}H_{12}BrN_3O_2$: C, 48.47; H, 3.75; N, 13.04. Found: C, 48.23; H, 3.54; N, 12.85.

General procedure for synthesis of 5-[3-(4-chlorophenyl)-(4-substituted-phenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1,3-dimethyl-1*H*,3*H*-pyrimidine-2,4-dione (5a–d). To a solution of 4-chlorobenzaldoxime (0.12 g, 0.77 mmol) in $CHCl_3$ (4 mL) NCS (0.11 g, 0.85 mmol) was added at room temperature while stirring. The reaction mixture changed the color from light yellow, through blue to green. Completion of the reaction was indicated by the turn the color of reaction mixture to yellow (40 min). The solution of 4-chlorobenzohydroximinoyl chloride was washed with small amounts of cold water (2 mL), dried over anhydrous $MgSO_4$, and immediately used for the next step. To the solution of 4-chlorobenzohydroximinoyl chloride the imine **3a–d** (0.7 mmol) was added followed by addition of triethylamine (0.11 mL, 0.77 mmol). The reaction mixture was refluxed for the time indicated in Table 2, concentrated under diminished pressure, and purified on silica gel packed column using AcOEt:*n*-hexane (1:1) as an eluent. The products **5a–d** were obtained as solid colorless materials, crystallized if necessarily from methanol.

The same procedure starting from the same molar amounts of substrates was applied for preparation of 4-methylbenzonitrile oxide **4b**. The 1,3-dipolar cycloaddition of **4b** to aldimines **3a–d** was carried out under conditions described earlier. The products **5e–h** were purified by silica gel packed column using a (1:1) mixture of *n*-hexane-ethyl acetate as eluent, in the form of colorless solids.

5-[3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (5a). ^{1}H NMR ($CDCl_3$): δ 3.39 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.64 (s, 1H, oxadiaz.), 7.09 (d, 2H, J = 7.7 Hz, arom.), 7.15 (t, 1H, J = 7.7 Hz, arom.), 7.25 (d, 2H, J = 7.7 Hz, arom.), 7.30 (dt, 2H, J = 8.6 Hz, 1.9 Hz, arom.), 7.52 (s, 1H, H-6), 7.57 (dt, 2H, J = 8.6, 1.9 Hz, arom.). ^{13}C NMR ($CDCl_3$): δ 27.9, 37.4, 94.6, 110.5, 123.8, 124.3 (2C), 126.0, 129.1 (2C), 129.3 (2C), 129.3 (2C), 137.0, 142.0, 142.1, 151.4, 154.8, 161.9. Anal. Calcd. for $C_{20}H_{17}ClN_4O_3$: C, 60.53; H, 4.32; N, 14.12. Found: C, 60.14; H, 3.98; N, 13.88.

5-[3-(4-chlorophenyl)-4-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (5b). ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H, CH_3, *p*-tol), 3.38 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.59 (s, 1H, oxadiaz.), 6.97 (d, 2H, J = 8.4 Hz, arom.), 7.05 (d, 2H, J = 8.4 Hz, arom.), 7.29 (d, 2H, J = 8.6 Hz, arom.), 7.51 (s, 1H, H-6), 7.56 (d, 2H, J = 8.6 Hz, arom.). ^{13}C NMR ($CDCl_3$) δ: 21.0, 28.0, 37.6, 94.8, 110.8, 124.0, 124.9 (2C), 129.1 (2C), 129.5 (2C), 130.1 (2C), 136.3, 137.0, 139.4, 142.3, 151.6, 155.1, 162.0. Anal. Calcd. for $C_{21}H_{19}ClN_4O_3$: C, 61.39; H, 4.66; N, 13.64. Found: C, 61.62; H, 4.65; N, 13.29.

5-[3-(3,4-bis-(4-chlorophenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (5c). ^{1}H NMR ($CDCl_3$): δ 3.39 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.59

(s, 1H, oxadiaz.), 7.10 (dt, 2H, J = 8.9 Hz, 2.4 Hz, arom.), 7.22 (dt, 2H, J = 8.9 Hz, 2.4 Hz, arom.), 7.32 (dt, 2H, J = 8.6 Hz, 2.2 Hz, arom.), 7.51 (s, 1H, H-6), 7.55 (dt, 2H, J = 8.6 Hz, 2.2 Hz, arom.). ^{13}C NMR ($CDCl_3$): δ 28.1, 37.6, 94.8, 110.3, 123.6, 126.0 (2C), 129.4 (2C), 129.5 (2C), 129.6 (2C), 131.9, 137.4, 140.9, 142.3, 151.5, 154.9, 162.1. Anal. Calcd. for $C_{20}H_{16}Cl_2N_4O_3$: C, 55.70; H, 3.74; N, 12.99. Found: C, 55.31; H, 3.39; N, 12.67.

5-[3-(4-chlorophenyl)-4-(4-bromo-phenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (5d). ^{1}H NMR ($CDCl_3$): δ 3.39 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.59 (s, 1H, oxadiaz.), 7.04 (d, 2H, J = 8.6 Hz, arom.), 7.32 (d, 2H, J = 8.7 Hz, arom.), 7.37 (d, 2H, J = 8.6 Hz, arom.), 7.50 (s, 1H, H-6), 7.55 (d, 2H, J = 8.7 Hz, arom.). ^{13}C NMR ($CDCl_3$): δ 28.1, 37.6, 94.7, 110.3, 119.6, 123.6, 126.2 (2C), 129.4 (2C), 129.5 (2C), 132.6 (2C), 137.4, 141.4, 142.4, 151.5, 154.8, 162.1. Anal. Calcd. for $C_{20}H_{16}BrClN_4O_3$: C, 50.50; H, 3.39; N, 11.78. Found: C, 50.09; H, 2.98; N, 11.39.

1,3-Dimethyl-5-[4-phenyl-3-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1H,3H-pyrimidine-2,4-dione (5e). ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3, *p*-tol), 3.39 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 6.66 (s, 1H, oxadiaz.), 7.08–7.15 (m, 5H, arom.), 7.21–7.26 (m, 2H, arom.), 7.53 (m, 3H, H-6, arom.). ^{13}C NMR ($CDCl_3$): δ 21.6, 28.0, 37.6, 94.2, 110.9, 122.5, 124.2 (2C), 125.7, 128.1 (2C), 129.3 (2C), 129.6 (2C), 141.5, 142.3, 142.5, 151.6, 155.6, 162.2. Anal. Calcd. for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 66.87; H, 4.98; N, 14.49.

1,3-Dimethyl-5-[3,4-di-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl)-1H,3H-pyrimidine-2,4-dione (5f). ^{1}H NMR ($CDCl_3$): 2.27 (s, 3H, CH_3, *p*-tol), 2.33 (s, 3H, CH_3, *p*-tol), 3.38 (s, 3H, CH_3), δ 3.41 (s, 3H, CH_3), 6.61 (s, 1H, oxadiaz.), 6.98 (d, 2H, J = 8.6 Hz, arom.), 7.03 (d, 2H, J = 8.6 Hz, arom.), 7.12 (d, 2H, J = 8.0 Hz, arom.), 7.52 (d, 2H, J = 8.0 Hz, arom.) 7.54 (s, 1H, H-6). ^{13}C NMR ($CDCl_3$): δ 21.0, 21.60, 28.0, 37.6, 94.2, 111.1, 122.5, 124.5 (2C), 128.2 (2C), 129.5 (2C), 129.9 (2C), 135.8, 139.8, 141.3, 142.2, 151.6, 155.8, 162.2. Anal. Calcd. for $C_{22}H_{22}N_4O_3$: C, 67.68; H, 5.68; N, 14.35. Found: C, 67.28; H, 5.33; N, 14.01.

5-[4-(4-chlorophenyl)-3-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (5g). ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, CH_3, *p*-tol), 3.39 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 6.60 (s, 1H, oxadiaz.), 7.10 (d, 2H, J = 8.9 Hz, arom.), 7.15 (d, 2H, J = 8.1 Hz, arom.), 7.20 (d, 2H, J = 8.9 Hz, arom.), 7.51 (d, 2H, J = 8.1 Hz, arom.) 7.54 (s, 1H, H-6). ^{13}C NMR ($CDCl_3$): δ 21.6, 28.1, 37.6, 94.2, 110.5, 122.1, 125.6 (2C), 128.2 (2C), 129.4 (2C), 129.7 (2C), 131.3, 141.3, 141.8, 142.3, 151.6, 155.5, 162.2. Anal. Calcd. for $C_{21}H_{19}ClN_4O_3$: C, 61.39; H, 4.66; N, 13.64. Found: C, 61.02; H, 4.34; N, 13.35.

5-[4-(4-Bromophenyl)-3-(4-methylphenyl)-4,5-dihydro-1,2,4-oxadiazol-5-yl]-1,3-dimethyl-1H,3H-pyrimidine-2,4-dione (5h). ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, CH_3, *p*-tol), 3.39 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 6.60 (s, 1H, oxadiaz.), 7.04 (d, 2H, J = 8.9 Hz, arom.), 7.15 (d, 2H, J = 8.1 Hz, arom.), 7.35 (d, 2H, J = 8.9 Hz, arom.), 7.51 (d, 2H, J = 8.1 Hz, arom.) 7.53 (s, 1H, H-6). ^{13}C NMR ($CDCl_3$): δ 21.6, 28.1, 37.6, 94.1, 110.5, 119.1, 122.1, 125.9 (2C), 128.1 (2C), 129.8 (2C), 132.3 (2C), 141.8, 142.3, 151.6, 155.5, 162.2. Anal. Calcd. for $C_{21}H_{19}BrN_4O_3$: C, 55.40; H, 4.21; N, 12.31. Found: C, 54.99; H, 3.85; N, 11.98.

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