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ORIGINAL PAPER

Aldimines of 5-aminouracil as reagents in 1,3-dipolar cycloaddition reaction

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Abstract The condensation of 5-aminouracil with aromatic aldehydes gave the appropriate *C*-arylimines, which were used in [2+3] cycloaddition with nitrile oxides derived from 4-substituted benzaldoximes. As a result of the dipolar cycloaddition reaction several hitherto unknown 5-(3,5-diphenyl-1,2,4-oxadiazol-4(5*H*)-yl)pyrimidine-2,4(1*H*,3*H*)-diones have been obtained in satisfactory yields.

Keywords Cycloadditions · Chlorination · Heterocycles · Nitrile oxides · Nucleosides · Schiff bases

Introduction

Pyrimidine nucleosides as components of nucleic acids and their important role as anticancer and antiviral agents inspire further search for new analogues with possible useful properties. The previous studies resulted in the discovery of several nucleoside analogues with an inhibitory effect on the growth of cancers and proliferation of viruses [1–3]. The most prominent representatives are 5-fluorouracil, trifluridine, and acedurid [3]. The modifications were mainly introduced on the C5 carbon atom of the uracil ring, since substituents at this location are not involved in the complementary base-pairing of DNA. Among other modifications, the introduction of a heterocyclic system to the uracil ring as an alternative has been considered (Fig. 1). The construction of a heterocyclic ring on the C5 carbon atom of the uracil ring was performed using different strategies. Among others, several approaches based on traditional syntheses of heterocyclic rings using 5-aminouracil as a building block have been reported [4–12]. The pyrrole ring was formed by a simple condensation of 5-aminouracil with 2,5-dimethoxytetrahydrofuran (**A**) [4]. In the reaction of 5-aminouracil with 1,4-dinitroimidazole, 5-(4-nitroimidazol-1-yl)uracil (**B**) was obtained [5]. Here, the reaction proceeds via an ANRORC degenerated transformation of the 1,4-dinitroimidazole ring. The introduction of a heteroaryl group into the uracil ring can be performed using other methods. The UV irradiation of persilylated 5-iodo-2′-deoxycytidine in the presence of thiophene leads to 5-(2-thienyl)-2′-deoxycytidine in moderate yield (**C**) [6]. The opposite variant of this reaction, when a mixture of 2-iodothiophene and 2-deoxycytidine is irradiated, is also known [6].

Several 5-heteroaryl-2′-deoxyuridines were obtained in the reaction of 5-iodo-2′-deoxyuridine with heteroaryltrialkyltin derivatives catalyzed by palladium complexes (**D**) [7, 8]. In recent years many attempts based on 1,3-dipolar cycloaddition reactions for the construction of heterocyclic systems on the uracil ring have been reported [9–12]. Thus **E** was synthesized in the reaction of a 5-ethynyluracil derivative with an appropriate nitrile oxide, generated from dibromoformaldoxime. In turn, using a nitrile oxide or *N*-methylnitrone derived from 5-formyluracil, uracil derivatives possessing isoxazoline, isoxazole, or isoxazolidine rings on the C5 carbon atom were obtained in satisfactory yields (e.g., **F**). The latter can be considered as an analogue of the natural *C*-nucleoside pseudouridine, a C-5-linked uridine containing a modified sugar moiety.

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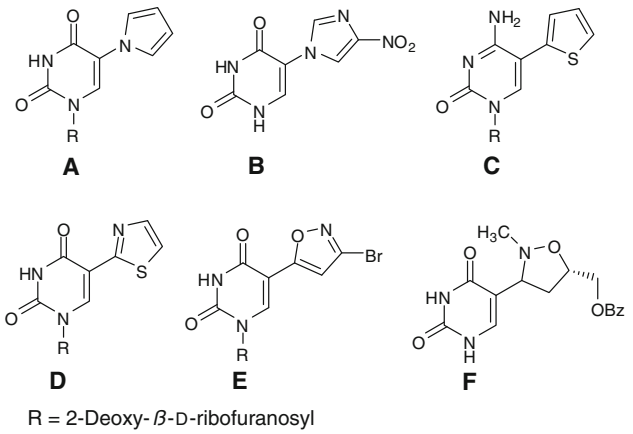


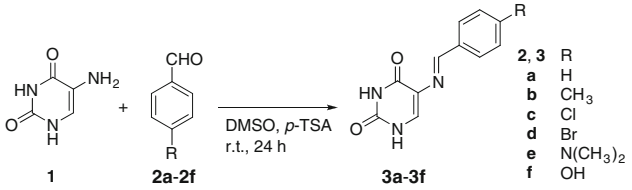
Fig. 1 Uracil derivatives possessing a 5-heterocyclic substituent

As a part of our research interest on the reactivity of uracil derivatives containing electron-withdrawing substituents, we utilized 5-formyluracil (2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde) as a suitable reagent for the preparation of Schiff bases, used further as dipolarophiles in the 1,3-cycloaddition reactions [13]. Our recent successful results prompted us to consider a different strategy involving 5-aminouracil as a substrate for the synthesis of imines and a subsequent [2+3] cycloaddition reaction. It is well known that in the case of imine Diels-Alder cycloaddition the nitrogen lone pair is *exo* in the transition state of the addition as a result of the lowest repulsion between lone pair and conjugated electrons of the diene [14]. The same type of interaction may be expected in the case of imines derived from 5-aminouracil where the *E*-geometry should be the most favored as a result of the electron repulsion of the nitrogen lone pair, the C4 carbonyl group, and the C5–C6 double bond of the uracil. The *E*-configuration has been observed in crystals of imines derived from 5-formyluracil and aromatic amines [13].

In the present paper we report our attempts to use 5-aminouracil for the formation of appropriate imines followed by their 1,3-dipolar cycloaddition reaction with nitrile oxides leading to various 5-(3,5-diphenyl-1,2,4-oxadiazol-4(5*H*)-yl)pyrimidine-2,4(1*H*,3*H*)-diones.

Results and discussion

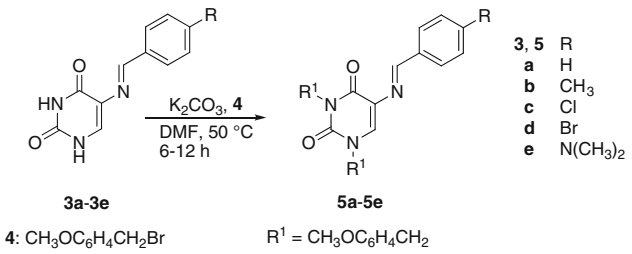
As starting materials for the formation of imines we chose monosubstituted benzaldehydes. Thus, 5-aminouracil (**1**) was treated with an equimolar amount of the appropriate aldehyde **2a–2f** in a polar aprotic solvent (Scheme 1). The reactions were carried out in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) at room temperature. After the consumption of starting material, the reaction mixture was poured onto ice. The obtained



Scheme 1

aldimines **3a–3f** were precipitated from the water slurry. The analysis of NMR spectra indicated that the applied procedure of isolation affords sufficiently pure products ready to be used in the next step without further purification. The yields were excellent.

As the obtained imines **3** were poorly soluble in chloroform, the solvent of choice for the preparation of nitrile oxides, their 4-methoxybenzyl derivatives **5a–5e** were selected due to their enhanced solubility. The imines **3a–3e** were treated with an excess of 4-methoxybenzyl bromide (**4**) in the presence of potassium carbonate as a base. The imine **3f** (R=OH) was excluded due to the possible formation of a benzyl ether on the 4-hydroxyl group present in the phenyl substituent. The benzylation was carried out in anhydrous DMF at slightly elevated temperature. When the TLC indicated the total consumption of starting imine **3**, the solution was cooled down to room temperature. The formed precipitate was filtered off, rinsed with methanol, and dried in a desiccator under diminished pressure (Scheme 2; Table 1). The products were used in the next step without further purification.



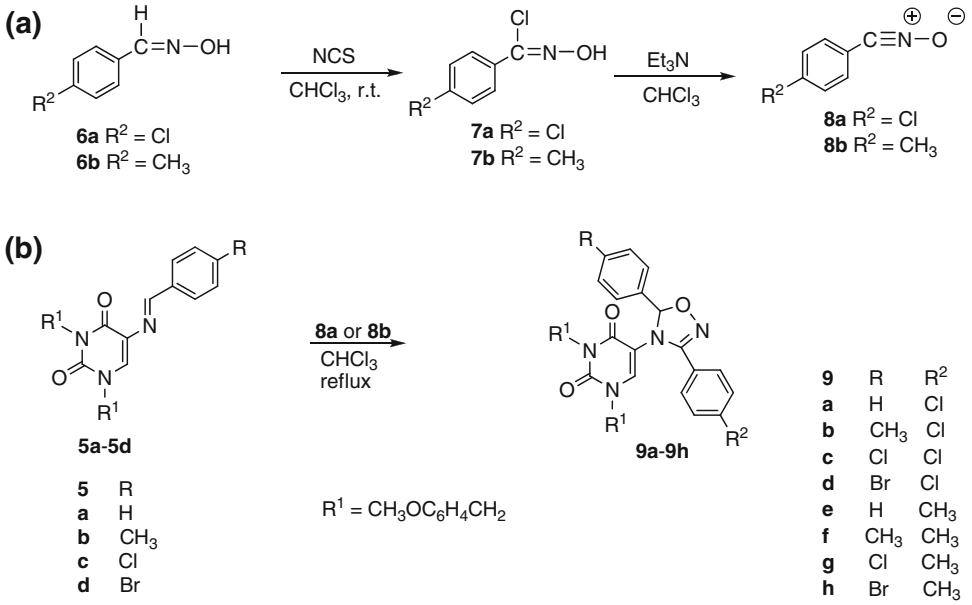
Scheme 2

Table 1 The protected imines **5a–5e**

Product **5**	R	Time/h	Yield[a]/%	M.p./°C
a	H	6	90	127–129
b	CH_3	12	54	139–140
c	Cl	8	88	140–141
d	Br	6	79	142–143
e	$N(CH_3)_2$	12	54	165–166

[a] Isolated yields

Scheme 3



The 1,3-dipole was generated in situ from 4-chlorobenzaldehyde oxime (**6a**) using *N*-chlorosuccinimide and triethylamine as a base in chloroform solution according to the modified procedure [15] (Scheme 3a). In the first trials of 1,3-dipolar cycloaddition, the reactions of the imines **5a**–**5d** with the appropriate nitrile oxide were carried out at room temperature. After a prolonged time of up to 72 h, the formation of a cycloadduct was not observed. Finally, the cycloaddition reactions of imines **5a**–**5d** with 4-chlorobenzonitrile oxide (**8a**) proceeded in boiling $CHCl_3$ (Scheme 3b). The products, 1,3-bis(4-methoxybenzyl)-5-[5-(4-substituted-phenyl)-3-(4-chlorophenyl)-1,2,4-oxadiazol-4(5*H*)-yl]pyrimidine-2,4(1*H*,3*H*)-diones **9a**–**9d**, were isolated in satisfactory yields using column chromatography (Table 2). The same procedure was applied when 4-methylbenzonitrile oxide (**8b**) was used as the 1,3-dipole. Also in this case, the cycloaddition resulted in satisfactory yields (cycloadducts **9e**–**9h**). The yields ranged from 25 to 52%. Apart from the desired products, in the post-reaction mixtures we observed mainly unreacted starting compounds used for the generation of nitrile oxides and also traces of aldimines. The structures of all newly obtained compounds **9a**–**9h** were confirmed by NMR spectroscopy and elemental analysis. The ^{1}H NMR spectra of the protected imines **5a**–**5d** in the range of 9.29–9.61 ppm exhibited a characteristic signal assigned to the proton of the CH=N group. This signal disappeared in the spectra of cycloadducts **9**. Here, a singlet derived from the proton present in the 4,5-dihydro-1,2,4-oxadiazole ring between 6.30 and 6.40 ppm was observed [16]. As mentioned in the "Introduction," the obtained imines derived from 5-aminouracil should have (*E*)-configuration around the C=N bond. The presence of a single bond between the C5 carbon atom of the uracil ring and the imine nitrogen atom allows for a free rotation around this bond, however the steric hindrance probably impedes free rotation. The 1,3-cycloaddition of nitrile oxide to a double bond is a suprafacial concerted reaction [17], however when the free rotation is possible, the attack of dipole can occur from both sides of the double bond. In these studies, we identified the formation of a single product—a racemate, which was the result of addition to the imine double bond. The yields ranging from moderate to satisfactory can be attributed to a high steric hindrance around the imine double bond in the stage of the adduct formation.

Table 2 The products of 1,3-dipolar cycloaddition **9a**–**9h**

Product **9**	R	R^2	Time/h	Yield[a]/%	M.p./°C
a	H	Cl	5	32	165–167
b	CH_3	Cl	5	52	146–147
c	Cl	Cl	6	38	183–185
d	Br	Cl	6	27	174–176
e	H	CH_3	5	25	90–92
f	CH_3	CH_3	6	31	144–145
g	Cl	CH_3	5	42	167–168
h	Br	CH_3	6	26	161–162

[a] Isolated yields

Conclusion

5-Aminouracil is a convenient substrate for the synthesis of appropriate imines in the reaction with aromatic aldehydes. The condensation occurs under mild conditions in the

presence of *p*-TSA as a catalyst. The obtained imines were reactive towards 1,3-dipoles, namely nitrile oxides generated from 4-substituted benzaldoximes in the reaction with NCS under basic conditions. The expected cycloadducts were obtained in moderate yields.

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 reported in parts per million relative to tetramethylsilane as an internal standard. Elemental analyses were performed using a Perkin-Elmer 240C apparatus; the results agreed favorably with calculated values. 4-Chlorobenzaldoxime (**6a**) and 4-methylbenzaldoxime (**6b**) were prepared according to known procedures [18]. 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 the synthesis of imines **3a–3f***

To a solution of 0.25 g of 5-aminouracil (**1**, 2 mmol) in 6 cm^3 of dry DMSO, the appropriate benzaldehyde **2a–2f** (2 mmol) and 10 mg of *p*-TSA were added. The reaction mixture was stirred for 24 h, and then poured onto 60 g of ice. The precipitated solid was filtered off, rinsed with 2 cm^3 of cold methanol, and dried in a vacuum desiccator over P_2O_5. The products **3a–3f** were obtained in very good yields as light yellow crystals and used for the next step without further purification.

5-(Benzylideneamino)pyrimidine-2,4(1H,3H)-dione (**3a**)
Yield 89%; m.p.: 302–304°C; the NMR spectrum was found comparable with the one reported in [19].

5-(4-Methylbenzylideneamino)pyrimidine-2,4(1H,3H)-dione (**3b**, $C_{12}H_{11}N_3O_2$)
Yield 93%; m.p.: 328–330°C; ^{1}H NMR (DMSO-d_6): δ = 11.36 (s, 1H, N–*H*), 11.15 (s, 1H, N–*H*), 9.31 (s, 1H, imine), 7.70 (d, 2H, $^{3}J_{H,H}$ = 7.8 Hz, arom.), 7.57 (s, 1H, H-6), 7.28 (d, 2H, $^{3}J_{H,H}$ = 7.8 Hz, arom.), 2.36 (s, 3H, –CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 161.5, 158.3, 150.2, 140.7, 137.7, 134.3, 129.4 (2C), 127.7 (2C), 122.4, 21.2 ppm.

5-(4-Chlorobenzylideneamino)pyrimidine-2,4(1H,3H)-dione (**3c**)
Yield 93%; m.p.: 351–353°C (Ref. [20] 345–346°C).

5-(4-Bromobenzylideneamino)pyrimidine-2,4(1H,3H)-dione (**3d**, $C_{11}H_8BrN_3O_2$)
Yield 96%; m.p.: 346–348°C; ^{1}H NMR (DMSO-d_6): δ = 11.40 (s, 1H, N–*H*), 11.23 (s, 1H, N–*H*), 9.40 (s, 1H, imine), 7.76 (d, 2H, $^{3}J_{H,H}$ = 8.7 Hz, arom.), 7.66 (d, 3H, $^{3}J_{H,H}$ = 8.7 Hz, arom., H-6) ppm; ^{13}C NMR (DMSO-d_6): δ = 161.3, 156.7, 150.0, 139.0, 136.1, 136.1 (2C), 129.6 (2C), 124.1, 121.7 ppm.

5-[4-(N,N-Dimethylamino)benzylideneamino]pyrimidine-2,4(1H,3H)-dione (**3e**, $C_{13}H_{14}N_4O_2$)
Yield 86%; m.p.: 322–324°C; ^{1}H NMR (DMSO-d_6): δ = 11.23 (s, 1H, N–*H*), 10.94 (d, 1H, $^{3}J_{H,H}$ = 5.1 Hz, N–*H*), 9.03 (s, 1H, imine), 7.60 (d, 2H, $^{3}J_{H,H}$ = 8.7 Hz, arom.), 7.39 (d, 1H, $^{3}J_{H,H}$ = 5.1 Hz, H-6), 6.73 (d, 2H, $^{3}J_{H,H}$ = 8.7 Hz, arom.), 2.98 (s, 6H, C*H*$_3$) ppm; ^{13}C NMR (DMSO-d_6): δ = 161.6, 158.8, 152.1, 150.2, 134.8, 129.5 (2C), 124.5, 123.6, 111.5 (2C), 39.52 (2C) ppm.

5-(4-Hydroxybenzylideneamino)pyrimidine-2,4(1H,3H)-dione (**3f**, $C_{11}H_9N_3O_3$)
Yield 88%; m.p. >300°C; ^{1}H NMR (DMSO-d_6): δ = 11.29 (s, 1H, N–*H*), 11.03 (d, 1H, $^{3}J_{H,H}$ = 4.8 Hz, N–*H*), 10.00 (s, 1H, –O*H*), 9.15 (s, 1H, imine), 7.64 (d, 2H, $^{3}J_{H,H}$ = 8.7 Hz, arom.), 7.47 (d, 1H, $^{3}J_{H,H}$ = 4.8 Hz, H-6), 6.84 (d, 2H, $^{3}J_{H,H}$ = 8.7 Hz, arom.) ppm; ^{13}C NMR (DMSO-d_6): δ = 161.5, 160.1, 158.5, 150.2, 136.0, 129.8 (2C), 128.2, 123.1, 115.6 (2C) ppm.

General procedure for the benzylation of imines

To a solution of imine **3a–3e** (1 mmol) in 6 cm^3 of dry DMF, 0.304 g solid K_2CO_3 (2.2 mmol) was added, and the reaction mixture was stirred for 30 min. After that time the first portion of *p*-methoxybenzyl bromide (**4**, 0.603 g, 3 mmol) was added, and the reaction was stirred for 3–4 h at 50°C. Then, the next portion of *p*-methoxybenzyl bromide (0.201 g, 1 mmol) was added, and the reaction mixture was heated for further 2–8 h, and poured onto 60 g of ice. The waxy residue was extracted by three portions (20 cm^3) of chloroform. The organic layer was dried over $MgSO_4$ and evaporated. Then 20 cm^3 MeOH was added. The precipitated solid was filtered off, rinsed with 2 cm^3 cold methanol, and dried in a vacuum desiccator over P_2O_5. The products **5a–5e** were obtained in good yields as light yellow crystals.

5-(Benzylideneamino)-1,3-bis(4-methoxybenzyl)-pyrimidine-2,4(1H,3H)-dione (**5a**, $C_{27}H_{25}N_3O_4$)
^{1}H NMR ($CDCl_3$): δ = 9.61 (s, 1H, imine), 7.82–7.74 (m, 2H, arom.), 7.52–7.44 (m, 3H, arom., H-6), 7.44–7.38 (m, 3H, arom.), 7.28 (d, 2H, $^{3}J_{H,H}$ = 8.7 Hz, arom.), 6.89 (d, 2H, $^{3}J_{H,H}$ = 8.7 Hz, arom.), 6.85 (d, 2H, $^{3}J_{H,H}$ = 8.7 Hz, arom.), 5.14 (s, 2H, –C*H*$_2$–), 4.92 (s, 2H, –C*H*$_2$–), 3.80 (s, 3H, –C*H*$_3$), 3.78 (s, 3H, –C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$): δ = 160.7, 160.3, 159.9, 159.3, 150.6, 139.6, 137.2, 131.1, 130.8 (2C), 130.0 (2C), 129.1, 128.7 (2C), 128.4 (2C), 127.2, 123.0, 114.6 (2C), 113.9 (2C), 55.4, 55.3, 52.2, 44.5 ppm.

1,3-Bis(4-methoxybenzyl)-5-(4-methylbenzylideneamino)-pyrimidine-2,4(1H,3H)-dione (**5b**, $C_{28}H_{27}N_3O_4$)
^{1}H NMR ($CDCl_3$): δ = 9.56 (s, 1H, imine), 7.73 (d, 2H, $^3J_{H,H}$ = 7.8 Hz, arom.), 7.60 (s, 1H, H-6), 7.48 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 7.28 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 7.22 (d, 2H, $^3J_{H,H}$ = 7.8 Hz, arom.), 6.89 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 6.84 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 5.14 (s, 2H, –CH_2–), 4.91 (s, 2H, –CH_2–), 3.79 (s, 3H, –CH_3), 3.77 (s, 3H, –CH_3), 2.38 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 159.4, 158.7, 158.4, 157.7, 149.0, 137.7, 129.2 (2C), 128.5 (2C), 128.4, 128.3, 128.2, 128.0 (2C), 127.5, 127.2, 125.7, 113.1 (2C), 112.4 (2C), 53.9, 53.8, 50.8, 43.0, 20.2 ppm.

1,3-Bis(4-methoxybenzyl)-5-(4-chlorobenzylideneamino)-pyrimidine-2,4(1H,3H)-dione (**5c**, $C_{27}H_{24}ClN_3O_4$)
^{1}H NMR ($CDCl_3$): δ = 9.61 (s, 1H, imine), 7.72 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 7.52–7.44 (m, 3H, arom., H-6), 7.37 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 7.28 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 6.90 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 6.85 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 5.14 (s, 2H, –CH_2–), 4.92 (s, 2H, –CH_2–), 3.80 (s, 3H, –CH_3), 3.78 (s, 3H, –CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 160.3, 160.0, 159.3, 159.0, 150.5, 140.3, 136.9, 135.8, 130.8 (2C), 130.0 (2C), 129.5 (2C), 129.0 (2C), 127.1, 122.6, 114.7 (2C), 113.9 (2C), 55.5, 55.4, 52.3, 44.5 ppm.

1,3-Bis(4-methoxybenzyl)-5-(4-bromobenzylideneamino)-pyrimidine-2,4(1H,3H)-dione (**5d**, $C_{27}H_{24}BrN_3O_4$)
^{1}H NMR ($CDCl_3$): δ = 9.61 (s, 1H, imine), 7.65 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 7.53 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 7.50–7.44 (m, 3H, arom., H-6), 7.27 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 6.90 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 6.85 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 5.14 (s, 2H, –CH_2–), 4.92 (s, 2H, –CH_2–), 3.80 (s, 3H, –CH_3), 3.78 (s, 3H, –CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 160.2, 160.0, 159.3, 159.1, 150.5, 140.3, 136.2, 132.0 (2C), 130.7 (2C), 130.0 (2C), 129.8 (2C), 129.0, 127.1, 125.4, 122.5, 114.7 (2C), 113.9 (2C), 55.5, 55.4, 52.3, 44.5 ppm.

1,3-Bis(4-methoxybenzyl)-5-[4-(N,N-dimethylamino)benzylideneamino]pyrimidine-2,4(1H,3H)-dione (**5e**, $C_{29}H_{30}N_4O_4$)
^{1}H NMR ($CDCl_3$): δ = 9.29 (s, 1H, imine), 7.66 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 7.49 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 7.32 (s, 1H, H-6), 7.26 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 6.88 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 6.84 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 6.67 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 5.14 (s, 2H, –CH_2–), 4.88 (s, 2H, –CH_2–), 3.79 (s, 3H, –CH_3), 3.77 (s, 3H, –CH_3), 3.02 (s, 6H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 161.1, 160.6, 159.8, 159.2, 152.4, 150.7, 136.5, 130.7 (2C), 130.1 (2C), 129.9 (2C), 129.3, 127.5, 125.1, 124.5, 114.5 (2C), 113.8 (2C), 111.6 (2C), 55.4, 55.3, 52.1, 44.4, 40.3 (2C) ppm.

General procedure for the synthesis of ***9a–9h***

To a solution of 4-chlorobenzaldoxime (**6a**, 2.2 equiv.) in 4 cm^3 $CHCl_3$, NCS (2.42 equiv.) was added at room temperature while stirring. The reaction mixture changed the color from light yellow via blue to green. Completion of the reaction was indicated when the color of the reaction mixture turned back to yellow. The solution was washed with small amounts of cold water (2 cm^3), dried over anhydrous $MgSO_4$, and immediately used for the next step. To this solution the imine **5a–5d** (1 equiv.) was added followed by addition of triethylamine (1.1 equiv.). The reaction mixture was refluxed for 2–4 h. After that time the next portion of triethylamine was added (1.1 equiv.), and reflux was continued for further 2–4 h. After that time, the solvent was removed under diminished pressure, and the residual oil was purified on a silica gel packed column using AcOEt:*n*-hexane (1:2) as an eluent. The products **9a–9d** were obtained in moderate yields as solid pale-yellow materials crystallized from AcOEt: *n*-hexane.

The same procedure starting from the same equimolar amounts of substrates was applied for preparation of 4-methylbenzonitrile oxide (**8b**). The 1,3-dipolar cycloaddition of **8b** to aldimines **5a–5d** was carried out under conditions described above. The cycloadducts **9e–9h** were obtained in moderate yields as solid pale-yellow materials crystallized from AcOEt: *n*-hexane.

1,3-Bis(4-methoxybenzyl)-5-[3-(4-chlorophenyl)-5-phenyl-1,2,4-oxadiazol-4(5H)-yl]pyrimidine-2,4(1H,3H)-dione (**9a**, $C_{34}H_{29}ClN_4O_5$)
^{1}H NMR ($CDCl_3$): δ = 7.47 (m, 3H, arom.), 7.44–7.31 (m, 4H, arom.), 7.28 (d, 2H, $^3J_{H,H}$ = 8.4 Hz, arom.), 6.99 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 6.83 (d, 2H, $^3J_{H,H}$ = 9.0 Hz, arom.), 6.81–6.71 (m, 5H, arom., H6), 6.34 (s, 1H, oxadiaz.), 5.01 (d, 1H, $^2J_{H,H}$ = 13.8 Hz, –CH_2–), 4.83–4.68 (m, 2H, –CH_2–), 4.48 (d, 1H, $^2J_{H,H}$ = 14.4 Hz, –CH_2–), 3.83 (s, 3H, –CH_3), 3.79 (s, 3H, –CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 160.3, 159.9, 159.3, 156.2, 150.2, 141.8, 137.0, 136.5, 130.2, 130.1 (2C), 129.6 (2C), 129.1 (2C), 129.0 (2C), 128.8 (2C), 128.4, 128.2 (2C), 126.2, 124.1, 114.6 (2C), 113.8 (2C), 113.5, 98.9, 55.5, 55.4, 52.1, 44.2 ppm.

1,3-Bis(4-methoxybenzyl)-5-[3-(4-chlorophenyl)-5-(4-methylphenyl)-1,2,4-oxadiazol-4(5H)-yl]pyrimidine-2,4(1H,3H)-dione (**9b**, $C_{35}H_{31}ClN_4O_5$)
^{1}H NMR ($CDCl_3$): δ = 7.44 (d, 2H, $^3J_{H,H}$ = 8.4 Hz, arom.), 7.35 (d, 2H, $^3J_{H,H}$ = 8.1 Hz, arom.), 7.27 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 7.15 (d, 2H, $^3J_{H,H}$ = 7.8 Hz, arom.), 6.99 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 6.87–6.70 (m, 7H, arom., H6), 6.33 (s, 1H, oxadiaz.), 5.01 (d, 1H, $^2J_{H,H}$ = 13.5 Hz, –CH_2–), 4.76 (d, 1H, $^2J_{H,H}$ = 13.5 Hz, –CH_2–), 4.72 (d, 1H, $^2J_{H,H}$ = 14.7 Hz, –CH_2–), 4.50

(d, 1H, $^2J_{H,H}$ = 14.7 Hz, –C*H*$_2$–), 3.83 (s, 3H, –C*H*$_3$), 3.79 (s, 3H, –C*H*$_3$), 2.39 (s, 3H, –C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$): δ = 160.4, 159.9, 159.2, 156.2, 150.2, 141.7, 140.2, 136.5, 133.9, 130.1 (2C), 129.6 (2C), 129.5 (2C), 129.1 (2C), 129.0 (2C), 128.4, 128.2 (2C), 126.3, 124.2, 114.6 (2C), 113.8 (2C), 113.6, 98.8, 55.4, 55.3, 52.1, 44.2, 21.5 ppm.

5-[3,5-Bis(4-chlorophenyl)-1,2,4-oxadiazol-4(5H)-yl]-1,3-bis(4-methoxybenzyl)pyrimidine-2,4(1H,3H)-dione (**9c**, $C_{34}H_{28}Cl_2N_4O_5$)

^{1}H NMR ($CDCl_3$): δ = 7.41 (*pseudo*-t, 4H, $^3J_{H,H}$ = 8.4 Hz, arom.), 7.33–7.25 (m, 4H, arom.), 7.00 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 6.88–6.79 (m, 4H, arom.), 6.79–6.72 (m, 3H, arom., H6), 6.32 (s, 1H, oxadiaz.), 5.02 (d, 1H, $^2J_{H,H}$ = 13.8 Hz, –C*H*$_2$–), 4.84–4.75 (m, 2H, –C*H*$_2$–), 4.48 (d, 1H, $^2J_{H,H}$ = 14.7 Hz, –C*H*$_2$–), 3.85 (s, 3H, –C*H*$_3$), 3.79 (s, 3H, –C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$): δ = 160.3, 160.0, 159.3, 156.2, 150.2, 141.5, 136.7, 136.1, 135.5, 130.2 (2C), 129.6 (2C), 129.5 (2C), 129.1 (2C), 129.0 (4C), 128.3, 126.1, 123.8, 114.6 (2C), 113.8 (2C), 113.4, 98.1, 55.5, 55.4, 52.0, 44.3 ppm.

1,3-Bis(4-methoxybenzyl)-5-[5-(4-bromophenyl)-3-(4-chlorophenyl)-1,2,4-oxadiazol-4(5H)-yl]pyrimidine-2,4(1H,3H)-dione (**9d**, $C_{34}H_{28}BrClN_4O_5$)

^{1}H NMR ($CDCl_3$): δ = 7.55–7.35 (m, 4H, arom.), 7.35–7.20 (m, 4H, arom.), 7.02 (d, 2H, $^3J_{H,H}$ = 8.4 Hz, arom.), 6.84 (s, 4H, arom.), 6.80–6.72 (m, 3H, arom., H6), 6.31 (s, 1H, oxadiaz.), 5.02 (d, 1H, $^2J_{H,H}$ = 13.5 Hz, –C*H*$_2$–), 4.85–4.71 (m, 2H, –C*H*$_2$–), 4.49 (d, 1H, $^2J_{H,H}$ = 14.4 Hz, –C*H*$_2$–), 3.86 (s, 3H, –C*H*$_3$), 3.79 (s, 3H, –C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$): δ = 160.3, 160.1, 159.3, 156.1, 150.2, 141.6, 136.7, 136.0, 132.0 (2C), 130.2 (2C), 129.8 (2C), 129.6 (2C), 129.1 (4C), 128.3, 126.2, 124.4, 123.8, 114.7 (2C), 113.9 (2C), 113.4, 98.1, 55.5, 55.4, 52.1, 44.3 ppm.

1,3-Bis(4-methoxybenzyl)-5-[3-(4-methylphenyl)-5-phenyl-1,2,4-oxadiazol-4(5H)-yl]pyrimidine-2,4(1H,3H)-dione (**9e**, $C_{35}H_{32}N_4O_5$)

^{1}H NMR ($CDCl_3$): δ = 7.51–7.45 (m, 2H, arom.), 7.44–7.30 (m, 5H, arom.), 7.11 (d, 2H, $^3J_{H,H}$ = 7.8 Hz, arom.), 7.06 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 6.83 (d, 2H, $^3J_{H,H}$ = 8.7 Hz, arom.), 6.79–6.68 (m, 5H, arom., H6), 6.40 (s, 1H, oxadiaz.), 5.00 (d, 1H, $^2J_{H,H}$ = 13.5 Hz, –C*H*$_2$–), 4.82 (d, 1H, $^2J_{H,H}$ = 13.5 Hz, –C*H*$_2$–), 4.69 (d, 1H, $^2J_{H,H}$ = 14.7 Hz, –C*H*$_2$–) 4.49 (d, 1H, $^2J_{H,H}$ = 14.7 Hz, –C*H*$_2$–), 3.82 (s, 3H, –C*H*$_3$), 3.78 (s, 3H, –C*H*$_3$), 2.38 (s, 3H, –C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$): δ = 160.4, 159.8, 159.2, 156.2, 150.4, 141.7, 140.7, 137.3, 130.3 (2C), 130.0, 129.5 (2C), 129.4 (2C), 128.7 (2C), 128.6, 128.1 (2C), 127.8 (2C), 126.4, 122.4, 114.5 (2C), 114.0, 113.8 (2C), 98.3, 55.4, 55.3, 52.1, 44.2, 21.7 ppm.

1,3-Bis(4-methoxybenzyl)-5-[3,5-bis(4-methylphenyl)-1,2,4-oxadiazol-4(5H)-yl]pyrimidine-2,4(1H,3H)-dione (**9f**, $C_{36}H_{34}N_4O_5$)

^{1}H NMR ($CDCl_3$): δ = 7.42–7.32 (m, 4H, arom.), 7.17–7.02 (m, 6H, arom.), 6.87–6.68 (m, 7H, arom., H6), 6.39 (s, 1H, oxadiaz.), 4.99 (d, 1H, $^2J_{H,H}$ = 13.5 Hz, –C*H*$_2$–), 4.82 (d, 1H, $^2J_{H,H}$ = 13.5 Hz, –C*H*$_2$–), 4.68 (d, 1H, $^2J_{H,H}$ = 14.7 Hz, –C*H*$_2$–), 4.51 (d, 1H, $^2J_{H,H}$ = 14.7 Hz, –C*H*$_2$–), 3.82 (s, 3H, –C*H*$_3$), 3.78 (s, 3H, –C*H*$_3$), 2.38 (s, 6H, –C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$): δ = 160.5, 159.8, 159.1, 156.7, 150.4, 141.7, 140.6, 139.9, 134.2, 130.2 (2C), 129.5 (2C), 129.4 (2C), 129.3 (2C), 128.6, 128.1 (2C), 127.8 (2C), 126.5, 122.5, 114.5 (2C), 114.1, 113.7 (2C), 98.3, 55.4, 55.3, 52.1, 44.2, 21.7, 21.5 ppm.

1,3-Bis(4-methoxybenzyl)-5-[5-(4-chlorophenyl)-3-(4-methylphenyl)-1,2,4-oxadiazol-4(5H)-yl]pyrimidine-2,4(1H,3H)-dione (**9g**, $C_{35}H_{31}ClN_4O_5$)

^{1}H NMR ($CDCl_3$): δ = 7.44–7.34 (m, 4H, arom.), 7.33–7.24 (m, 2H, arom.), 7.16–7.02 (m, 4H, arom.), 6.89–6.69 (m, 7H, arom., H6), 6.38 (s, 1H, oxadiaz.), 5.01 (d, 1H, $^2J_{H,H}$ = 13.8 Hz, –C*H*$_2$–), 4.83 (d, 1H, $^2J_{H,H}$ = 13.8 Hz, –C*H*$_2$–), 4.75 (d, 1H, $^2J_{H,H}$ = 14.4 Hz, –C*H*$_2$–), 4.50 (d, 1H, $^2J_{H,H}$ = 14.4 Hz, –C*H*$_2$–), 3.84 (s, 3H, –C*H*$_3$), 3.78 (s, 3H, –C*H*$_3$), 2.38 (s, 3H, –C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$): δ = 160.4, 159.9, 159.2, 156.7, 150.4, 141.4, 140.9, 135.8, 130.3 (2C), 129.5 (2C), 129.4 (4C), 129.0 (2C), 128.5, 127.8 (2C), 126.3, 122.1, 114.6 (2C), 113.9, 113.8 (2C), 97.5, 55.5, 55.3, 52.0, 44.3, 21.7 ppm.

1,3-Bis(4-methoxybenzyl)-5-[5-(4-bromophenyl)-3-(4-methylphenyl)-1,2,4-oxadiazol-4(5H)-yl]pyrimidine-2,4(1H,3H)-dione (**9h**, $C_{35}H_{31}BrN_4O_5$)

^{1}H NMR ($CDCl_3$): δ = 7.45 (d, 2H, $^3J_{H,H}$ = 8.4 Hz, arom.), 7.36 (*pseudo*-t, 4H, $^3J_{H,H}$ = 7.8 Hz, arom.), 7.14–7.02 (*pseudo*-t, 4H, arom.), 6.88–6.78 (m, 4H, arom.), 6.77–6.71 (m, 3H, arom., H6), 6.37 (s, 1H, oxadiaz.), 5.00 (d, 1H, $^2J_{H,H}$ = 13.5 Hz, –C*H*$_2$–), 4.83 (d, 1H, $^2J_{H,H}$ = 13.5 Hz, –C*H*$_2$–), 4.74 (d, 1H, $^2J_{H,H}$ = 14.4 Hz, –C*H*$_2$–), 4.50 (d, 1H, $^2J_{H,H}$ = 14.4 Hz, –C*H*$_2$–), 3.84 (s, 3H, –C*H*$_3$), 3.78 (s, 3H, –C*H*$_3$), 2.38 (s, 3H, –C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$): δ = 160.4, 159.9, 159.2, 156.7, 150.4, 141.4, 141.0, 136.4, 131.9 (2C), 130.3 (2C), 129.7 (2C), 129.6 (2C), 129.5 (2C), 128.5, 127.8 (2C), 126.3, 124.2, 122.0, 114.6 (2C), 113.9, 113.8 (2C), 97.6, 55.5, 55.4, 52.1, 44.3, 21.7 ppm.

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