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Synthesis of novel 5-substituted pyrazole derivatives as cannabinoid antagonists

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Abstract—A facile seven-step sequence was developed from 4′-bromopropiophenone, utilizing a Suzuki-type coupling with an alkene, to give several novel 5-substituted pyrazole derivatives in overall yields of 11–31%. They are potent CB1 antagonists and have binding affinities similar to SR 141716A. Like SR 141716A, they may prove to be clinically useful for the treatment of obesity.

Great progress has been made in cannabinoid research since the Sanofi group's 1994 discovery[1] of the CB1 antagonist SR 141716A. This compound is a pyrazole derivative (Fig. 1) with substituents in the 1-, 3-, 4-, and 5-positions. The fact that it binds selectively to CB1 receptors without producing cannabimimetic activity in in vivo experiments in mice[2] suggests that the binding and activation of cannabinoid receptors are separable events. To examine this hypothesis we embarked on a program to synthesize cannabinoids with a pyrazole template and study their pharmacological properties.[3,4] In summary, we prepared SR 141716A analogs in which the 1-, 3-, 4-, and 5-positions of the pyrazole core were replaced by other substituents known to impart agonist activity in THCs (tetrahydrocannabinols). Our results suggested that the 3-position is involved in agonism and receptor activation whereas the 1-, 4-, and 5-positions seem to be involved with antagonism. They support the hypothesis that binding and activation are separate events and that the substituents at 1- and 5-positions are primarily responsible for the antagonist activity of SR 141716A. Further examination[4] of the 5-substituents revealed that the retention of the phenyl group is critical for both receptor affinity and antagonism since they decreased when the phenyl was replaced by an alkyl chain. It was also found that substitution of the *para*-position of the phenyl by an alkyl chain (pentyl) increased binding affinity and antagonism. Our structure activity relationships (SAR) studies were consistent with those of others[5–10] as discussed in our paper[4] and supported the molecular modeling studies of Thomas et al.[5,11] who had suggested a superpositioning of the *para*-position of the 5-substituent in SR 141716A with the pentyl side chain in Δ^9-THC. Based on these findings an analog (Fig. 1) with a *para*-pentylphenyl substituent at the 5-position, O-1302 (K_i = 2.1 ± 0.08 nM for CB1 receptors) was selected for further study. Previous work on the development of antagonists in our laboratory had shown that the alkyl side chain of Δ^8-THC has a fundamental effect on the pharmacological activity. It was found[12] that the side

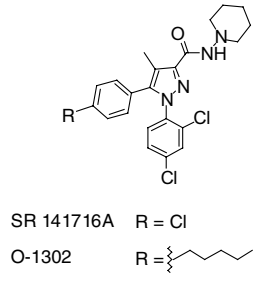

Figure 1. Structures of SR 141716A and O-1302.

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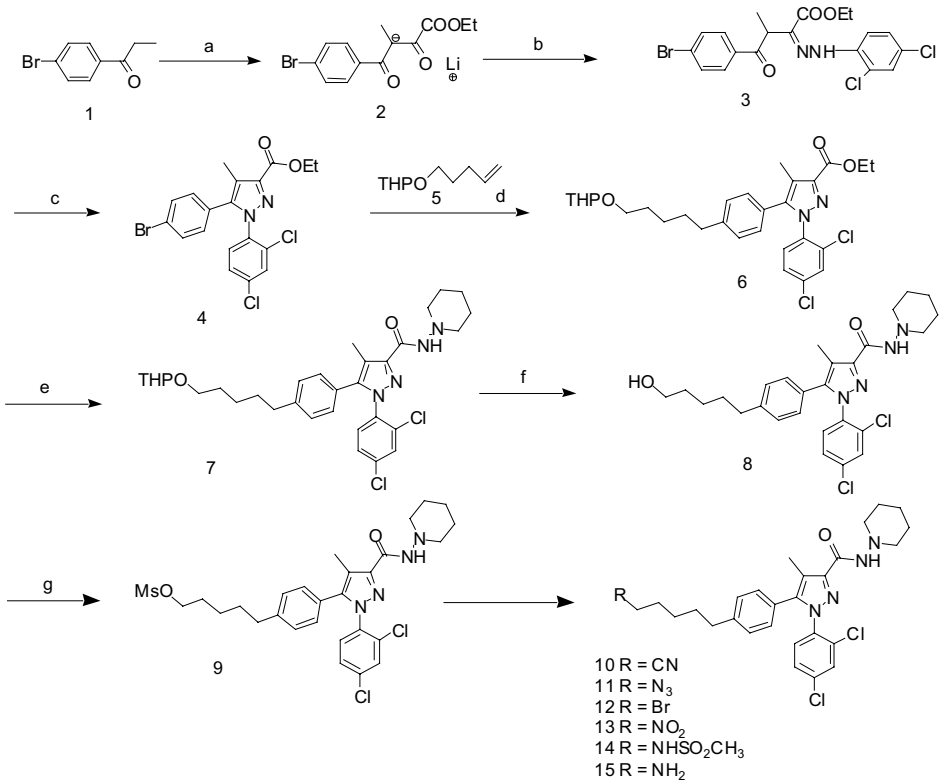
chain can be modified effectively to produce high affinity ligands at the CB1 receptor, with antagonist, partial agonist or full agonist effects. With this background we undertook to synthesize analogs of O-1302, which had various substituents at the terminal carbon of the pentyl chain. The importance of this class of compounds is enhanced by the reported success of SR 141716A (Romonabant) in Phase III clinical trials[13] for obesity. Another compound SLV 319, based on a closely related template (pyrazoline derivative) is also in Phase I trials for obesity.[14]

We have developed a flexible route to the synthesis of O-1302 analogs, which allows the introduction of a variety of substituents on the terminal carbon of the pentyl chain. The compounds prepared were **8** and **10**–**15** (Scheme 1). All the analogs except **15** (K_i = 38 nM) showed CB1 binding affinities in the range of 1–5.5 nM and some of the compounds (**8** and **10**–**12**) showed better CB2/CB1 selectivity (CB2/CB1 ratio, 64–137) than SR 141716A (K_i = 12 nM for CB1; K_i = 702 nM for CB2; CB2/CB1 ratio, 57).[15] The binding affinities were determined using the procedures described by us[4,15,16] elsewhere. A detailed pharmacological profile of these analogs as antagonists is ongoing and will be published elsewhere. In this paper the synthetic route to these analogs is presented.

The synthesis[17] of the target compounds **8** and **10**–**15** was achieved via the tetrahydropyranyl-carbethoxy derivative **6**, obtained by using a Suzuki-type coupling[18] of the alkene **5** (prepared from the commercially available 4-pentene-1-ol by treatment with dihydropyran/catalytic amount of HCl) with the known[6] pyrazole **4** (Scheme 1). Treatment of the ester **6** with a mixture of 1-aminopiperidine and trimethylaluminum[19] in CH_2Cl_2 formed the desired amide **7** in 78% yield. Other methods via the acid (acid chloride, mixed anhydride, DCC etc.) did not prove satisfactory. Deprotection (PTSA/methanol) followed by mesylation gave the key intermediate **9**. The seven-step sequence from **1** to **9** was achieved in an overall yield of 36%. The treatment of **9** with NaCN (DMF, 23 °C, 2 d)[20] formed the target compound **10** (63%). Similarly, treatment with NaN_3 or LiBr or $NaNO_2$ gave the respective compounds **11** (69%), **12** (70%), and **13** (30%). In the case of **13** a nitroso derivative was also isolated (35%) but it proved to be unstable. The sulfonamide analog **14** was also prepared (86%) from the mesylate **9** by treatment with $NaH/NH_2SO_2CH_3$ in DMF/benzene. The reduction of **11** with $LiAlH_4$ in THF formed the amine **15** (100%). The target compounds **10**–**15** were thus obtained from **1** in overall yields of 11–31%.

In summary, we have developed a facile seven-step sequence for the synthesis of the key intermediate **9** from commercially available 4′-bromopropiophenone (**1**) in an overall yield of 36%. This key intermediate was used to synthesize the novel 5-substituted pyrazole analogs **10**–**15**, which have CB1 binding affinities similar to SR



Scheme 1. (a) Reagents and conditions: (a) LiN($SiMe_3$), ether, 23 °C, 0.75 h; $(COOEt)_2$, 23 °C 16 h, 97%; (b) 2,4-dichlorophenyl hydrazine hydrochloride, ethanol, 23 °C, 16 h, 72%; (c) AcOH, reflux, 2 d, 99%; (d) **5**, 9-BBN, 23 °C, 16 h; K_3PO_4, $Pd(PPh_3)_4$, anhydrous dioxane, 120 °C, 2.5 d, 75%; (e) 1-aminopiperidine, Me_3Al, CH_2Cl_2, 1 h, **6**, CH_2Cl_2, 23 °C, 2 d, 78%; (f) PTSA, overall yield to **9** = 36% and to target compounds **10**–**15** = 11–31%.

141716A and are presently undergoing pharmacological study as antagonists of CB1 receptors like SR 141716A. They may prove to be clinically useful for the treatment of obesity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.01.165.

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17. All new compounds were fully characterized. ^{1}H NMR spectra were recorded on a JEOL Eclipse 300 spectrophotometer using $CDCl_3$ as the solvent with tetramethylsilane as an internal standard. Similarly, ^{13}C NMR were recorded at 75 MHz using $CDCl_3$. Mass spectra were obtained with Agilent 1100 Series LC/MSD spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and were found to be within ±0.4% of calculated values. The data for target compound **10** is included as an example; oil: ^{1}H NMR δ 7.65 (s, 1H), 7.42 (dd, 1H, J = 1.7, 0.8 Hz), 7.27 (m, 2H, J = 1–3 Hz), 7.10 (d, 2H, J = 8.1 Hz), 7.02 (d, 2H, J = 8.1 Hz), 2.34 (t, 2H, J = 7.0 Hz), 2.87 (br t, 4H, J = 5.5 Hz), 2.60 (t, 2H, J = 7.6 Hz), 2.37 (s, 3H), 1.75 (quint, 4H, J = 5.5 Hz), 1.66 (m, 2H), 1.64 (m, 2H), 1.48 (m, 2H), 1.44 (m, 2H); ^{13}C NMR δ 160.1, 144.3, 144.0, 142.5, 136.3, 135.6, 133.1, 130.6, 130.1, 129.4, 128.4, 127.7, 126.2, 119.6, 117.8, 57.0, 35.3, 30.1, 28.3, 25.1, 25.4, 23.3, 17.0, 9.4. MS, *m/z*: 524 (M+1). Anal. Calcd for $C_{28}H_{31}Cl_2N_5O{\cdot}0.1EtOAc$: C, 63.96; H, 6.01; N, 13.13. Found: C, 63.99; H, 6.14; N, 12.99. The presence of the solvent was confirmed by ^{1}H NMR.
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