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3,7-Diarylpyrazolo[1,5-α]pyrimidines의 개선된 One-pot Regioselective 합성과 CB1R 활성

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Improved One-pot Regioselective Synthesis of 3,7-Diarylpyrazolo[1,5-α]pyrimidines and Their CB1R Activity

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요 약: 본 연구는 3,7−diarylpyrazolo [1,5− α]pyrimidines의 효과적인 one−pot regioselective 합성을 보여준다. 더욱이, 그 유도체는 뛰어난 CB1R 저해 활성을 나타냈다. 3,7−position에 diaryl group이 치환된 pyrazolo [1,5− α]pyrimidine은 CB1R 후보로서 가능성 있는 pharmacophore이다.

Abstract: This study demonstrates an effective one-pot regioselective synthesis of 3,7-diarylpyrazolo [1,5- α]pyrimidines. Moreover, the derivatives obtained were effective CB1R antagonists. These pyrazolo [1,5- α]pyrimidines with diaryl groups at the 3,7-positions are potential pharmacophores for CB1R candidates.

Keywords: *aminopyrazoles, aryl ketoesters, regioselective synthesis, 3,7-diarylpyrazolo[1,5-a]pyrimidines*

1. Introduction

The cannabinoid 1 receptor (CB1R) is a member of the G-protein- coupled receptor (GPCR) family and mainly distributed within the central nervous system (CNS) and periphery[1]. CB1 antagonists regulate neuronal, cardiac, reproductive, and immune functions and control locomotor activity, learning, memory, emotion, motivation, and appetite[2]. They could also target multiple tissues involved in metabolic homeostates[3].

In general, N-heterocyclic compounds are used in drug discovery research as backbones of pharmacophores. Among these, pyrazolopyrimidines have been used as scaffolds in pharmaceutical agents that have exhibited high degrees of biological activity[4−8]. In particular, pyrazolo[1,5- α]pyrimidines exhibit various biological activities including antimicrobial[9,10], antitumor[11], antischistosomal[12], andantianxiety[13] activities, have been shown to act as estrogen receptor antagonists[14] and kinase insert domain receptors (KDR)[15], and interact strongly with tyrosine kinase[16]. The most common synthetic route for pyrazolo [1,5- α]pyrimidines involves the reaction between an aminopyrazole and a bidentate electrophile such as a malondialdehyde[17], a Mannich base[18,19], or an unsaturated nitrile[20].

Our research focuses on disubstituted pyrazolo [1,5- α]pyrimidines, which have two regioisomers, such as **1**

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Table 1. Reaction Conditions for the Conjugated Addition of Compounds **3** and **4**

Entry	Conditions	Yields(%)[a]	
		7	8
1	Acetic acid, 105 ℃	93	-
2	EtOH, TsOH, reflux	80	
3	Dioxane, AcOH (0.1 mL), 95 ℃	45	28
4	DMF, 95 ℃	10	5
5	Triethylamine, 90 ℃	-	30
6	Pyridine, 90 ℃	-	90

[a] Isolated yield

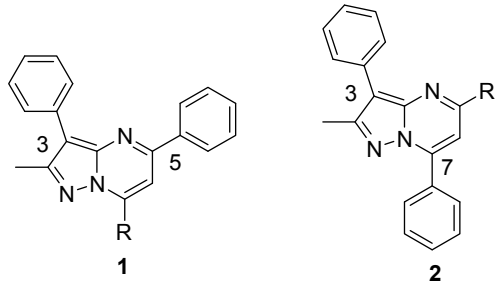


Figure 1. Regioisomers of pyrazolo[1,5-α]pyrimidine.

and **2** in Figure 1. In general, 3,5-diarylpyrazolo[1,5-α]pyrimidine **1** can be synthesized by reacting an arylaminopyrazole with either an arylketoester[21] or arylenone[22] under acidic conditions. However, neither of these methods has been satisfactory for the preparation of 3,7-diarylpyrazolo [1,5-α]pyrimidines **2**. Recently, transition metal-mediated C-C coupling reactions using aluminum chloride ($AlCl_3$) have been used to synthesize **2** via multi-step reactions[23] that are not suitable for one-pot syntheses. This study describes a new regioselective synthesis for 3,7-diarylpyrazolo [1,5-α] pyrimidines using a one-pot reaction.

2. Experimental

2.1. Chemistry

The ^{1}H NMR spectra were recorded using a Varian 300 MHz spectrometer using DMSO-d_6 as the solvent. The chemical shifts (d ppm) are reported relative to the internal standard, and the *J* values are reported in Hz. The mass spectra were recorded using an LCQ Deca XP plus liquid chromatography–massspectrometry (LC/MS). The reagents and solvents were purchased from commercial suppliers and used as received without further purification.

2.1.1. 7-Chloro-5-(4-chloro-phenyl)-2-methyl-pyrazolo [1,5-α] pyrimidine (7) and 5-chloro-7-(4-chloro-phenyl)-2-methyl- pyrazolo [1,5-α]pyrimidine (8)

A solution of **3** (100 mg, 1.03 mmol) and **4** (295 mg, 1.3 mmol) in N_2 atmosphere was stirred and reacted for 3–12 h under conditions listed in Table 1. The resulting mixture was evaporated *in vacuo*, and the residue was washed sequentially with the aqueous solutions of $NaHCO_3$ and ethylacetate. The organic layer was dried with anhydrous $MgSO_4$ and concentrated to yield a crude reactant, which was then stirred with $POCl_3$ and heated to 80 ℃ for 1 h. Then, the mixture was evaporated *in vacuo*, and the residue was washed sequentially with the aqueous solutions of $NaHCO_3$ and ethylacetate. The organic layer was dried with anhydrous $MgSO_4$ and concentrated to yield a crude reactant, which was then purified by column chromatography (hexane/EtOAc = 10 : 1) to yield the desired compound as a yellowish solid.

2.1.2. 5-(4-Chloro-phenyl)-2-methyl-6H-pyrazolo[1,5-α]pyrimidin -7-one (5)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 12.38 (bs, 1H, 7.84 (d, 2H, J = 4.5 Hz), 7.64 (d, 2H, J = 8.0 Hz), 6.03 (s, 1H), 6.01(s, 1H), 3.32 (bs, 1H), 2.31 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm 155.9, 152.2, 147.9, 142.3, 135.7, 132.2, 129.0, 129.0, 93.9, 89.3, 14.0. MS (EI) 260 (M^+)

2.1.3. 7-(4-Chloro-phenyl)-2-methyl-4H-pyrazolo[1,5-α]pyrimidin-5-one (6)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 12.05 (bs, 1H), 8.02 (d, 2H, 4.5Hz), 7.78 (d, 2H, J = 8.0 Hz), 6.22 (s, 1H), 6.03 (s, 1H), 2.17 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm 153.1, 150.6, 146.6, 140.3, 136.2, 135.6, 128.2, 128.2, 101.1, 93.1, 14.0. MS (EI) 260 (M^+)

2.1.4. 7-Chloro-5-(4-chloro-phenyl)-2-methyl-pyrazolo[1,5-α] pyrimidine (7)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.98 (d, 2H, J = 8.5 Hz), 7.46 (d, 2H, J = 8.5 Hz), 7.27 (s, 1H), 6.56 (s, 1H), 2.57 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm 156.8, 154.5, 150.56, 138.5, 137.1, 135.2, 129.5, 129.4, 128.8, 128.7, 104.6, 98.4, 15.1. HRMS calc. for $C_{16}H_{18}FNO$ 278.1367 (M^+), found 278.0251.

2.1.5. 5-Chloro-7-(4-chloro-phenyl)-2-methyl-pyrazolo[1,5-α] pyrimidine (8)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.98 (d, 2H, J = 8.0Hz), 7.52 (d, 2H, J = 8.0 Hz), 6.79 (s, 1H), 6.46 (s, 1H), 2.48 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm 156.4, 150.1, 149.6, 146.6, 138.0, 130.9, 130.8, 129.3, 129.2, 107.0, 96.9, 15.0. HRMS calc. for $C_{16}H_{18}FNO$ 278.1367 (M^+), found 278.0251.

General procedure: Amination of regioisomers 27 and 28

A stirred solution of 27 or 28 (1.0 equiv), diisopropylethylamine (2 equiv) and *L*-prolinol (1.1 equiv) in acetonitrile under N_2 atmosphere was heated to 90 ℃ for 3 h. The reaction mixture was evaporated *in vacuo* and concentrated to afford the crude product, which was then purified by column chromatography (hexane/EtOAc = 3 : 1) to afford the desired compound as a white solid (> 90% yield).

2.1.6. 7-Chloro-3-(4-chloro-phenyl)-2-methyl-5-phenyl-pyrazolo [1,5-α] pyrimidine (27)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.07 (m, 2H), 7.75 (d, J=8.00Hz, 2H), 7.47 (m, 5H), 7.24 (s, 1H), 2.68 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm 155.9, 153.8, 147.2, 138.4, 136.132.6, 131.2, 131.0, 130.8, 130.3, 129.2, 128.9, 128.7, 127.7, 127.5, 110.1, 106.7, 105.3, 14.8. MS (EI) 354 (M^+)

2.1.7. 5-Chloro-3-(4-chloro-phenyl)-2-methyl-7-phenylpyrazolo [1,5-α] pyrimidine (28)

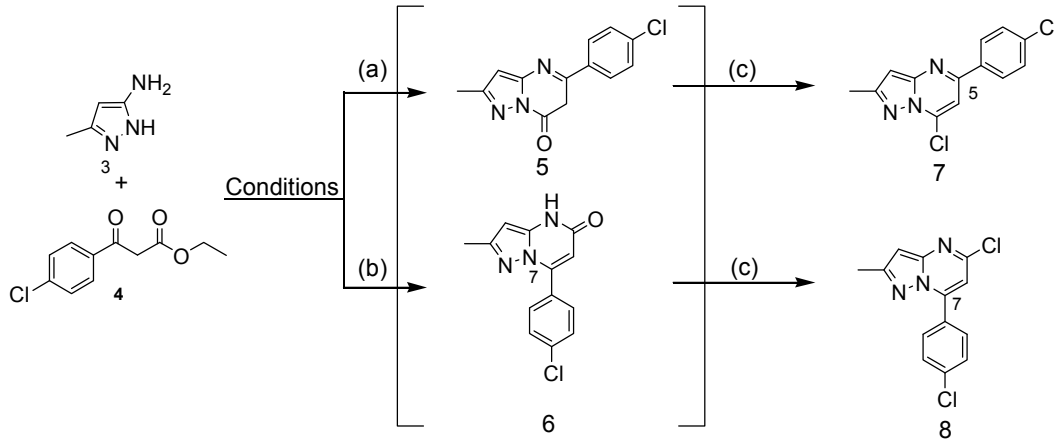
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.04 (d, J =5.5 Hz, 2H), 7.57 (m, 3H), 7.43 (d, J = 8.5 Hz, 2H), 6.84 (s, 1H), 2.58 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm 167.3, 153.6, 152.1, 150.7, 147.8, 138.1, 133.1, 132.7, 131.8, 130.4, 130.3, 129.6, 129.1, 108.1, 107.9, 93.7, 92.2, 14.7. MS (EI) 354 (M^+)

2.1.8. {1-[3-(4-Chlorophenyl)-2-methyl-5-phenyl-pyrazolo[1,5-α] pyrimidin-7-yl] -pyrrolidin-2-yl}methanol (29)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.06 (d, J = 9.5 Hz , 2H), 7.81 (d, J = 8.5 Hz , 2H), 7.48-7.26 (m, 5H), 6.35 (s, 1H), 5.87 (bs, 1H), 4.21 (m, 1H), 3.84-3.80 (m, 2H), 3.75-3.60 (m, 2H), 2.60 (s, 3H), 2.14 (m, 3H), 1.95 (m, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm 169.1, 162.5, 160.1, 157.3, 155.7, 129.3, 128.9, 125.3, 115.5, 106.8, 105.9, 102.4, 100.3, 55.2, 40.4, 37.2, 36.5, 36.1, 28.3. HRMS calc. for $C_{16}H_{18}FNO$ 418.9186 (M^+), found 419.1660.

2.1.9. {1-[3-(4-Chlorophenyl)-2-methyl-7-phenyl-pyrazolo[1,5-α] pyrimidin-5-yl] -pyrrolidin-2-yl}methanol (30)

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.94 (d, J = 10.0 Hz 2H), 7.57-7.53 (m, 5H), 6.17 (s, 1H), 5.12 (br, 1H), 4.46 (m, 1H), 3.78-3.52 (m, 4H), 2.47 (s, 3H), 2.15-1.99 (m, 3H), 1.78-1.69 (m, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ ppm 157.4, 151.0, 149.5, 147.6, 138.8, 134.2, 131.8, 131.4, 130.4, 130.0, 129.9, 129.8, 128.8, 128.6, 127.8, 127.4, 106.3, 87.5, 65.5, 61.3, 50.4, 29.3, 22.8, 14.8. HRMS calc. for $C_{16}H_{18}FNO$ 418.9186 (M^+), found 419.1651



Scheme 1. Reagents and conditions: (a) AcOH, 105 ℃, 3 h; (b) pyridine, 90 ℃, 12 h; (c) $POCl_3$, 80 ℃, 3 h.

2.2. Biology

2.2.1. Cell Culture and Adipocyte Differentiation

Mouse 3T3-L1 preadipocytes (ATCC CL-173, Manassas, VA, USA) were maintained in Dulbecco's modified Eagle's medium (DMEM, Gibco, Carlsbad, CA, USA) containing 10% (v/v) calf serum and antibiotics. For differentiation, cells at 2 days after reaching confluence were cultured in the medium comprising DMEM supplemented with 10% (v/v) fetal bovine serum (FBS), 10 μg/ml insulin, 0.5 mM 3-isobutyl-1-methylxanthine (IBMX) and 1 μM dexamethasone. After 2 days, the culture medium was changed to DMEM containing 10% FBS and 10 μg/ml insulin. The medium was replaced again with fresh DMEM containing 10% FBS after another 2 days. The adipocytes were used at 6 ~ 8 days after the initiation of differentiation.

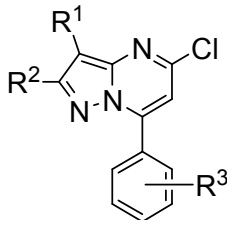
3. Results and Discussion

As a first approach, we explored the regiospecific synthesis of mono- aryl pyrazolo [1,5-α]pyrimidine analogs such as 5- and 7-arylpyrazolo [1,5-α]pyrimidines. We report here a novel regioselective synthetic route to 7-arylpyrazolo [1,5-α]pyrimidine as shown in Scheme 1 via a one-pot reaction. The reaction of 5-methyl-3-aminopyrazole (**3**) with ethyl 4-chlorobenzoylacetate (**4**) under acidic conditions afforded 5-(4-chlorophenyl) pyrazolo [1,5-α]pyrimidin-7-one (**5**), which was then treated with $POCl_3$ to afford a 5-(4-chlorophenyl)-2-methyl pyrazolo [1,5-α]pyrimidine analog (**7**). The reaction of **3** with **4** in pyridine afforded 7-(4-chlorophenyl)-2-methylpyrazolo [1,5-α]pyrimidin-7-one (**6**), which was then treated with $POCl_3$ to afford the 7-(4-chlorophenyl)pyrazolo [1,5-α]pyrimidine analog (**8**).

To optimize the reaction conditions, we preferentially examined the synthesis of 7-arylpyrazolo [1,5-α]pyrimidine obtained from the reaction of **3** with **4**. The synthetic pathways for the various pyrazolo [1,5-α]pyrimidine regioisomers are shown in Scheme 1. The key intermediates **5** and **6** were synthesized using a conjugate addition reaction under the various reaction conditions listed in Table 1. Under acidic conditions, product **7**, which contains an aryl group at the 5-position,was obtained in high yields (Table 1, entries 1 and 2). When a small amount of acid such as AcOH was added, products were obtained in low yields and with no regioselectivity (Table 1, entries 3 and 4). Under basic conditions, pyrazolo [1,5-α]pyrimidine **8**, which contains an aryl group at the 7-position, was obtained with high regioselectivity. Optimal results were achieved in pyridine at 90 ℃ for 12 h (90% yield).

The structures of **7** and **8** were confirmed from their ^{1}H and ^{13}C NMR spectra. Single crystals for X-ray diffraction analyses were obtained by there crystallization of

Table 2. Pyrazolo [1,5-α]pyrimidine Analogs Synthesized via Conjugate Addition under Basic Conditions



Compound	R^1	R^2	R^3	Yield (%)
9	H	Me	H	95
10	Ph	Me	H	80
11	4-MeOPh	Me	4-F	90
12	4-MePh	Me	4-F	85
13	2,4-ClPh	Me	4-F	73
14	4-ClPh	Me	2-Br	75
15	4-ClPh	Me	3-Br	81
16	4-ClPh	Me	4-Br	70
17	4-ClPh	Me	3-MeO	98
18	4-ClPh	Me	3,4-diMeO	90
19	4-ClPh	Me	4-CF3	85
20	4-ClPh	n-Pr	4-F	77
21	4-ClPh	n-Bu	4-F	84
22	4-ClPh	$MeOCH_2$	4-F	85
23	4-ClPh	$EtOCH_2$	4-F	85
24	4-MePh	Me	3-Furan	60

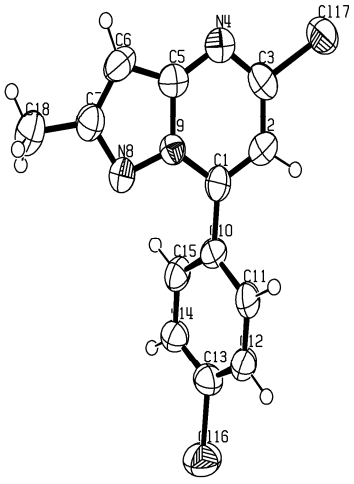


Figure 2. X-ray crystallographic analysis of **8**.

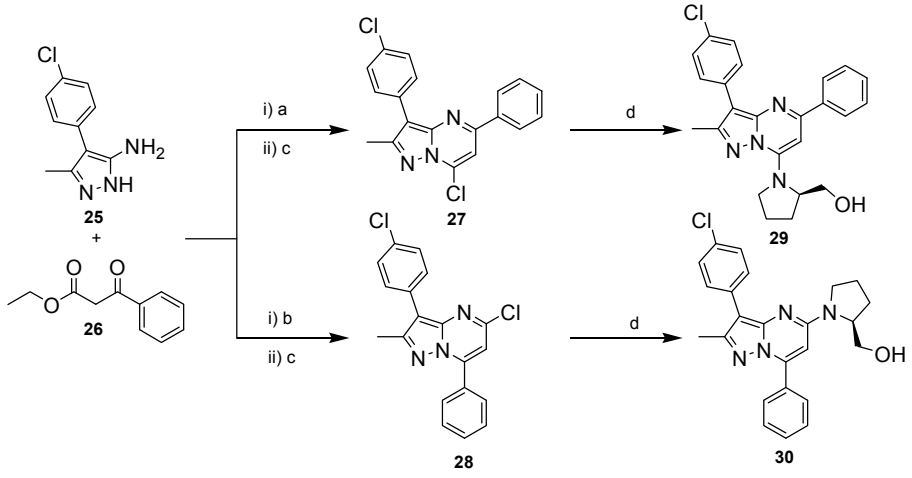
8 from ethanol. An ORTEP-3 representation of the X-ray crystal structure of **8** is shown in Figure 2.

To fully characterize our proposed method, we synthesized pyrazolo [1,5-α]pyrimidine analogs with various steric interactions by changing the substituents R^1, R^2 and R^3 by using different 3-aminopyrazoles as the starting materials. Table 2 lists the results. Among the 12 compounds containing a methyl group on R^2, compounds **9**–**19** were obtained in good to excellent yields (70 − 98%) with both electron-rich and electron-deficient R^3 substituents. Compounds with bulkyphenyl R1 substituents, such as 3- and 4-chlorophenyl, 4-methylphenyl, and 4-methoxyphenyl groups, were obtained in good to excellent yields. Compounds **19**–**23**, which contained alkylgroups of various lengths, such as methyl, propyl, butyl, methoxymethyl, and ethoxymethyl groups were also obtained in fair to excellent yields (77 − 85%). However, compound 24, which featured a heterocyclic 3-furan group at R^3, was obtained in poor yields (60%). Thus, various regioselective products were synthesized in fair to excellent yields, confirming that regioselectivity can be

Table 3. CB1 Inhibitory Activity of Pyrazolo [1,5-α]pyrimidines **29** and **30a–t**

Compound	R	IC_{50} (mM)[a]	Compound	R	IC_{50} (mM)[a]
29		<5%[b]	30k	3-Et	0.10
30a		0.09	30l	4-OMe	<5%[b]
30b	4-F	0.065	30m	3-OMe	0.2
30c	3-F	0.093	30n	2-OMe	0.79
30d	2-F	0.36	30o	4-Br	<5%[b]
30e	4-Me	<5%[b]	30p	3-Br	<5%[b]
30f	3-Me	0.21	30q	2-Br	<5%[b]
30g	2-Me	0.30	30r	4-Cl	0.35
30h	4-CF_3	<5%[b]	30s	3-Cl	0.10
30i	3-CF_3	0.10	30t	2-Cl	0.49
30j	2-CF_3	<5%[b]	Rimonabant		0.001

[a] Average value of at least two measurements
[b] % inhibition at 1 mM



Scheme 2 Reagents and conditions: (a) AcOH, 105 ℃, 3 h; (b) pyridine, 90 ℃, 12 h; (c) $POCl_3$, 80 ℃, 3 h; (d) *L*-prolinol, DIEA, 80 ℃, 1 h.

maintained with substituents sporting various steric and electronic effects.

The aminated products **29** and **30** were synthesized to confirm regioselectivity. Two synthetic routes (acidic and basic conditions) are shown in **Scheme 2**. The 3,5-diaryl intermediate **27** was synthesized by the addition of 4-(4-chlorophenyl)-5-methyl-*2H*-3-aminopyrazole **25** to ethyl benzoylacetate **26** under acidic conditions followed by chlorination with $POCl_3$. The amination of the key intermediate **27** with *L*-prolinol in diisopropylethylamine afforded compound **29** as the final product. Compound **30**, a pyrazolo[1,5]pyrimidine with a 3,7-diaryl moiety, was prepared by a condensation reaction under weakly basic conditions (pyridine), sequentially followed by chlorination and amination reactions. The structures of these aminated products were established by various NMR methods including ^{1}H-^{13}C correlation spectroscopy (COSY), hetero nuclear single-quantum correlation (HSQC), and hetero nuclear multiple-bond correlation (HMBC) analyses.

The synthesized pyrazolo [1,5-α]pyrimidine analogs

were tested for their ability to inhibit CB1. Table 3 lists the inhibitory activities.

Interestingly, among the regioisomers **29** and **30a**, **30a** was the only compound to exhibit significant CB1 inhibition (IC_{50} = 0.09 mM). 3,5-Diarylpyrazolo [1,5-α]pyrimidine (29) did not exhibit any CB1 antagonist activity. SAR studies of 3,7-diaryl-pyrazolo [1,5-α]pyrimidines were carried out using reactions of 4-chlorophenyl ketoester with various aryl aminopyrazoles. Our initial efforts focused on the optimization of substituents at the 7-aryl position.

Compounds with bulky substituents such as chlorine, bromine, and methoxy groups at the 7-aryl position did not exhibit any biological activity. Conversely, compounds with small substituents such as hydrogen and fluorine exhibited relatively high degrees of activity (**30a-c**). The *meta*-derivatives exhibited more activity than the *ortho*- and *para*-derivatives. Among these, compound **30b** had the highest degree of bioactivity (IC_{50} = 0.065 mM). These results demonstrate for the first time that non *cis*-diaryl pharmacophores behave as CB1 antagonists. Thus, the size and position of substituents in pyrazolo [1,5-α]pyrimidines significantly affects CB1 binding affinities.

In summary, a new series of pyrazolo [1,5-α]pyrimidines containing diaryl moieties at the 3,7-positions were synthesized under regioselective reaction conditions that involved a one-pot conjugate addition of aryl-3-aminopyrazoles to aryl ketoesters. This strategy resulted in excellent yields and regioselective products. Sterically hindered regioisomers, 3,7-diarylpyrazolo[1,5-α]pyrimidines and 3,5-diarylpyrazolo [1,5-α]pyrimidines, were successfully prepared under acidic and basic conditions, respectively. This report demonstrates an effective one-pot regioselective synthesis of 3,7-diaryl pyrazolo [1,5-α]pyrimidines. Moreover, the derivatives obtained were effective CB1 antagonists. These pyrazolo [1,5-α]pyrimidines with diaryl groups at the 3,7-positions are potential pharmacophores that are worthy of further testing for the treatment of obesity related metabolic diseases.

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