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Synthesis of the 7-Azaindole (1*H*-Pyrrolo[2,3-*b*]pyridine) Analogous to Cannabimimetic JHW 200

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Abstract: Cannabinoid agonists have been suggested to have potential therapeutic uses. The synthesis of a new cannabimimetic analogue of JHW 200 possessing a 7-azaindole unit instead of an indole moiety is described. The approach used for indole derivatives failed, and a new strategy that involves the reaction of a nitrile and 1-naphtyl magnesium bromide was studied.

Keywords: Amino-alkyl-indole, 7-azaindole, cannabimimetic, Grignard condensation

INTRODUCTION

For thousands of years, preparations of the plant *Cannabis sativa* have been used not only for recreational purposes but also in traditional medicinal chemistry.[1] Following the identification of Δ^9-tetrahydrocannabinol[2] (Δ^9-THC) (**1**) (Fig. 1),

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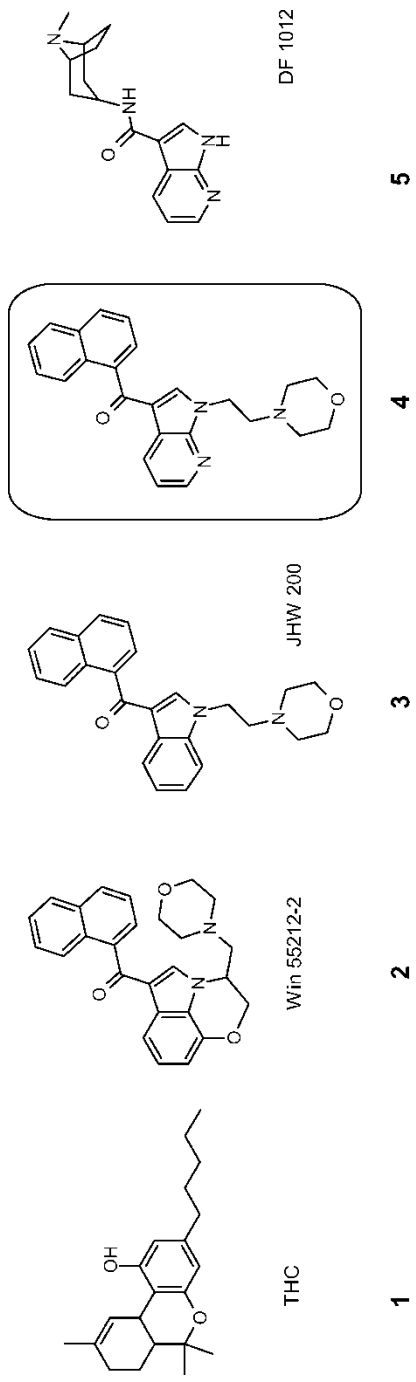


Figure 1. Structure of compounds.

one of the most psychoactive components of marijuana, a large range of new structures binding to cannabinoid receptors have been reported.[3–5] The cannabinoid ligands may be useful agents to treat some disorders such as chronic inflammatory disease,[5] obesity[6] (the CB1 antagonist SR 141716 is actually under clinical trials), Parkinson's disease,[7] and cancer.[8]

Among the nonclassical cannabinoids, we particularly are interested in the class of amino-alkyl-indoles (AAI). This class of compounds was reported in 1992,[9] and one of the most studied compound is WIN 55212-2 (**2**). Less rigid analogues of (**2**), JHW compounds,[5] were then considered for their ability to bind to cannabinoid receptors. In our research to find new cannabinoid agonists, JHW 200[5] (**3**) (CB1 $K_i = 42$ nM) was used as a reference compound.

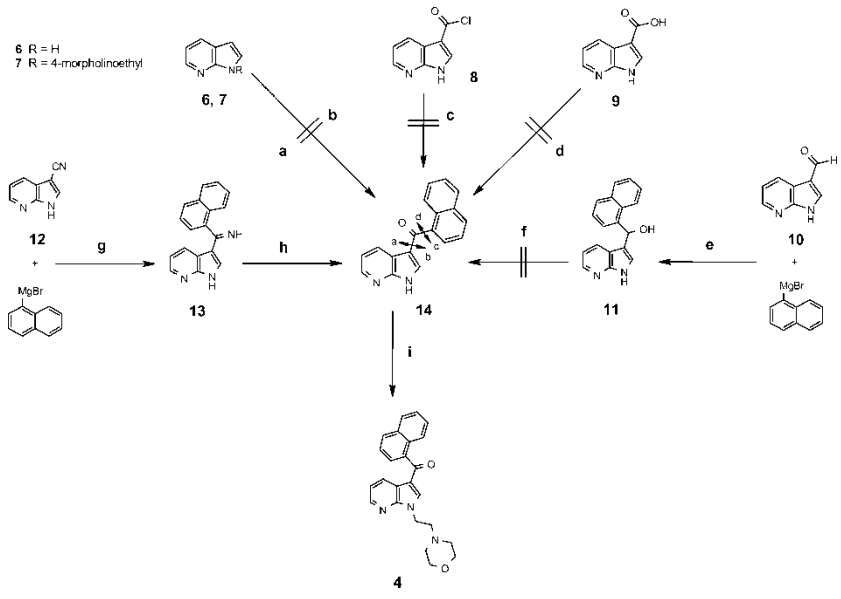
On the other hand, azaindoles have been the subject of investigations in medicinal chemistry because they are considered indole bioisosters.[10–12] They are potential pharmaceuticals agents.[10] For example, DF 1012 (**5**) (7-azaindolylcarboxy-*endo*-tropanamide),[13] an antitussive candidate drug, is actually under investigation in phase II clinical trials. Moreover, recent reports show great interest in replacing the indole ring with a 7-azaindole unit in isogranulatimide[11] and staurosporine analogues[12] designed to increase the interactions with the target enzyme(s).

In this article, we report the synthesis of {1-(2-morpholin-4-yl-ethyl)-1H-pyrrolo[2,3-*b*]pyridin-3-yl}-naphthalen-1-yl-methanone (**4**), an analogue of the cannabimimetic JHW 200 (**3**) possessing a 7-azaindole moiety instead of the indole moiety.

RESULTS AND DISCUSSION

To access AAI, Eisenstat et al.[14] proposed two main approaches: in the first one, the indole anion (obtained from ethyl-magnesium bromide and indole) reacts with an excess of 1-napthoyl chloride. This strategy was not efficient (**a**, Scheme 1) with 7-azaindole (**6**). The AAI have also been prepared another way, using Friedel–Crafts acylation of indole. Moreover, Zang et al.[15] reported good yields in the reaction of 7-azaindole with a large range of acyl chlorides, but in our hands 7-azaindole (**6**) and its 1-alkyl derivative (**7**) do not react with 1-naphtoyl chloride (**b,** Scheme 1). This 1-alkyl derivative (**7**) resulted from the reaction of N-(2-chloroethyl)morpholine hydrochloride with the 7-azaindole anion obtained from compound (**6**) and sodium hydride. The lack of reactivity of the 3-position of the 7-azaindole compared to the same position of the indole, implied in these two procedures, is probably due to the withdrawing effect of the pyridyl nitrogen atom.

The Suzuki coupling often offers a good method to obtain aryl ketones. Unfortunately, the palladium-catalyzed coupling of 1-naphtylboronic acid with 7-azaindol-3-carboxylic acyl chloride (**8**)[13–16] (**c**[17], Scheme 1) or



Scheme 1. Strategies used to obtain compound (**4**): Reagents and conditions: (**a**) 1) EtMgBr 2) 1-Napthoyl chloride, ether, rt, 1 h. (**b**) $AlCl_3$ (3 equiv.), CH_2Cl_2, rt, 1 h. (**c**) 1-Naphthylboronic acid, Cs_2CO_3, $Pd(PPh_3)_4$, toluene, 100°C, 16 h. (**d**) 1-Naphthylboronic acid, pivalic anhydride, $Pd(OAc)_2$, diphenyl(ferrocenyl)phosphane (DPPF), THF, 60°C, 16 h. (**e**) THF, reflux, 2 h, 45%. (**f**) Pyridinium dichromate, CH_2Cl_2. (**g**) THF, reflux, 2 h, 45%. (**h**) H_2SO_4 (1M), reflux, 2 h, 85%. (**i**) 1) NaH, DMF, 0°C, 30 min, 2) N-(2-chloroethyl)morpholine hydrochloride, DMF, 60°C, 6 h, 85%.

7-azaindol-3-carboxylic acid (**9**)[13–16] (**d**[18], Scheme 1) does not yield the desired compound.

We then investigated a Grignard approach to (**14**). Reactions of acyl chlorides or carboxylic esters with organometallic reagents led to poor yields of ketones, due to the difficulty of stopping the ketone from being converted into the tertiary alcohol. We have used two other pathways to obtain the compound (**14**). Addition of 1-naphtyl magnesium bromide on 3-formyl-7-azaindole (**10**) (obtained in 50% yield from 7-azaindole according the Robinson's procedure[16]) led to the secondary alcohol (**11**) in 45% yield. Attempts to oxidate the secondary alcohol (**11**) (**f**, Scheme 1) via pyridinium dichromate were unsuccessful, whereas 3-acetyl-7-azaindole was obtained in good yield from 3-(2-hydroxyethyl)-7-azaindole.[19] The use of different solvents, glacial acetic acid, or other oxidation methods (Swernoxydation) did not improve this result.

Lastly, the reaction of 1-naphtyl magnesium bromide with 3-cyano-7-azaindole (**12**) afforded the corresponding imine (**13**) with fairly good yield

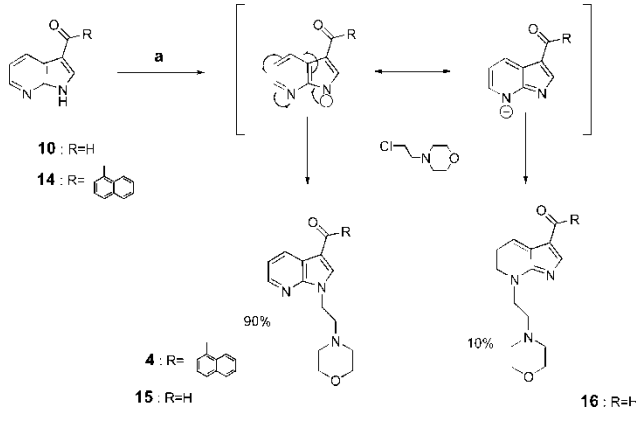
(45%). 3-Cyano-7-azaindole (**12**) can be obtained from 3-formyl-7-azaindole (**10**) according to Robinson's method in two steps[16] with poor yields. Alternatively, (**12**) was prepared in four steps from succinonitrile.[13] The imine (**13**) was easily hydrolyzed with diluted sulfuric acid into the corresponding ketone (**14**). Compound (**14**) was then alkylated as described for (**7**). N-Alkylation of the 7-azaindole anion was performed in an aprotic solvent (DMF) and at low temperature to avoid N-alkylation on the pyridine ring. Literature[10] showed that 7-azaindole is alkylated on the pyridyl nitrogen atom ring by heating. The analysis of the crude alkylation product of (**14**) showed the presence of another product (10%): this nonisolated product might be the 7-alkylated compound, as obtained and characterized in the alkylation crude of 3-formyl-7-azaindole (**10**) (Scheme 2) beside the main 1-alkylated compound.

In conclusion, the synthesis of an analogue of JHW 200 with a 7-azaindole moiety is described. The preparation of others analogues with a 5-azaindole moiety are in progress. Biological properties of these compounds, especially their ability to bind to cannabinoid receptors, will be evaluated.

EXPERIMENTAL

Apparatus and Procedures

^{1}H and ^{13}C NMR spectra were recorded on a AC-300 Bruker instrument. Column chromatography was performed on Merck silica gel (0.040–0.063 mm). IR spectra were recorded on a Brucker Vector 22



Scheme 2. Mechanism of the N-alkylation of the 3-formyl-7-azaindole (**10**): Reagents and conditions: (**a**) 1) NaH, DMF, 0°C, 30 min, 2) N-(2-chloroethyl)morpholine hydrochloride, DMF, 60°C, 6 h.

instrument. APCI$^+$ (atmospheric pressure chemical ionization) mass spectra were obtained on a LC-MS system Thermo Electron Surveyor MSQ.

4-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-1-yl)ethyl]morpholine (7). A solution of 7-azaindole (**6**) (1 g, 8.5 mmol) in DMF (7 mL) was added under nitrogen to a cooled (0°C) suspension of sodium hydride (1.24 g, 31 mmol; 60% in mineral oil) in anhydrous DMF (7 mL). The resulting mixture was stirred for 30 min. N-(2-Chloroethyl)morpholine hydrochloride (2.15 g, 11.5 mmol) was added, and the resulting solution was stirred at 50°C for 6 h. After cooling at room temperature, 4 mL of water were added; the mixture was filtered and the residue washed with DMF. The solution was concentrated, and the product was purified by column chromatography [$CHCl_3$/EtOH: 8/2 (v/v)] to give (**7**) as a yellow oil (1.27 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (m, 4H), 2.73 (t, 2H, $J = 6.7$ Hz), 3.62 (m, 4H), 4.40 (t, 2H, $J = 6.7$ Hz), 6.40 (d, 1H, $J = 3.6$ Hz), 7.00 (dd, 1H, $J = 8.0$, 4.9 Hz), 7.25 (d, 1H, $J = 3.6$ Hz), 7.85 (dd, 1H, $J = 8.0$, 1.5 Hz), 8.28 (dd, 1H, $J = 4.9$, 1.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.6, 53.6, 58.2, 66.9, 99.4, 115.6, 120.5, 128.4, 128.7, 142.6, 147.4; LC/MS m/z 232 (MH^+, 95%).

[1-(2-Morpholinoethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl](1-naphthyl)methanol (11). A solution of 1-bromonaphthalene (1.41 g, 6.8 mmol) in THF (2 mL) was slowly added to a stirred suspension of magnesium (0.16 g, 6.8 mmol) in anhydrous THF (5 mL). After refluxing 2 h, the mixture was cooled to room temperature and a solution of 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (**10**) (0.2 g, 1.3 mmol) in hot THF (5 mL) was slowly added and refluxed for 2 h. Water (2 mL) was added; the precipitate was filtered and washed with THF. The solution was concentrated; water (10 mL) and Et_2O (10 mL) were added. The precipitate was collected by filtration, washed with Et_2O, and dried to give (**11**) as a white solid (0.16 g, 45%), mp 127°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.9 (d, 1H, $J = 4.4$ Hz), 6.65 (d, 1H, $J = 4.4$ Hz), 6.95 (dd, 1H, $J = 7.7$, 4.6 Hz), 7.20 (d, 1H, $J = 2.2$ Hz), 7.4 (m, 2H), 7.55 (t, 1H, $J = 7.4$ Hz), 7.82 (d, 2H, $J = 8.0$ Hz), 7.9 (d, 2H, $J = 7.7$ Hz), 8.15 (dd, 1H, $J = 4.4$, 1.4 Hz), 8.2 (d, 1H, $J = 7.4$ Hz), 11.45 (bs, 1H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 66.3, 115.0, 117.7, 118.2, 123.8, 124.2, 125.3, 125.6, 127.4, 128.4, 130.3, 133.4, 140.3, 142.4, 148.7; LC/MS m/z 275 (MH^+, 98%).

1-(2-Morpholinoethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (15) and 7-(morpholinoethyl)-7*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (16). These compounds were obtained according to the same chemical procedure described for compound (**7**) using compound (**10**) as the starting material. The crude product was purified by column chromatography [$CHCl_3$/EtOH: 8/2 (v/v)] to afford two isomers.

1-(2-Morpholinoethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (**15**) as an oil (0.36 g, 69%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (m, 4H), 2.76

(t, 2H, $J = 6.2$ Hz), 3.62 (m, 4H), 4.4 (t, 2H, $J = 6.2$ Hz), 7.19 (dd, 1H, $J = 8.1$, 4.7 Hz), 7.95 (s, 1H), 8.33 (dd, 1H, $J = 4.7$, 1.6 Hz), 8.46 (dd, 1H, $J = 8.1$, 1.6 Hz), 9.90 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 42.0, 53.6, 57.8, 66.9, 116.2, 117.5, 118.8, 130.4, 138.9, 144.8, 148.4, 184.6; LC/MS m/z 260 (MH^+, 98%).

7-(Morpholinomethyl)-7*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (**16**) as an oil (0.054 g; 10%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49 (m, 4H), 2.95 (t, 2H, $J = 6.0$ Hz), 3.62 (m, 4H), 4.81 (t, 2H, $J = 6$ Hz), 7.16 (dd, 1H, $J = 7.6$, 6.4 Hz), 7.87 (d, 1H, $J = 6.4$ Hz), 8.38 (s, 1H), 8.81 (d, 1H, $J = 7.6$ Hz), 9.97 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.7, 53.6, 57.1, 66.8, 113.4, 119.2, 126.8, 132.7, 134.5, 151.4, 155.8, 184.8; LC/MS m/z 260 (MH^+, 97%).

1-Naphthyl(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methanimine (13). This compound was obtained according to the same chemical procedure described for compound (**11**) using compound (**12**) as the starting material. The crude product obtained from 1-bromonaphtalene and 1*H*-pyrrolo[2,3-*b*] pyridine-3-carbonitrile (**12**) was treated after evaporation of THF by a diluted solution of hydrochloric acid. The acidic aqueous layer was washed with Et_2O (3 × 15 mL) and treated by a solution of sodium hydroxide until it reached pH 9. The precipitate was collected by filtration, washed with water, and dried to give (**13**) as a white solid (0.17 g, 45%), mp 138 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.40 (bs, 1H), 7.15 (m, 2H), 7.50 (m, 4H), 7.80 (d, 1H, $J = 7.7$ Hz), 7.90 (d, 1H, $J = 8$ Hz), 8.05 (d, 1H, $J = 7.7$ Hz), 8.30 (d, 1H, $J = 4.4$ Hz), 8.50 (d, 1H, $J = 7.4$ Hz), 10.9 (bs, 1H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 114.9, 117.1, 124.6, 125.2, 125.4, 126.2, 126.6, 128.3, 128.6, 129.9, 130.1, 132.6, 133.2, 139.0, 143.7, 150.1, 170.7; LC/MS m/z 272 (MH^+, 96%).

Naphthalen-1-yl-(1H-pyrrolo[2,3-*b*]pyridin-3-yl)methanone (14). A mixture of the imine (**13**) (0.16 g, 0.59 mmol) in diluted sulfuric acid 1 M solution (15 mL) was refluxed for 2 h. The solution was cooled at room temperature, diluted with water (10 mL), and filtered. A concentrated solution of sodium hydroxide was added until precipitation. The precipitate is collected by filtration, washed with water, and dried to give (**14**) as a white solid (0.072 g, 45%), mp 125°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.30 (m, 1H), 7.55 (m, 3H), 7.75 (m, 1H), 7.85 (m, 1H), 8.05 (m, 3H), 8.35 (m, 1H), 8.55 (m, 1H), 12.65 (bs, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 115.8, 118.4, 124.9, 125.2, 126.2, 126.3, 126.9, 128.3, 129.8, 130.1, 133.4, 136.8, 137.6, 144.7, 149.3, 191.4; LC/MS m/z 273 (MH^+, 98%).

[1-(2-Morpholinoethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl](1-naphthyl)methanone (4). This compound was obtained according to the same chemical procedure described for compound (**7**) using compound (**14**) as the starting material. The crude product obtained from (**14**) was treated after evaporation of THF by a diluted solution of hydrochloric acid. The acidic aqueous layer

was washed three times with $CHCl_3$ and treated with a solution of sodium hydroxide until it reached pH 9. The precipitate was extracted with ether; the organic layers were dried and concentrated to afford a brown oil, which was purified by column chromatography [$CHCl_3$/EtOAc: 5/5 (v/v)] to give (**4**) as a yellow oil (0.085 g, 85%). IR (neat): 2960, 1630, 1695, 1115 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (m, 4H), 2.70 (t, 2H, $J = 6.1$ Hz), 3.45 (m, 4H), 4.35 (t, 2H, $J = 6.1$ Hz), 7.35 (m, 1H), 7.45 (m, 3H), 7.65 (m, 2H), 7.9 (m, 2H), 8.15 (m, 1H), 8.4 (m, 1H), 8.7 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.6, 53.4, 57.7, 66.8, 115.7, 118.8, 119.3, 124.4, 125.7, 126.0, 126.4, 126.9, 128.3, 130.4, 130.7, 131.1, 133.8, 138.2, 138.8, 144.5, 148.3, 192.0; LC/MS m/z 386 (MH^+, 100%).

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