An Efficient One-Pot Synthesis of Diarylpyrazolo [1,5-*a*]pyrimidine from Isoflavones

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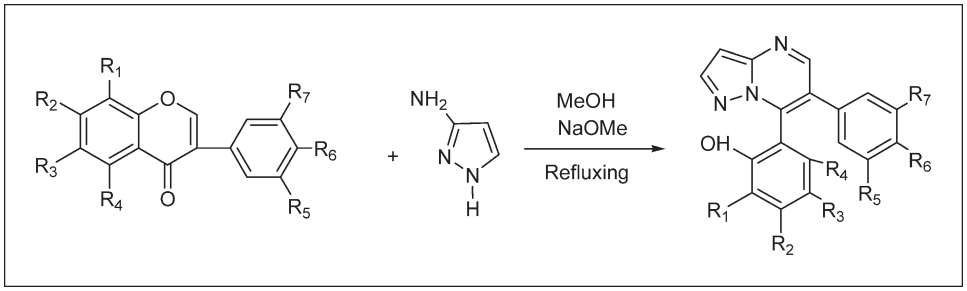

Direct synthetic methods of 6,7-diphenylpyrazolo[1,5-*a*]pyrimidine derivatives have been developed. Cyclocondensation of isoflavones with 3-aminopyrazole in the presence of sodium methoxide as alkali promoter gave 6,7-diphenylpyrazolo[1,5-*a*]pyrimidines in moderate to good yields.

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INTRODUCTION

Pyrazolo[1,5-*a*]pyrimidine, although virtually unknown as natural products, are an important pharmaceutical targets (Scheme 1) [1]. They and related fused heterocycles are of interest as potential bioactive molecules. Pyrazolo[1,5-*a*]pyrimidines exhibited biological activities, such as cSRC kinase inhibitors involved with ischemic brain pathology [2], cyclin dependent kinase 1 inhibitor [3], HIV reverse transcriptase inhibitors [4], CCR1 antagonists [5], protein kinase inhibitors [6], cGMP degradation inhibitors, or herbicidal and fungicidal activities [7].

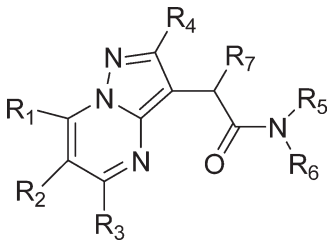
Numerous methods for the synthesis of pyrazolo[1,5-*a*]pyrimidine have been reported in the last 20 years, which involved the reaction between aminopyrazoles and 1,3-bise-lectrophilic compounds, such as β-dicarbonyl, alkoxymethylene-β-dicarbonyl [8], and β-enaminone compounds [9]. It was reported that the chromone fragment present in isoflavones can generate a 1,3-diketone equivalent which readily react with amidines [10], guanidine [11], sulfocarbamides [12], and hydrazine [13] to form the corresponding 2-substituted pyrimidines and diarylpyrazoles. Recently, we have reported the high-throughput synthesis of 3,4-diarylpyrazoles, 4,5-biphenyl-2-pyrimidinylguanidine and 2, 3-diarylpyrimido[1,2-*a*] benzimidazole by using one-step reaction of hydrazine [14], biguanidine [15], and 2-aminobenzimidazole [16] with isoflavones respectively. Herein, we report a new strategy for the preparation of the unknown class of 6,7-diphenylpyrazolo [1,5-*a*]pyrimidines from isoflavones.

RESULTS AND DISCUSSION

We designed the cyclocondensation of isoflavone **1**, which can generate a 1,3-dicarbonal equivalent in the presence of alkali, with 3-aminopyrazoles **2** to synthesize 6,7-diphenylpyrazolo[1,5-*a*]pyrimidines **3** (Scheme 2). Thus, treatment of ipriflavone (7-isopropoxyisoflavone) **1a** with 3-aminopyrazole **2** (1.1 equiv) in refluxed ethanol in the presence of sodium hydroxide (3 equiv) for 12 h afforded 6-phenyl-7-(2-hydroxy-4-isopropoxyphenyl) pyrazolo[1,5-*a*]pyrimidine **3a** [38%] (Table 1, entry 1). We then turned our attention to optimize the conditions of the cyclocondensations between isoflavone **1a** and 3-aminopyrazole **2** (Table 1). Thus when NaOH (5*M*) was used as base, **3a** obtained in 38% yield (entry 1). It was also found that Et_3N was ineffective in providing the desired condensation product (entry 2). A comparative reactivity study of bases in the reaction showed that NaOMe proved to be most effective for the cyclocondensation (entry 3). Further study with varying NaOMe equivalents revealed that 3.0 equiv of base is necessary to obtain a high yield of **3a** (entries 3–6). MeOH was a solvent of choice, since reactions in THF, DMF, or EtOH gave lower yields (entries 6–10). Compound **3a** was obtained in high yield when ratio of **1a**:**2** (1:1.3) were used (entry 12).

Next, the condensation of a variety of structurally divergent isoflavones **1** with **2** were performed to illustrate this concise and general method for the synthesis of **3**.

Scheme 1



The wide range of isoflavones (**1a–1t**) reacted efficiently with **2** under the basic conditions to afford the respective products **3** (12–45 h) in moderate to excellent yields (Table 2). All products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, MS, and elemental analysis. Single crystal X-ray diffraction analysis of **3a** (Fig. 1) was used to corroborate the postulated structures unequivocally, which added additional evidence for the structures identification. The reaction has a general character and isoflavone **1** with various substituent on the both aryl rings (e.g. alkoxy groups) gave **3** in high yields (Table 2). The yields, however, decrease when the number of the hydroxyl group on the aryl rings increase. For example, isoflavones, **1a, 1b**, **1d**, **1f**, **1i**, **1k**, **1l**, **1m**, **1q**, and **1t** (Table 2, entries 1, 2, 4, 6, 9, 11–13, 17, 20), which do not contain hydroxyl group gave **3** in about 80% yields. Isoflavone with one hydroxyl group, **1c**, **1e**, **1j**, **1o**, and **1s** (Table 2, entries 3, 5, 10, 15, 19) afforded **3** in about 65% yield while isoflavone with two free hydroxyl groups such as **1g** and **1h** (Table 2, entries 7, 8) gave desired products in about 60% yields. Consideration of Genistein (4′,5,7-trihydroxyisoflavon) (Table 2, entry 14) with **2** produced **3n** (45%) was well but in lower yield.

The yields of **3** are directly dependant on the number of free hydroxyl group present on the engaged isoflavone. Because the hydroxyls at isoflavones **1** under the basic conditions would be oxyanions, which possess stronger electron donability than alkoxy and benzyoxyl groups, they might prevent condensation of the reaction.

Further experimentation and mechanistic studies are required to fully understand the regioselective of the cyclocondensation of isoflavone **1** with pyrazoles **2**. As reported [17], isoflavone may undergo ring opening reaction in the presence of alkali to form a α,β-unsaturated ketone intermediate **5** (Scheme 3). Attack of the primary amine group from the 3-aminoprazole **2** on the β-carbon in **5**, followed by the ring closure reaction between produce **3**. Additionally, the choice of base is very important for the cyclocondensations of aminopyrazoles with isoflavone. Intermediate **5** was showed to undergo conversion to ketone **6** [18] at high concentration of base by elimination of $HC(OMe)_3$ molecule. On the other hand, the isoflavone ring would be hard to open and produce intermediate **5** in the lower concentration of base.

CONCLUSIONS

In summary, we have developed a useful method for the construction of fused 6,7-diphenylpyrazolo[1,5-*a*] pyrimidines derivatives by the cyclocondensation of 3-aminopyrazole with isoflavone in methanol and the presence of sodium methoxide. It is an efficient and regioselective approach toward the synthesis 6,7-diphenylpyrazolo[1,5-*a*]pyrimidines. The yields of pyrazolo[1,5-*a*] pyrimidine derivatives are excellent, most between 70–80%. On the basis of the present investigation, we are now carrying out research on the applications of 6,7-diphenylpyrazolo[1,5-*a*] pyrimidines in pharmacology.

EXPERIMENTAL

Melting points were measured on X-5 micro melting point apparatus, which is uncorrected. IR spectra were recorded on Fourier transform Infrared Spectrometer. The ^{1}H-NMR spectra were recorded at 300.00 MHz on Bruker DRX-300 Advance spectrometer; chemical shifts (δ scale) are reported in parts per million (ppm) downfield from Me_4Si which was used as the internal standard for all NMR spectra. ^{1}H-NMR spectra are reported in order: multiplicity and approximate coupling constant (*J* value) in hertz (Hz), number of protons; signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), and br s (broad signal). The ^{13}C-NMR spectra were recorded at 75.00 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). The MS instrument is LTQ ESI-MS. The elemental analyses were performed with an Elementar Analysensyteme GmbH Vario EL III. All the products are

Scheme 2. The designed cyclocondensation route of isoflavones 1 with aminopyrazoles 2.

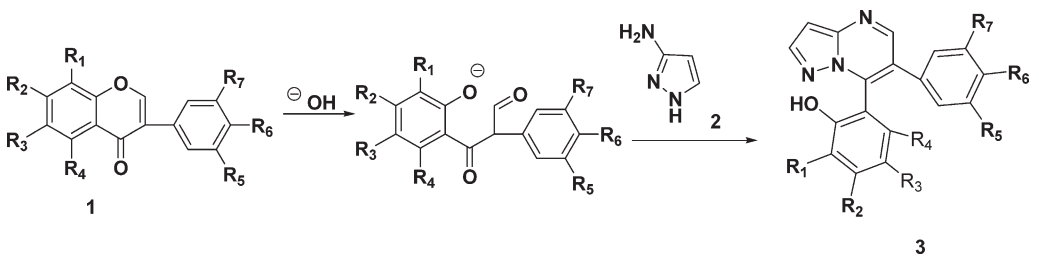
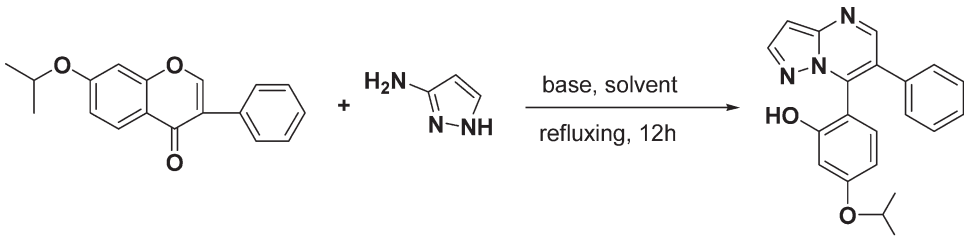


Table 1

Optimization of cyclocondensation of isoflavone **1a** with 3-aminepyrazole **2**[a].



1a **2** **3a**

Entry	Solvent	Base	Molar ratios (eq.) **1a**/**2**/base	**3a** Yield/%[b]
1[c]	EtOH	NaOH	1/1.1/3	38
2	EtOH	Et_3N	1/1.1/3	0
3	EtOH	NaOMe	1/1.1/2	53
4	EtOH	NaOMe	1/1.1/3	70
5	EtOH	NaOMe	1/1.1/4	64
6	EtOH	NaOMe	1/1.1/5	45
7	THF	NaOMe	1/1.1/3	30
8[d]	DMF	NaOMe	1/1.1/3	25
9	MeOH	NaOMe	1/1.2/3	75
10	MeOH	NaOMe	1/1.3/3	88
11	MeOH	NaOMe	1/1.4/3	85
12	MeOH	NaOMe	1/1.5/3	89

[a] All reactions were carried out with isoflavone **1a** (2 mmol) and 3-aminopyrazole **2** and different kind of base until the formation in appropriate solvents (20 mL) was completed as monitored by TLC(24 h, refluxing).
[b] Isolated yield based on isoflavone.
[c] Reactions with EtOH, MeOH, and THF as solvent were carried out under the boiling point.
[d] The reaction with DMF as solvent was carried at 100°C.

new compounds, which were characterized by IR, ^{1}H-NMR, and ^{13}C-NMR spectra. X-Ray crystallography dates were given by Bruker Smart-1000 CCD diffactometer. All other commercially obtained reagents were used as received. Thin-layer chromatography (TLC): silica gel 60 GF_{254} plate; and the eluant of column chromatography is the mixture of petroleum ether and ethyl acetate at volume ratio of 1:1.

General procedure for the synthesis of diarylpyrazolo[1,5-*a*]pyrimidine 3. The isoflavone **1a–1t** (2 mmol), 3-aminepyrazol **2** (2.6 mmol), and sodium methoxide (6, 8, 10, and 12 mmol were used for 0, 1, 2, and 3 free hydroxyl group of **1**) were refluxed in methanol (40 mL) for 12–45 h. All reactions were monitored by TLC, which showed the disappearances of the starting materials. The reaction mixture was then concentrated to 10 mL by using rotary evaporator, the condensate was poured into a 10% HCl (15 mL) and a light yellow precipitate formed. This precipitate was collected by filtration and washed with distilled water until the pH value of the filtrate was 7. Finally, the precipitate was recrystallized from absolute ethanol or purified on silica gel column chromatography ($CHCl_3$:CH_3OH = 20:1), **3** were obtained.

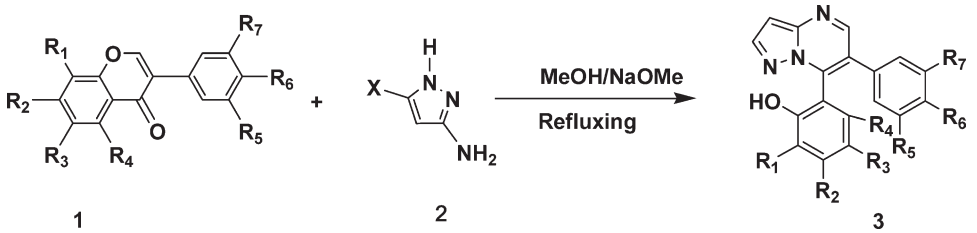
6-Phenyl-7-(2-hydroxyl-4-isopropoxyphenyl)pyrazolo[1,5-*a*]pyrimidine(3a). m. p. 248–250°C; IR (KBr), ν (cm^{-1}): 3314, 2977, 1684, 1610, 1519, 1423, 1386, 1235, 1113, 993, 837, 796, 699; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.26 (d, 6H), 4.53 (m, 1H), 6.35 (d, J = 8.4 Hz, 1H), 6.40 (s, 1H), 6.80 (s, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.31 (s, 5H), 8.14 (s, 1H), 8.61 (s, 1H), 9.73 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 21.8, 69.3, 96.1, 102.7, 106.2, 110.3, 122.1, 127.3, 128.2, 129.3, 131.6, 135.3, 142.6, 144.3, 147.7, 150.5, 156.9, 159.7. ESI-MS: *m*/*z* (rel intensity) 368 (M+Na, 52), 346 (M + 1, 100). Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found C, 73.10; H, 5.58; N, 12.20.

6-Phenyl-7-(2-hydroxyl-4-methoxy-6-methyphenyl)pyrazolo[1,5-*a*]pyrimidine (3b). m. p. 242.0–242.2°C; IR (KBr), ν (cm^{-1}): 3489, 3240, 3172, 3056, 2997, 1595, 1513, 1453, 1335, 1283, 1197, 1160, 1132, 1039, 831; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.71 (s, 3H), 3.72 (s, 3H), 6.28 (s, 2H), 6.81 (d, J = 1.9 Hz, 1H), 7.32 (s, 5H), 8.13 (d, J = 1.9 Hz, 1H), 8.63 (s, 1H), 9.71 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 19.0, 54.9, 96.1, 98.7, 106.2, 110.7, 122.6, 127.6, 128.2, 128.8, 135.3, 138.2, 141.9, 144.4, 147.7, 150.4, 156.6, 160.9. EIMS: *m*/*z* (rel intensity) 354 (M+Na, 38), 332 (M + 1, 100). Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.173; N, 12.68; Found C, 72.55; H, 5.21; N, 12.72.

6-(4-Methoxyphenyl)-7-(2,4-dihydroxylphenyl)pyrazolo[1,5-*a*]pyrimidine (3c). m. p. 245.0–245.7°C; IR (KBr), ν (cm^{-1}): 3142, 2958, 2836, 1709, 1605, 1506, 1458, 1209, 1238, 1179, 836; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.73 (s, 3H,), 6.22 (d, J = 8.2 Hz, 2H), 6.35 (s, 1H), 6.76 (s, 1H), 6.86 (d, 2H), 7.22 (d, J = 8.2Hz, 2H), 8.10 (s, 1H), 8.57 (s, 1H), 9.54 (s, 1H), 9.56 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6 / TMS, δ (ppm)]: 55.5, 96.5, 103.1, 107.1, 109.6, 114.2, 122.2,

Table 2

Synthesis of 6,7-diphenylpyrazolo[1,5-*a*]pyrimidines 3 by the cyclocondensations of aminopyrazoles **2** with isoflavones **1**[a].



1 2 3

Entry	Substrate	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Product/yield[b]/time **3**		
1	**1a**	H	*i*-OPr	H	H	H	H	H	**3a**	88	12
2	**1b**	H	OMe	H	Me	H	H	H	**3b**	79	13
3	**1c**	H	OH	H	H	H	OMe	H	**3c**	65	24
4	**1d**	H	OMe	H	OMe	H	OMe	H	**3d**	86	15
5	**1e**	H	OH	H	H	H	H	H	**3e**	61	20
6	**1f**	H	OMe	H	H	H	OMe	H	**3f**	82	12
7	**1g**	H	OH	H	H	H	OH	H	**3g**	58	32
8	**1h**	H	OH	H	H	*i*-Pr	OH	*i*-Pr	**3h**	62	35
9	**1i**	H	OMe	H	H	H	H	H	**3i**	76	13
10	**1j**	H	OMe	H	H	H	OH	H	**3j**	74	22
11	**1k**	Br	*i*-OPr	H	H	H	H	H	**3k**	82	14
12	**1l**	H	OMe	H	H	*i*-Pr	OMe	*i*-Pr	**3l**	77	16
13	**1m**	H	OMe	OMe	OMe	H	OMe	H	**3m**	86	18
14	**1n**	H	OH	H	OH	H	OH	H	**3n**	45	42
15	**1o**	H	OMe	H	H	*i*-Pr	OH	*i*-Pr	**3o**	80	28
16	**1p**	H	OMe	H	OMe	*i*-Pr	OMe	*i*-Pr	**3p**	76	18
17	**1q**	Br	OMe	H	H	H	OMe	H	**3q**	77	15
18	**1r**	H	OH	H	OH	*i*-Pr	OH	*i*-Pr	**3r**	48	45
19	**1s**	H	OMe	H	H	Br	OH	Br	**3s**	70	26
20	**1t**	H	OEt	H	H	H	OMe	H	**3t**	83	13

[a] Reaction conditions. For a detailed experimental operation, see Experimental section. **1** (2 mmol), **2** (2.6 mmol), $NaOCH_3$ (**3**: 6, 8, 10, and 12 mmol were used for 0, 1, 2, and 3 free hydroxyl group of **1**), 70°C.
[b] Isolated yield after silica gel chromatography.

128.0, 131.0, 131.9, 143.2, 144.5, 148.1, 151.2, 157.3, 159.0, 160.2; ESI-MS: *m/z* (rel intensity) 437 (95), 356 (M + Na, 40), 437.12 (51), 334 (M + 1, 100), 318 (13), 274 (25). Anal. Calcd for C19H15N3O3: C, 68.46; H, 4.54; N, 12.61; Found C, 68.52; H, 4.61; N, 12.71.

6-(4-Methoxyphenyl)-7-(2-hydroxyl-4,6-dimethoxyphenyl)-pyrazolo[1,5-*a*]pyrimidine (3d). m. p. 248.6–249.3°C; IR (KBr), ν (cm^{-1}): 3129, 3011, 2955, 2837, 1605, 1509, 1462, 1370, 1201, 1167, 1114, 1029, 935, 825; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.51 (s, 3H), 3.69(s, 3H), 3.73 (s, 3H), 6.06 (s, 1H), 6.11(s, 1H), 6.75 (s, 1H), 6.89 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 8.07 (s, 1H), 8.56 (s, 1H), 9.69 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 55.0, 55.5, 89.9, 93.7, 95.8, 100.3, 113.6, 123.0, 127.6, 129.8, 139.9, 143.9, 147.6, 150.3, 156.8, 158.7, 158.9, 162.2; ESI-MS: *m/z* (rel intensity) 400 (M + Na, 68), 378 (M + 1, 100), 274 (22). Anal. Calcd for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13; Found C, 66.86; H, 5.12; N, 11.18.

6-Phenyl-7-(2,4-dihydroxylphenyl)pyrazolo[1,5-*a*]pyrimidine (3e). m.p. 240.7–242.5°C; IR (KBr), ν (cm^{-1}): 3132, 2971, 1611, 1536, 1456, 1264, 1168, 1521, 1447, 1247, 1203, 1100, 1021, 834; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 6.23 (s, 1H), 6.37 (d, J = 7.4 Hz, 1H), 6.78 (s, 1H), 6.86 (d, J = 7.4 Hz, 1H), 7.25 (m, 5H), 8.12 (s, 1H), 8.60 (s, 1H), 9.58 (s, 2H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 160.3, 157.3, 151.0, 148.5, 135.9, 132.0, 129.8, 128.7, 127.7, 126.7, 125.1, 122.5, 108.8, 107.1, 103.1, 96.5. ESI-MS: *m/z* (rel intensity) 388 (63), 365 (40), 346 (63), 330 (M + Na, 11), 304 (M + 1, 26), 274(52). Anal Calcd for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32; N, 13.85; Found C, 71.21; H, 4.26; N, 13.77.

6-(4-Methoxyphenyl)-7-(2-hydroxyl-4-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine (3f). m. p. 247.8–248.5°C; IR (KBr), ν (cm^{-1}): 3142, 2962, 2889, 1614, 1504, 1449, 1319, 1250, 1202, 1087, 1034, 833; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.73 (s, 6H), 6.38–6.45 (m, 2H), 6.78 (s, 1H), 6.88 (d, J = 8.6 Hz, 2H), 7.00 (d, 1H), 7.23 (d, J = 8.6 Hz, 2H), 8.11 (s, 1H), 8.60 (s, 1H), 9.82 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 55.0, 96.1, 101.2, 104.8, 110.7, 113.7, 121.8, 127.3, 130.5, 131.5, 142.2, 144.1, 147.6, 150.7, 156.8, 158.5, 161.3; ESI-MS: *m/z* (rel intensity) 370 (M+Na, 60), 348 (M + 1, 100). Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10; Found C, 66.09; H, 4.81; N, 11.89.

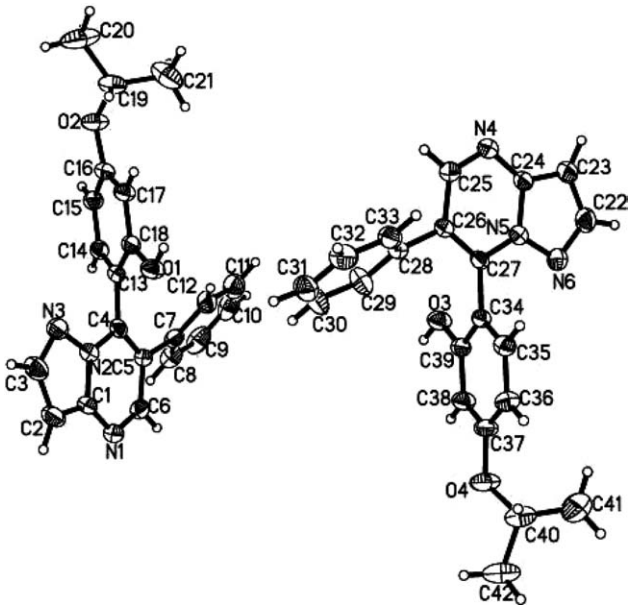


Figure 1. Single-crystal X-ray structural analysis of 3a.

6-(4-Hydroxylphenyl)-7-(2,4-dihydroxylphenyl)pyrazolo[1,5-*a*]pyrimidine (3g). m. p. 240.6–240.8°C; IR (KBr), ν (cm^{-1}): 3138, 2923, 1611, 1545, 1505, 1455, 1251, 1179, 1110, 837; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 6.21(d, J = 8.0 Hz, 1H), 6.63 (s, 1H), 6.68 (d, J = 7.6 Hz, 2H), 6.75 (s, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.96 (s, 1H), 7.09 (d, J = 7.6 Hz, 2H), 8.09 (s, 1H), 8.55 (s, 1H), 9.73 (bs, 3H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 160.1, 157.3, 157.2, 151.2, 148.0, 144.4, 143.0, 131.9, 130.9, 126.3, 122.6, 115.6, 109.7, 107.0, 103.0, 96.4; ESI-MS: *m*/*z* (rel intensity) 437 (100), 346 (M + Na, 22), 319 (M + 1, 73), 274 (60), 267 (43). Anal. Calcd for $C_{18}H_{13}N_3O_3$: C, 67.71; H, 4.10; N, 13.16; Found C, 67.69; H, 3.99; N, 13.01.

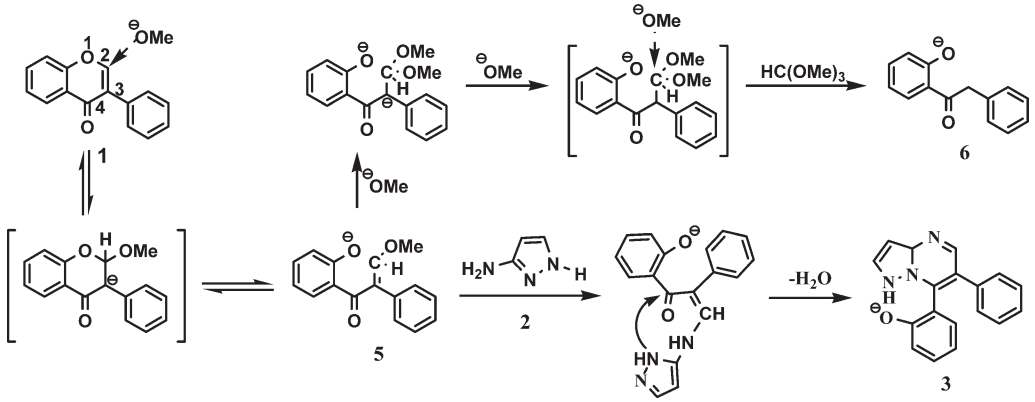
6-(3,5-Diisopropyl-4-hydroxylphenyl)-7-(2,4-dihydroyphenyl)pyrazolo[1,5-*a*]pyrimidine (3h). m. p. 244.2–245.9°C; IR (KBr), ν (cm^{-1}): 3140, 2956, 2869, 2833, 1622, 1496, 1306, 1251, 1190, 1156, 955, 788; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.20 (m, 12H), 3.2 (m, 2H), 6.19 (s, 1H), 6.37 (s, 1H), 6.74 (s, 1H), 6.95 (s, 2H), 8.06–8.10 (m, 2H), 8.64 (s, 1H), 9.49–9.55 (d, 2H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 159.4, 156.7, 150.6, 149.8, 147.2, 143.9, 142.5, 134.9, 130.9, 126.1, 124.2, 122.5, 109.7, 106.5, 102.3, 95.8, 25.9, 22.7; ESI-MS: *m*/*z* (rel intensity) 477 (22), 437 (12), 426 (9), 404 (M+1, 100), 274 (20). Anal. Calcd for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25; N, 10.41; Found C, 71.39; H, 6.19; N, 10.37.

6-Phenyl-7-(2-hydroxyl-4-methoxyphenyl)pyrazolo[1,5-*a*]-pyrimidine (3i). m. p. 240.3–240.8°C; IR (KBr), ν (cm^{-1}): 3135, 2959, 1615, 1537, 1497, 1273, 1200, 1164, 1112, 829; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.67 (s, 3H), 6.42 (m, 2H), 6.80 (s, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.25 (m, 5H), 8.12 (s, 1H), 8.60 (s, 1H), 9.81 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 55.5, 96.6, 101.6, 105.3, 110.8, 122.6, 127.8, 128.7, 129.8, 132.1, 135.7, 143.1, 144.7, 148.5, 151.0, 157.5, 161.9; ESI-MS: *m*/*z* (rel intensity) 444 (100), 437 (50), 424 (30), 402 (76), 360 (38), 318(M + 1, 44), 274(19). Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24; Found C, 72.00; H, 4.82; N, 13.41.

6-(4-Hydroxyphenyl)-7-(2-hydroxy-4-methoxyphenyl)-pyrazolo[1,5-*a*]pyrimidine (3j). m. p. 242.2–244.2°C; IR (KBr), ν (cm^{-1}): 3272, 3118, 2936, 2665, 1596, 1495, 1442, 1382, 1316, 1235, 1204, 1172, 829; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.74 (s, 3H), 6.42 (m, 2H), 6.69 (d, J = 8.3 Hz, 2H), 6.77 (s, 1H), 6.97 (d, 1H), 7.11 (d, J = 8.3 Hz, 2H), 8.10 (s, 1H), 8.57 (s, 1H), 9.53 (s, 1H), 9.77 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 55.0, 96.0, 101.2, 104.8, 110.9, 115.1, 122.2, 125.6, 130.0, 130.5, 131.5, 142.1, 143.9, 147.5, 150.8, 156.8, 161.3; ESI-MS: *m*/*z* (rel intensity) 437 (39), 432 (22), 356 (M + Na, 34), 334 (M + 1, 100), 318 (26), 276 (68), 274 (43) . Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61; Found C, 68.53; H, 4.61; N, 12.70.

6-Phenyl-7-(2-hydroxyl-3-bromo-4-isopropoxyphenyl)pyrazolo[1,5-*a*]pyrimidine (3k). m. p. 210.2–210.9°C; IR (KBr), ν (cm^{-1}): 3140, 2980, 2901, 1607, 1486, 1445, 1403, 1323, 1258, 1192, 1105, 1102, 971, 839; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.06 (s, 12H), 3.12–3.20 (m, 2H), 3.64 (s, 3H), 3.71 (s, 3H), 6.41 (d, J = 8.0 Hz, 1H), 6.49 (s, 1H), 6.76 (s, 1H), 6.94 (d, J = 8.0 Hz, 1H), 7.07 (s, 2H) 8.09 (s, 1H), 8.67 (s, 1H), 9.71 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 162.0, 157.5, 153.9, 151.0, 148.1, 144.6, 142.8, 141.3, 131.7, 131.2, 125.7, 122.5, 111.7, 105.4, 101.8, 96.5, 62.3, 55.6, 26.3, 24.2; ESI-MS: *m*/*z* (rel intensity) 437 (M + Na, 57), 424 (M − 1, 19), 368 (38), 346 (100), 274

Scheme 3. Proposed mechanism for the formation of 3.



(19). Anal. Calcd for $C_{21}H_{18}BrN_3O_2$: C, 59.45; H, 4.28; N, 9.90; Found C, 59.41; H, 4.22; N, 9.84.

6-(3,5-Diisopropyl-4-methoxylphenyl)-7-(2-hydroxy-4-methoxyphenyl)pyrazolo[1,5-*a*] pyrimidine(3l). m. p. 204.3–206.8°C; IR (KBr), ν (cm^{-1}): 3452, 3140, 2956, 2873, 1642, 1623, 1496, 1468, 1306, 1078, 1014, 971, 892; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.06 (s, 12H), 3.16 (m, 2H), 3.64 (s, 3H), 3.71 (s, 3H,), 6.41 (d, J = 8.0 Hz, 1H), 6.49 (s, 1H), 6.76 (s, 1H), 6.94 (d, J = 8.0 Hz, 1H), 7.07 (s, 2H), 8.09 (s, 1H), 8.67 (s, 1H), 9.71 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 162.0, 157.5, 153.9, 151.0, 148.1, 144.6, 142.8, 141.3, 131.7, 131.2, 125.7, 122.5, 111.7, 105.4, 101.8, 96.5, 62.3, 55.6, 26.3, 24.2; ESI-MS: *m*/*z* (rel intensity) 454 (M+Na, 34), 432 (M + 1, 100). Anal. Calcd for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74; Found C, 71.20; H, 6.52; N, 9.49.

6-(4-Methoxyphenyl)-7-(2-hydroxyl-4,5,6-trimethoxyphenyl)pyrazolo[1,5-*a*]pyrimidine (3m). m. p. 240.2–241°C; IR (KBr), ν (cm^{-1}): 3136, 2976, 2930, 1616, 1509, 1429, 1296, 1249, 1185, 1115, 1032, 830; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.33 (t, J = 6.9 Hz, 3H), 3.74 (s, 3H), 4.00 (q, J = 6.9 Hz, 3H), 6.40 (m, 2H), 6.76 (s, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.98 (s, 1H), 7.23 (d, J = 8.6 Hz, 2H), 8.09 (s, 1H), 8.57 (s, 1H), 9.64 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 15.1, 55.6, 63.5, 96.5, 102.3, 105.9, 111.2, 114.3, 122.3, 127.9, 131.0, 132.0, 142.8, 144.5, 148.1, 151.2, 157.3, 159.1, 161.2 ESI-MS: *m*/*z* (rel intensity) 437 (19), 390(35), 384 (M + Na, 80), 362(M + 1, 100). Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63; Found C, 71.01; H, 5.06; N, 11.59.

6-(4-Hydroxylphenyl)-7-(2,4,6-trihydroxylphenyl)pyrazolo[1,5-*a*]pyrimidine (3n). m. p. 204.2–210.9°C; IR (KBr), ν (cm^{-1}): 3143, 2936, 2838, 1613, 1509, 1467, 1366, 1256, 1185, 1096, 1034, 994, 826; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.43 (s, 3H), 3.71 (m, 9H), 6.32 (d, J = 9.1 Hz, 1H), 6.91 (m, 2H), 7.28–7.33 (m, 2H), 8.12 (d, 1H, J = 9.1 Hz), 8.61 (s, 1H), 9.58 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 158.8, 154.9, 151.6, 151.2, 150.4, 147.5, 143.9, 139.4, 134.0, 130.0, 127.3, 122.6, 113.7, 104.3, 96.0, 95.5, 60.4, 60.1, 55.6, 55.0; ESI-MS: *m*/*z* (rel intensity) 430(M+Na, 76), 408 (M + 1, 100). Anal. Calcd for $C_{22}H_{21}N_3O_5$: C, 64.86; H, 5.20; N, 10.31; Found C, 64.79; H, 5.00; N, 10.22.

6-(3,5-Diisopropyl-4-hydroxylphenyl)-7-(2-hydroxy-4-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine (3o). m. p. 246.5–247.2°C; IR (KBr), ν (cm^{-1}): 3546, 3133, 2962, 2580, 1612, 1535, 1467, 1312, 1238, 1202, 1105, 1025, 788; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.05 (s, 12H), 3.23 (m, 2H), 3.71 (s, 3H), 6.45 (d, 1H, J = 8.5 Hz), 6.50 (s, 1H), 6.76 s, 1H), 6.93 (m, 3H), 8.08 (s, 1H), 8.13 (s, 1H), 8.68 (s, 1H), 9.81 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 161.4, 157.0, 150.7, 150.1, 147.4, 143.9, 141.9, 134.9, 131.2, 126.0, 124.2, 122.6, 111.4, 104.9, 101.3, 95.8, 55.1, 26.0, 22.7; ESI-MS: *m*/*z* (rel intensity) 440 (M + Na, 22), 418 (M + 1, 100). Anal. Calcd for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06; Found C, 71.89; H, 649; N, 9.98.

6-(3,5-Diisopropyl-4-methoxyphenyl)-7-(2-hydroxyl-4,6-dimethoxyphenl)pyrazolo[1,5-*a*]pyrimidine (3p). m. p. 242.0–243.7°C; IR (KBr), ν (cm^{-1}): 3148, 2962, 2872, 1627, 1502, 1463, 1356, 1304, 1249, 1196, 1159, 1004, 939, 808; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 0.85 (s, 12H), 2.96 (m, 2H), 3.24 (s, 3H), 3.49 (s, 3H), 3.57 (s, 3H), 5.86 (s, 1H), 5.89 (s, 1H), 6.53 (s, 1H), 6.83 (s, 2H), 7.86 (s, 1H), 8.41 (s, 1H), 9.54 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 162.4, 158.5, 157.1, 153.4, 150.0, 147.5, 143.9, 140.7, 140.1, 131.1, 124.8, 124.5, 123.9, 123.1, 95.8, 94.9, 93.8, 90.0, 61.9, 55.4, 55.2, 25.9, 24.7, 23.6; ESI-MS: *m*/*z* (rel intensity) 488 (38), 484 (M + Na, 60), 462 (M + 1, 100).Anal. Calcd for $C_{27}H_{31}N_3O_4$: C, 70.26; H, 6.77; N, 9.10; Found C, 70.12; H, 6.47; N, 8.95.

6-(4-Methoxyphenyl)-7-(2-hydroxyl-3-bromo-4-methoxyphenyl)pyrazolo[1,5-*a*] pyrimidine (3q). m. p. 202.8–204.3°C; IR (KBr), ν (cm^{-1}): 3488, 2940, 1600, 1490, 1451, 1396, 1250, 1205, 1049, 829, 787; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.86 (d, 6H), 6.80 (s, 1H), 6.52 (s, 1H), 6.90 (s, 1H, J = 8.4 Hz), 7.08 (s, 1H), 7.24 (s, 1H, J = 8.4 Hz), 7.36–7.48 (d, 2H), 8.13 (s, 1H,), 8.59 (s, 1H), 10.15 (d, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 56.6, 96.7, 96.9, 100.9, 112.8, 114.3, 122.5, 130.4, 131.0, 134.0, 134.4, 144.7, 145.0, 151.0, 151.3, 157.0; ESI-MS: *m*/*z* (rel intensity) 505 (22), 453 (27), 426 (M + 1, 100). Anal. Calcd for $C_{20}H_{16}BrN_3O_3$: C, 56.35; H, 3.78; N, 9.86; Found C, 56.41; H, 3.84; N, 9.97.

6-(3,5-Diisopropyl-4-hydroxylphenyl)-7-(2,4,6-trihydroxylphenyl)pyrazolo[1,5-*a*]pyrimidine (3r). m. p. 248.4–249.6°C; IR (KBr), ν (cm^{-1}): 3207, 2962, 1876, 1648, 1565, 1443, 1295, 1191, 1158, 833; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.15 (d, 12H, J = 6.2 Hz), 3.30 (m, 2H), 6.00 (s, 1H), 6.09 (s, 1H), 6.62 (s, 1H), 7.21 (s, 2H), 7.87 (s, 1H), 8.01 (s, 1H), 8.07 (s, 1H), 10.30 (s, 1H), 13.32 (s, 1H), 15.03 (s, 1H); ^{13}C-NMR[75 MHz, DMSO-d_6/TMS, δ (ppm)]: 179.4, 163.7, 162.5, 150.1, 148.5, 142.7, 141.1, 134.7, 131.1, 125.1, 123.7, 119.9, 107.1, 101.9, 98.0, 91.6, 26.2, 23.0. ESI-MS: *m*/*z* (rel intensity) 462 (32), 442 (M + Na, 44), 420 (M + 1, 100), 346 (50). Anal. Calcd for $C_{24}H_{25}N_3O_4$: C, 68.72; H, 6.01; N, 10.02; Found C, 68.81; H, 6.21; N, 10.15.

6-(4-Hydroxyl-3,5-dibromophenyl)-7-(2-hydroxyl-4-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine (3s). m. p.185.1–189.5°C; IR (KBr), ν (cm^{-1}): 3466, 2922, 1601, 1543, 1466, 1299, 877, 785; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 3.84 (s, 3H), 6.46 (d, 1H, J = 7.8 Hz), 6.80 (s, 1H), 7.09 (s, 1H, J = 7.8 Hz), 7.48 (d, 2H), 8.14 (s, 1H,), 8.63 (s, 1H), 9.98 (t, 2H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 55.0, 96.3, 100.3, 101.1, 105.5, 111.4, 119.8, 129.1, 131.5, 132.9, 134.0, 140.8, 142.5, 144.4, 147.7, 150.2, 156.6, 161.6; ESI-MS: *m*/*z* (rel intensity) 491 (M + 1, 19), 477 (100), 431 (40). Anal. Calcd for $C_{19}H_{13}Br_2N_3O_3$: C, 46.46; H, 2.67; N, 8.56; Found C, 46.52; H, 2.71; N, 8.84.

6-(4-Methoxyphenyl)-7-(2-hydroy-4-ethoxyphenyl)pyrazolo[1,5-*a*]pyrimidin (3t). m. p. 240.2–241°C; IR (KBr), ν (cm^{-1}): 3136, 2976, 2930, 1616, 1509, 1429, 1296, 1249, 1185, 1115, 1032, 830; ^{1}H-NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 1.33 (t, J = 6.9 Hz, 3H), 3.74 (s, 3H), 4.00 (q, J = 6.9 Hz, 3H), 6.40 (m, 2H), 6.76 (s, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.4 Hz), 7.23 (d, J = 8.6 Hz, 2H), 8.09 (s, 1H), 8.57 (s, 1H), 9.64 (s, 1H); ^{13}C-NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 15.1, 55.6, 63.5, 96.5, 102.3, 105.9, 111.2, 114.3, 122.3, 127.9, 131.0, 132.0, 142.8, 144.5, 148.1, 151.2, 157.3, 159.1, 161.2; ESI-MS: *m*/*z* (rel intensity) 437 (19), 390(35), 384 (M + Na, 80), 362(M + 1, 100). Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63; Found C, 71.01; H, 5.06; N, 11.59.

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REFERENCES AND NOTES

[1] Pyrazol[1,5-*a*]pyrimidine compound as cannabinoid receptor antagonists. PCT Int. WO2007046548, 2007.

[2] Mukaiyama, H.; Nishimura, T.; Kobayashi, S.; Komatsu, Y. Bioorg Med Chem 2008, 16, 909.

[3] Huang, S.; Lin, R.; Yu, Y.; Lu, Y.; Connolly, P.; Chiu, G.; Li, S.; Emanuel, S.; Middleton, S. Bioorg Med Chem Lett 2007, 17, 1243.

[4] Saggar, S.; Sisko, J.; Tucker, T.; Tynebor, R.; Su, D.; Anthony, N. US Pat. 2,007,021,442, 2007.

[5] Zhang, P.; Pennell, M.; Wright, J.; Chen, W.; Leleti, M.; Li, Y.; Li, L.; Xu, Y. PCT Int. WO 2007002293, 2007, Chemocentryx.

[6] (a) Chiu, G.; Li, S.; Connolly, P.; Middleton, S.; Emanuel, S.; Huang, S.; Lin, R.; Lu, Y. PCT Int. WO 2006130673, 2006, Janssen Pharmaceutica, N.V., Belgium; (b) Dwyer, M.; Paruch, K.; Alvarez, C.; Doll, R.; Keertikar, K.; Duca, J; Fischmann, T.; Hruza, A.; Madison, V.; Lees, E.; Parry, D.; Seghezzi, W.; Sgambellone, N.; Shanahan, F.; Wiswellb, D.; Guzia, T. Bioorg Med Chem Lett 2007, 17, 6216.

[7] (a) Elnagdi, M. H.; Elmoghayar, M. R. H.; Elgemeie, G. H.; Adv Heterocycl Chem 1987, 41, 319; (b) Quiroga, J.; Hormaza, A.; Insuasty, B.; Saitz, C.; Jullian, C.; Cannete, A. J Heterocycl Chem 1998, 35, 61; (c) El-Taweel, F.; Abu Elmaati, T. J. Chin Chem Soc 2002, 49, 1051; (d) Daniels, R.; Kim, K.; Lebois, E.; Muchalski, H.; Hughes, M.; Lindsley, C. Tetrahedron Lett 2008, 49, 305.

[8] (a) Simon, C.; Constantieux, T.; Rodriguez, J.; Eur J Org Chem 2004, 24, 4957; (b) Quiroga, J; Portilla, J; Abonia, R.; Insuasty, B.; Nogueras, M.; Cobo, J Tetrahedron Lett 2007, 48, 6352; (c) Quiroga, J; Mejia, D; Insuasty, B; Abonia, R; Nogueras, M; Sanchez, A; Cobo, J. J Heterocycl Chem 2002, 39, 51.

[9] Kenner, G. W.; Lythgoe, B.; Todd, A. R.; Topham, A. J Chem Soc 1943, 87, 388.

[10] (a) Burness, D. M. J Org Chem 1956, 21, 97; (b) Xie, F. C.; Zhao, H. B.; Zhao, L. Z.; Lou, L. G.; Hu, Y. H. Bioorg Med Chem Lett 2009, 19, 275.

[11] Sherman, W. R.; Taylor, E. C., Jr. Org Synth 1957, 37, 15.

[12] (a) Foster, H. M.; Snyder, H. R.; Org Synth 1963 4, 638; (b) Crosby, D. G.; Berthold, R. V.; Johnson, H. E. Org Synth 1963, 43, 68.

[13] Zhang, Z.-T.; Tan, D.-J.; Xue, D. HeIv Chim Acta 2007, 90, 2096.

[14] Zhang, Z.-T.; Xu, F.-F.; Gao, M.-X.; Qiu, L. J Comb Chem 2009, 11, 880.

[15] Zhang, Z.-T.; Qiu, L.; Xue, D.; Wu, J.; Xu, F.-F. J Comb Chem 2010, 12, 225.

[16] Szab, V.; Zsuga, M. React Kinet Catal Lett 1976, 3, 229.

[17] V. Szabó, M. Zsuga. Reactions of isoflavone and 2-hydroxyisoflavanone with sodium ethoxide in anhydrous ethanol[J]. React Kinet Catal Lett 1976, 5, 229.

[18] Varga, M.; Bátori, S.; Kövári-Rádkai, M.; Prohászka-Német, I.; Vitányi-Morvai, M.; Böcskey, Z.; Bokotey, S.; Simon, K.; Hermecz, I. European J Org Chem 2001, 20, 3911.