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Condensation of 2-(4-chlorophenyl)-1-(2,4-dihydroxyphenyl)ethanone with *N*,*N*-dimethylformamide dimethyl acetal: an effective approach to 3-(4-chlorophenyl)-7-methoxy-4*H*-chromen-4-one, N,O- and N,N-heterocycles

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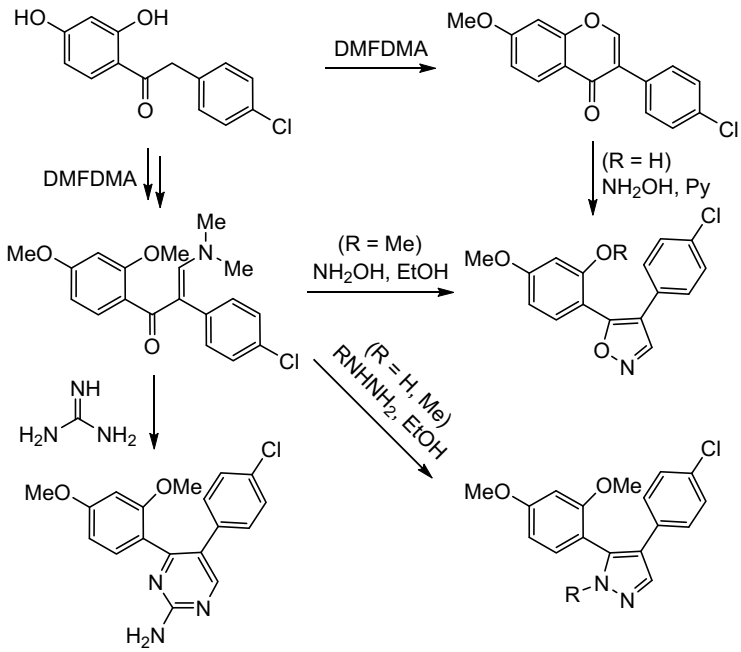


A convenient sequence for the preparation of 2-(4-chlorophenyl)-1-(2,4-dimetoxyphenyl)-3-(dimethylamino)prop-2-en-1-one has been developed. It has been demonstrated that the use of 1-(2,4-dihydroxyphenyl)ethanone or 1-(2-hydroxy-4-methoxyphenyl)ethanone in a condensation reaction with *N*,*N*-dimethylformamide dimethyl acetal leads to their heterocyclization to give an isoflavone. Reactions of the enamino ketone with *N*,*O*- and *N*,*N*-binucleophiles have been studied; as the result, 4,5-diarylisoxazole, 4,5-diarylpyrazoles, and 4,5-diaryl-substituted 2-aminopyrimidine have been obtained in good yields.

Keywords: deoxybenzoin, *N*,*N*-dimethylformamide dimethyl acetal, enamino ketone, 2-hydroxydeoxybenzoin, isoflavone, heterocyclization.

Derivatives of 1,2-diphenylethanone (deoxybenzoin or 2-phenylacetophenone) are widely used in condensation reactions to synthesize various heterocyclic compounds. Moreover, 2-hydroxydeoxybenzoins are often considered as precursors to isoflavones and, given their availability and synthetic potential, are frequently used in flavonoid synthesis.[1]

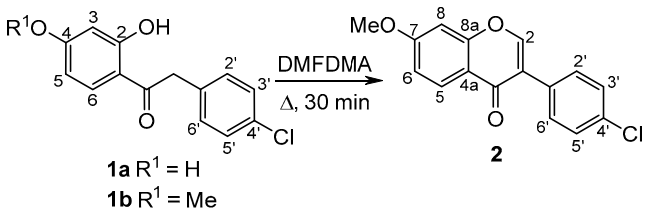
It is known that enamino ketones can be used for the preparation of substituted isoxazoles, pyrazoles, and pyrimidines.[2,3] In each case, the cyclization reaction proceeds *via* C–C–C + N–O, C–C–C + N–N, C–C–C + N–C–N ring formation to yield the corresponding heterocycle. The ring formation may proceed *via* two possible mechanisms differing in the order of their key steps, namely, nucleophilic attack and amine exchange reaction, which give two regioisomeric products.

In the context of our ongoing interest in the synthetic potential of enamino ketones, we set out to explore the use

of 1,2-diphenylethanones as key intermediates in the synthesis of 2-(4-chlorophenyl)-1-(2,4-dimethoxyphenyl)-3-(dimethylamino)prop-2-en-1-one.

We discovered that, unexpectedly, the reaction of 2-(4-chlorophenyl)-1-(2,4-dihydroxyphenyl)ethanone (**1a**) with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA, 3 equiv) results only in the formation of 3-(4-chlorophenyl)-7-methoxy-4*H*-chromen-4-one (**2**) in a 75% yield. When 2-(4-chlorophenyl)-1-(2-hydroxy-4-methoxyphenyl)ethanone (**1b**) was used, isoflavone **2** was obtained in a 92% yield (Scheme 1). It must be noted that the use of equimolar reagent quantities also resulted in compound **2**, but with lower yields (52%). It was reported previously that the use of DMFDMA in reactions with deoxybenzoin leads to hydroxyisoflavones, but under different conditions, i.e., refluxing in benzene for 4 h with reagent molar ratio 1 : 0.2.[4] In our case (reflux for 20–30 min, reagent ratio 1 : 1–3 equiv), the heterocyclization was accompanied by methylation of the hydroxyl group to give 7-methoxyisoflavone **2**. Thus, this synthetic method can be successfully used for an efficient one-step synthesis of 3-aryl-7-methoxy-4*H*-chromen-4-ones.

Scheme 1



We assume that the chroman-4-one system is formed as a result of *C*-formylation of the methylene group followed by cyclization. The hydroxyl group methylation occurs due to the presence of a strong base MeO^- formed *in situ* during the reaction, which is consistent with literature data.[5]

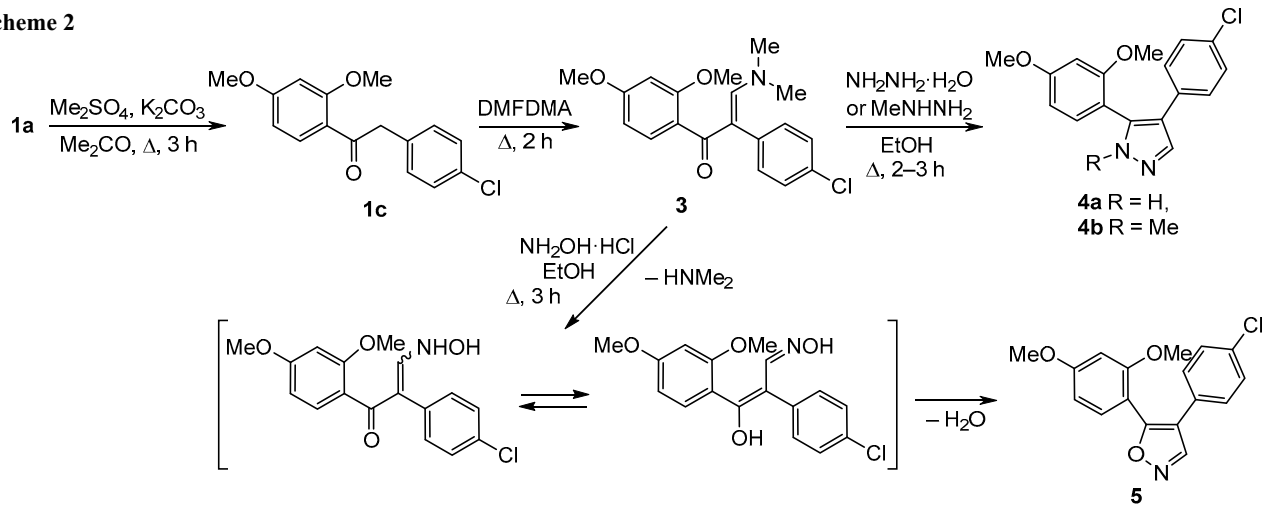
2-(4-Chlorophenyl)-1-(2,4-dimetoxyphenyl)ethanone (**1c**) is the most convenient precursor to the desired enamino ketone **3**, as it eliminates the possibility of cyclization to isoflavone. We obtained compound **1c** by a complete methylation of 2-(4-chlorophenyl)-1-(2,4-dihydroxyphenyl)-ethanone (**1a**) with dimethyl sulfate in acetone in the presence of K_2CO_3 in a 91% yield. Subsequent reaction of compound **1c** with DMFDMA gave 2-(4-chlorophenyl)-1-(2,4-dimethoxyphenyl)-3-(dimethylamino)prop-2-en-1-one (**3**) in 94% yield (Scheme 2). Previously, DMFDMA has been used to obtain enamino ketones with *o*-OSO_2Ph group (yields up to 58%)[6] and *o*-OBn group (yield 70%).[7]

To introduce pharmacologically significant heterocyclic moieties of pyrazole, aminopyrimidine, and isoxazole, we then used the enamino ketone **3** in the cyclization reactions with N,N- and N,O-binucleophiles – hydrazine, *N*-methylhydrazine, guanidine, and hydroxylamine. Heating compound **3** with a small excess (1.2 equiv) of $NH_2NH_2 \cdot H_2O$, *N*-methylhydrazine, or $NH_2OH \cdot HCl$ in an ethanol solution gave the corresponding pyrazoles **4a**,**b** and isoxazole **5**, respectively, in high yields (Scheme 2). Initially, the dimethylamino group of compound **3** is substituted *via* addition–elimination.[8] The subsequent cyclization leads to the corresponding target 4,5-diaryl-pyrazoles and 4,5-diarylisoxazole.

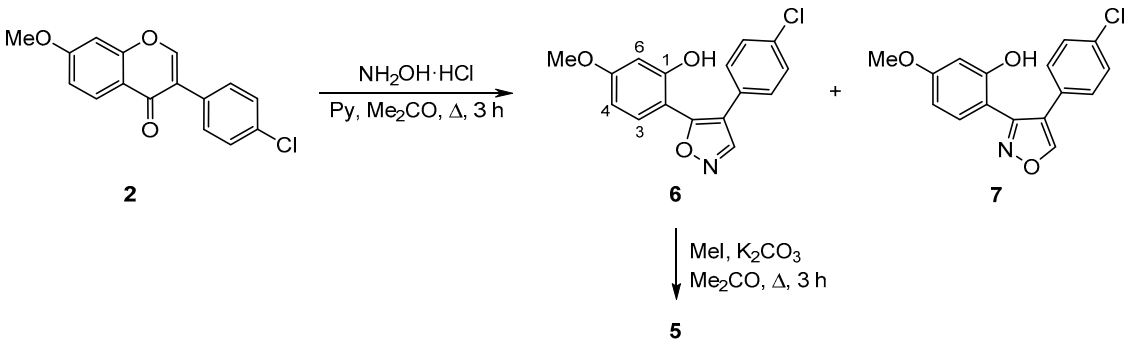
It should be noted that similar 4,5-diaryl-substituted pyrazoles and isoxazoles have been previously obtained *via* isoflavone recyclization reactions under the action of hydrazines and NH_2OH, resulting usually in mixtures of regioisomeric products, i.e., pyrazoles and isoxazoles, and corresponding 2-aminochromones and 5-aminoisoxazoles.[9,10] In our case, the only products were compounds **4** and **5**, as is evidenced by NMR data. For example, the signals of pyrazole protons in the ^1H NMR spectra of compounds **4a**,**b** are located at 7.63 and 7.66 ppm, respectively, fully in accordance with the literature data.[9] The peak of the isoxazole proton of compound **5** is observed at 8.78 ppm, which confirms the formation of the said product, since for its regioisomer the corresponding signal would have been observed in the weaker field region (9.4–9.8 ppm).[10]

To confirm the structure of compound **5**, we have carried out the counter synthesis starting with 7-methoxy-isoflavone **2**. The reaction of compound **2** with $NH_2OH \cdot HCl$ in pyridine proceeded as a nucleophilic attack of NH_2OH at C-2 and C-4 atoms with opening of the pyran-4-one ring and resulted in a mixture of 4,5-diarylisoxazole **6** as the

Scheme 2



Scheme 3



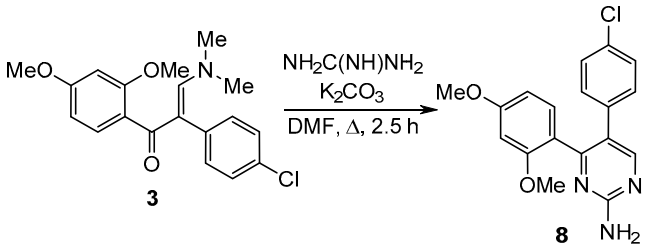
major product and trace amounts of 3,4-diarylisoxazole **7**, which were separated by crystallization (Scheme 3). The ^{1}H NMR signal of the isoxazole proton of compound **6** is located at 8.78 ppm, which corresponds to a similar signal of compound **5**; the OH signal is observed at 9.87 ppm and disappears when D_2O is added. The chemical shift of the phenol OH group in the ^{1}H NMR spectrum measured in $CDCl_3$ can be used to reliably distinguish isoxazole regioisomers (**6** and **7**).[10] The H atom of the hydroxyl group in the regioisomer **7** forms an intramolecular hydrogen bond of chelate type with the isoxazole ring N atom and is expected to resonate at 9.0–9.6 ppm. Conversely, the analogous H atom of OH group in regioisomer **6** cannot form such a hydrogen bond and is expected to appear at a higher field (6.5–7.0 ppm). The OH group signal of compound **6** is observed at 6.44 ppm and disappears when D_2O is added, confirming the formation of the particular regioisomer.

As an additional proof, an alkylation reaction of 2-[4-(4-chlorophenyl)isoxazol-5-yl]-5-methoxyphenol (**6**) was carried out. Treatment of compound **6** with MeI in acetone with K_2CO_3 as a base resulted in the formation of compound **5** in a 84% yield; all physicochemical properties of compound **5** obtained by two different pathways were identical.

We have demonstrated in our previous work[8] that reaction of enamino ketones with guanidine carbonate proceeds smoothly when refluxing the reaction mixture in DMF with K_2CO_3 as a base. Reaction of compound **3** with guanidine carbonate under the described conditions (DMF/K_2CO_3) was complete in 2.5 h, giving the 4,5-diaryl-substituted 2-aminopyrimidine **8** in 97% yield (Scheme 4).

The present work shows that 2-methoxydeoxybenzoins are the optimal parent compounds for the synthesis of enamino ketones from deoxybenzoins; it was discovered that the reaction of DMFDMA with 2-hydroxydeoxybenzoins gives 3-aryl-7-methoxychromones with high yields. Introducing 2-aryl-1-(2,4-dimethoxyphenyl)-3-(dimethylamino)prop-2-en-1-one into heterocyclization reaction with 1,2-N,N-, 1,2-N,O-, and 1,3-N,N-binucleophiles gave new pyrazole, isoxazole, and pyrimidine derivatives, respectively. In comparison to a classic method, isoflavone recyclization, the described approach gives higher yields of products and higher regioselectivity.

Scheme 4



Experimental

^{1}H and ^{13}C, as well as ^{1}H–^{13}C HSQC NMR spectra were recorded on a Mercury-400 spectrometer (400 and 100 MHz, respectively). The TMS signal was used as an internal standard. Mass spectra were recorded on an Agilent 1100 LC/MSD instrument using atmospheric pressure chemical ionization. Elemental analyses were performed using a Perkin-Elmer CHN Analyzer. Melting points were determined using a Kofler type Leica Galen III micro hot stage microscope. All solvents used were purified and dried by standard procedures. Reaction progress and identity of obtained compounds were monitored by TLC on Merck 60 F_{254} silica gel plates using CH_2Cl_2–MeOH mixtures as eluents.

2-(4-Chlorophenyl)-1-(2,4-dihydroxyphenyl)ethanone (**1a**) was prepared as described previously.[11]

2-(4-Chlorophenyl)-1-(2-hydroxy-4-methoxyphenyl)-ethanone (**1b**). Dry K_2CO_3 (2.76 g, 0.02 mol) was added to a mixture of compound **1a** (2.62 g, 0.01 mol) and dimethyl sulfate (1.04 ml, 0.011 mol) in anhydrous acetone (20 ml) at room temperature. The mixture was heated to reflux for 2 h, and the progress was monitored by TLC (visualization with $FeCl_3$). The solution was cooled, treated with water (100 ml), and acidified with 36% HCl to pH 5–6. The precipitate was filtered off, washed with cold water, and recrystallized from MeOH. Yield 2.58 g (94%), mp 85–86°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.83 (3H, s, OCH_3); 4.28 (2H, s, $COCH_2$); 6.4 (1H, s, H-3); 6.46 (1H, d, *J* = 9.2, H-5); 7.27 (4H, s, H-2',3',5',6'); 7.91 (1H, d, *J* = 9.21, H-6); 12.47 (1H, s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 44.9 ($CO\underline{C}H_2$); 56.2 (OCH_3); 103.1 (C-3); 107.8 (C-5); 113.4 (C-1); 128.6 (C-3',5' Ar); 129.8 (C-2',6'); 131.4 (C-1'); 131.9 (C-6); 133.6 (C-4'); 165.1 (C-2); 166.8 (C-4); 203.7 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 277 $[M+H]^+$ (100). Found, %: C 64.94; H 4.52. $C_{15}H_{13}ClO_3$. Calculated, %: C 65.11; H 4.74.

2-(4-Chlorophenyl)-1-(2,4-dimethoxyphenyl)ethanone (**1c**). Dry K_2CO_3 (4.14 g, 0.03 mol) was added to a mixture

of compound **1a** (2.62 g, 0.01 mol) and dimethyl sulfate (2.37 ml, 0.025 mol) in anhydrous acetone (20 ml) at room temperature. The mixture was heated to reflux for 3 h, and the progress was monitored by TLC. The solution was cooled, treated with water (100 ml), and acidified with 36% HCl to pH 5–6. The precipitate was filtered off, washed with cold water, and recrystallized from MeOH. Yield 2.64 g (91%), mp 70–71°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.84 (3H, s, 4-OCH_3); 3.92 (3H, s, 2-OCH_3); 4.18 (2H, s, $COCH_2$); 6.52 (1H, d, *J*= 9.2, H-5); 6.55 (1H, s, H-3); 7.15 (2H, d, *J*= 8.8, H-3',5'); 7.25 (2H, d, *J* = 8.8, H-2',6'); 7.63 (1H, d, *J*= 9.2, H-6). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 44.3 ($CO\underline{C}H_2$); 55.9 (2,4-OCH_3); 97.6 (C-3); 106.4 (C-5); 113.7 (C-1); 128.4 (C-3',5'); 129.7 (C-2',6'); 131.2 (C-1'); 132.3 (C-6); 133.9 (C-4'); 162.4 (C-2); 166.8 (C-4); 202.4 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 291 $[M+H]^+$ (100). Found, %: C 65.93; H 5.04. $C_{16}H_{15}ClO_3$. Calculated, %: C 66.10; H 5.20.

3-(4-Chlorophenyl)-7-methoxy-4*H*-chromen-4-one (**2**). A mixture of compound **1a** (2.62 g, 0.01 mol) or **1b** (2.76 g, 0.01 mol) and DMFDMA (2.65 ml, 0.02 mol) was stirred for 30 min under reflux. After completion of the reaction, the mixture was cooled to room temperature. The solvent was evaporated, and the residue was recrystallized from MeOH. Yield 1.94 g (75%) if obtained from compound **1a**; 2.62 g (92%) if obtained from compound **1b**, mp 197–198°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.92 (3H, s, OCH_3); 7.00 (1H, d, *J*= 7.6, H-6); 7.02 (1H, s, H-8); 7.40 (2H, d, *J* = 8.4, H-2',6'); 7.60 (2H, d, *J* = 8.4, H-3',5'); 8.04 (1H, d, *J* = 7.6, H-5); 8.31 (1H, s, H-2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 55.6 (OCH_3); 100.4 (C-8); 114.6 (C-6); 118.3 (C-4a); 122.9 (C-3); 127.9 (C-5); 128.5 (C-1'); 129.32 (C-3',5'); 130.4 (C-2',6'); 134.8 (C-4'); 153.7 (C-2); 158.8 (C-8a); 166.9 (C-7); 178.4 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 287 $[M+H]^+$ (100). Found, %: C 66.87; H 3.65. $C_{16}H_{11}ClO_3$. Calculated, %: C 67.03; H 3.87.

2-(4-Chlorophenyl)-1-(2,4-dimethoxyphenyl)-3-(dimethylamino)prop-2-en-1-one (**3**). A mixture of compound **1c** (2.9 g, 0.01 mol) and DMFDMA (2.65 ml, 0.02 mol) was stirred for 2 h under reflux. After completion of the reaction, the mixture was cooled to room temperature. The solvent was evaporated, and the residue was recrystallized from EtOH. Yield 3.26 g (94%), mp 141–142°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.71 (6H, s, $N(CH_3)_2$); 3.70 (3H, s, 4-OCH_3); 3.80 (3H, s, 2-OCH_3); 6.43 (1H, s, H-3); 6.46 (1H, d, *J*= 7.6, H-5); 7.01 (1H, d, *J* = 7.6, H-6); 7.07 (2H, d, *J* = 8.4, H-2',6'); 7.1 (1H, s, $C\underline{H}N(CH_3)_2$); 7.23 (2H, d, *J* = 8.4, H-3',5'). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 46.6 ($N(CH_3)_2$); 55.4 (2,4-OCH_3); 102.3 (C-3); 111.9 ($\underline{C}$=$CHN(CH_3)_2$); 112.6 (C-6); 119.4 (C-1); 128.2 (C-6); 128.6 (C-3',5'); 130.1 (2C); 133.4; 136.7; 154.5; 162.7; 168.2; 196.4. Mass spectrum, *m*/*z* (I_{rel}, %): 346 $[M+H]^+$ (100). Found, %: C 65.78; H 5.64; N 3.92. $C_{19}H_{20}ClNO_3$. Calculated, %: C 65.99; H 5.83; N 4.05.

Synthesis of 4-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-1*H*-pyrazole (**4a**) **and 4-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-1-methyl-1*H*-pyrazole** (**4b**) (General method). Hydrazine hydrate (0.06 ml, 0.0012 mol) or methylhydrazine (0.05 ml, 0.0012 mol) was added to a mixture of compound **3** (0.34 g, 0.001 mol) in anhydrous EtOH (10 ml). The solution was refluxed with stirring for 2–3 h. After completion of the reaction, the mixture was cooled to room temperature. The solvent was evaporated, and the residue was recrystallized from EtOH.

4-(4-Chlorophenyl)-5-(2,4-dimethoxyphenyl)-1*H*-pyrazole (**4a**). Yield 0.29 g (93%), mp 145–146°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.82 (6H, s, 2,4-OCH_3); 6.56 (1H, d, *J*= 7.6, H-5); 6.57 (1H, s, H-3); 7.10 (2H, d, *J*= 8.4, H-3',5'); 7.12 (2H, d, *J*= 8.4, H-2',6'); 7.18 (1H, d, *J*= 7.6, H-6); 7.63 (1H, s, CH pyrazole); 12.77 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 56.4 (2,4-OCH_3); 98.6 (C-3); 107.4 (C-5); 112.4 (C-1); 118.2 (C pyrazole); 128.6 (C-3',5'); 129.4 (C-2',6'); 133.6 (C-6); 132.8 (CH pyrazole); 133.2 (C-1'); 134.3 (C-4'); 143.6 (C pyrazole); 158.7 (C-2); 161.9 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 315 $[M+H]^+$ (100). Found, %: C 64.63; H 4.62; N 8.74. $C_{17}H_{15}ClN_2O_2$. Calculated, %: C 64.87; H 4.80; N 8.90.

4-(4-Chlorophenyl)-5-(2,4-dimethoxyphenyl)-1-methyl-1*H*-pyrazole (**4b**). Yield 0.28 g (87%), mp 149–150°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.78 (6H, s, 2,4-OCH_3); 3.91 (3H, s, CH_3N); 6.54 (1H, d, *J*= 7.6, H-5); 6.59 (1H, s, H-3); 7.12 (2H, d, *J*= 8.4, H-3',5'); 7.16 (2H, d, *J*= 8.4, H-2',6'); 7.21 (1H, d, *J*= 7.6, H-6); 7.66 (1H, s, CH pyrazole). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 38.9 (NCH_3); 55.8 (2,4-OCH_3); 98.4 (C-3); 107.2 (C-5); 111.8 (C-1); 119.6 (C pyrazole); 128.8 (C-3',5'); 129.6 (C-2',6'); 132.3 (C-6); 133.9 (C-4'); 134.5 (C-1'); 137.1 (CH pyrazole); 139.4 (C pyrazole), 158.6 (C-2); 161.4 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 329 $[M+H]^+$ (100). Found, %: C 65.59; H 5.03; N 8.24. $C_{18}H_{17}ClN_2O_2$. Calculated: C 65.75; H 5.21; N 8.52.

4-(4-Chlorophenyl)-5-(2,4-dimethoxyphenyl)isoxazole (5). I. Hydroxylamine hydrochloride (0.08 g, 0.0012 mol) was added to a mixture of compound **3** (0.34 g, 0.0010 mol) in anhydrous EtOH (10 ml), and the solution was refluxed with stirring for 3 h. After completion of the reaction, the mixture was cooled to room temperature. The solvent was evaporated, and the residue was recrystallized from EtOH. Yield 0.28 g (90%), mp 77–78°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.54 (3H, s, 2-OCH_3); 3.86 (3H, s, 4-OCH_3); 6.61 (1H, d, *J*= 7.6, H-5); 6.63 (1H, s, H-3); 7.30 (4H, s, H-2',3',5',6'); 7.34 (1H, d, *J*= 7.6, H-6); 8.78 (1H, s, CH isoxazole). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 55.6 (4-OCH_3); 56.8 (2-OCH_3); 98.7 (C-3); 100.4 (C isoxazole); 106.6 (C-1); 107.3 (C-5); 127.1 (C-6); 128.6 (C-2',6' Ar); 129.4 (C-3',5' Ar); 134.4 (C-4' Ar); 135.1 (C-1'); 152.4 (CH isoxazole); 158.2 (C isoxazole); 159.4 (C-2); 161.7 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 316 $[M+H]^+$ (100). Found, %: C 64.44; H 4.21; N 4.19. $C_{17}H_{14}ClNO_3$. Calculated, %: C 64.67; H 4.47; N 4.44.

II. Dry K_2CO_3 (0.83 g, 0.006 mol) was added to a mixture of compound **6** (1.00 g, 0.0033 mol) and methyl iodide (0.23 ml, 0.0036 mol) in anhydrous acetone (5 ml) at room temperature. The mixture was heated to reflux for

3 h, and the progress of the reaction was monitored by TLC (visualization with $FeCl_3$). The solution was cooled, diluted with water (100 ml), and acidified with 36% HCl to pH 5–6. The precipitate was filtered off, washed with cold water, and recrystallized from *i*-PrOH. Yield 0.98 g (84%).

2-[4-(4-Chlorophenyl)isoxazol-5-yl]-5-methoxyphenol (**6**). Hydroxylamine hydrochloride (0.15 g, 0.0021 mol) was added to a solution of compound **2** (0.20 g, 0.0007 mol) in anhydrous pyridine (5 ml), and the solution was refluxed with stirring for 3 h. Progress of the reaction was monitored by TLC (CH_2Cl_2–MeOH, 7:3). Two spots were observed with different R_f values: the spot with R_f 0.08 did not give a dark-green color with an alcoholic solution of $FeCl_3$, the spot with R_f 0.39 gave a dark-green color with an alcoholic solution of $FeCl_3$. After completion of the reaction, the reaction mixture was poured into water (100 ml), and the precipitate containing product **6** and trace amounts of compound **7** was filtered and crystallized from MeOH. Yield of product **6** 0.17 g (81%), mp 165–167°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.78 (3H, s, 5-OCH_3); 6.46 (1H, d, *J* = 7.6, H-4); 6.48 (1H, s, H-6); 7.20 (1H, d, *J* = 7.6, H-3); 7.28 (2H, d, *J* = 8.2, H-3',5'); 7.35 (2H, d, *J* = 8.2, H-2',6'), 8.78 (1H, s, CH isoxazole); 9.87 (1H, s, OH). ^{1}H NMR spectrum (DMSO-d_6 + D_2O), δ, ppm (*J*, Hz): 3.78 (3H, s, 5-OCH_3); 6.46 (1H, d, *J* = 7.6, H-4); 6.48 (1H, s, H-6); 7.20 (1H, d, *J* = 7.6, H-3); 7.28 (2H, d, *J* = 8.2, H-3',5'); 7.35 (2H, d, *J* = 8.2, H-2',6'), 8.78 (1H, s, CH isoxazole). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.75 (3H, s, 5-OCH_3); 6.38 (1H, d, *J* = 7.6, H-4); 6.44 (1H, s, 1-OH); 6.49 (1H, s, H-6); 7.10 (1H, d, *J* = 7.6, H-3); 7.22 (2H, d, *J* = 8.4, H-2',6'); 7.29 (2H, d, *J* = 8.4, H-3',5'); 8.34 (1H, s, CH isoxazole). ^{1}H NMR spectrum ($CDCl_3$+D_2O), δ, ppm (*J*, Hz): 3.75 (3H, s, 5-OCH_3); 6.38 (1H, d, *J* = 7.6, H-4); 6.49 (1H, s, H-6); 7.10 (1H, d, *J* = 7.6, H-3); 7.22 (2H, d, *J* = 8.4, H-2',6'); 7.29 (2H, d, *J* = 8.4, H-3',5'); 8.34 (1H, s, CH isoxazole). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 55.9 (OCH_3); 100.6 (C isoxazole); 104.4 (C-6); 107.6 (C-4); 108.5 (C-2); 127.3 (C-3); 128.7 (C-2',6'); 129.6 (C-3',5'); 134.2 (C-4'); 134.9 (C-1'); 152.6 (CH isoxazole); 154.8 (C-1); 159.1 (C isoxazole); 163.4 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 302 $[M+H]^+$ (100). Found, %: C 63.43; H 3.92; N 4.36. $C_{16}H_{12}ClNO_3$. Calculated, %: C 63.69; H 4.01; N 4.64.

5-(4-Chlorophenyl)-4-(2,4-dimethoxyphenyl)pyrimidin-2-amine (**8**). Dry K_2CO_3 (0.14 g, 0.001 mol) was added to a mixture of compound **3** (0.34 g, 0.001 mol) and guanidinium carbonate (0.22 g, 0.0012 mol) in anhydrous DMF (10 ml) at room temperature. The mixture was heated to reflux for 2.5 h, and the progress was monitored by TLC. The solution was cooled, diluted with cold water (50 ml), and acidified with 36% HCl to pH 5–6. The precipitate was filtered off, washed with cold water, and recrystallized from MeOH. Yield 0.32 g (97%), mp 140–141°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.28 (3H, s, 2-OCH_3); 3.82 (3H, s, 4-OCH_3); 6.38 (1H, s, H-3); 6.61 (1H, d, *J* = 8.4, H-5); 7.09 (2H, d, *J* = 7.2, H-3',5'); 7.27 (2H, d, *J* = 7.2, H-2',6'); 7.39 (1H, d, *J* = 8.4, H-6); 8.53 (1H, s, CH pyrimidine); 8.55 (2H, br. s, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 55.6 (4-OCH_3); 56.2 (2-OCH_3); 99.3 (C-3); 107.4 (C-5); 117.6 (C-1); 122.3 (C pyrimidine); 128.8 (C-2',6'); 129.4 (C-3',5'); 132.4 (C-6); 134.6 (C-4'); 135.1 (C-1'); 149.6 (CH pyrimidine); 158.6 (C-2); 159.4 (C pyrimidine); 161.8 (C-4); 163.3 (C pyrimidine). Mass spectrum, *m*/*z* (I_{rel}, %): 342 $[M+H]^+$ (100). Found, %: C 63.04; H 4.51; N 12.06. $C_{18}H_{16}ClN_3O_2$. Calculated, %: C 63.25; H 4.72; N 12.29.

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