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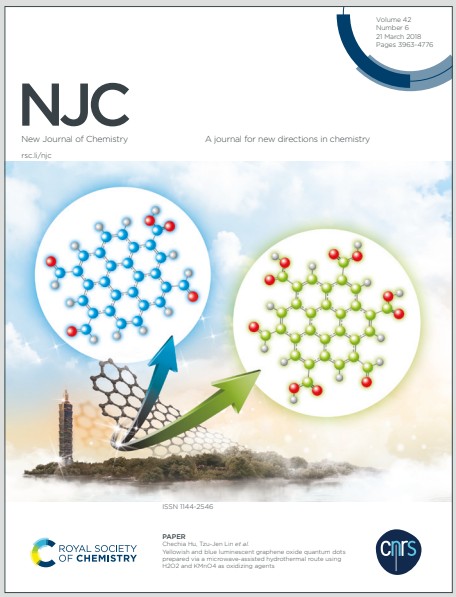

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New synthesis of N1- and N2-substituted pyrazolo[4,3-*b*]pyridine-5-one derivatives as CB2 receptor ligands

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Derivatives of 7-hydroxy-5-oxopyrazole[4,3-*b*]pyridine-6-carboxamide scaffold have been reported recently as potent and selective agonists/inverse agonists of the cannabinoid type-2 receptor (CB2R), but the synthetic way adopted has not yet allowed to explore fully the structure-activity relationship. Herein, we describe a novel synthetic approach, based on the use of a 2-tetrahydropyranyl(THP)-protected precursor, that has open the way to obtain either N1- or N2-substituted analogs endowed with agonist or inverse agonist activity, respectively, at CB2 receptor.

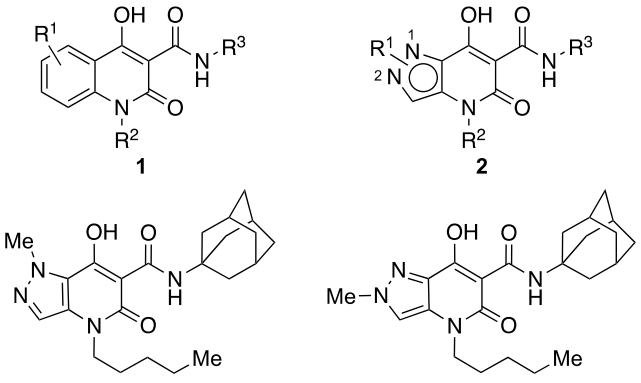
Introduction

The main receptors of the endocannabinoid system that have been identified so far are type-1 cannabinoid receptor (CB1R) and type-2 cannabinoid receptor (CB2R).[1,2] During the last decades, several pharmaceutical companies and academic research laboratories have shown a particular interest in the development of new selective agonists or inverse agonists of cannabinoid receptors as potential therapeutic agents for different conditions. In particular, CB2R agonists have been proposed as therapy for diverse pain conditions, including acute pain, chronic inflammation, and neuropathic pain, which does not cause overt psychotropic effects as CB1R activation does.[3,4] Furthermore, CB2R agonists could be helpful for the treatment of neurodegenerative and neuroinflammatory diseases, such as amyotrophic lateral sclerosis, Huntington's chorea and cerebellar ataxia.[5] Recently, several compounds with excellent *in vitro* activities have been described, some of which have passed the preclinical evaluation and have entered clinical trials.[6,7] On the other hand, CB2R-specific inverse agonists have been shown to modulate the migration of immune cells *in vivo* and promise to lead to the identification of immunomodulatory agents.[8]

Our research group has been working for several years on the design and synthesis of new quinolone derivatives, with the goal of identifying increasingly potent and selective CB2 ligands (e.g. compounds **1**) endowed with improved physicochemical properties.[9] As a recent development of this research, it is worth mentioning the isosteric replacement-based approach of the benzene ring of **1** with the pyrazole nucleus, generating a new class of compounds, namely the 7-hydroxy-5-oxopyrazolo[4,3-*b*]pyridine-6-carboxamide derivatives (**2**), whose structure is shown in Figure 1. As far as structure-activity relationships are concerned, the R^1 substituent on the pyrazole ring is decisive for the functional activity of the compounds, as the derivatives substituted at N1 activate the CB2 receptor, thereby acting as agonists, while the isomers substituted at N2 show a different profile, being inverse agonists or antagonists at the same receptor.[10]

Among the various synthesized molecules, compounds **2a** and **2b** (also referred to as COR1023 and COR1022, respectively) (Figure 1) stand out as new cannabinoid ligands, displaying in *in vitro* studies high binding affinity for the CB2R, with K_i values of 0.18 ± 0.01 nM and 0.9 ± 0.1 nM, respectively. In addition, COR1022 and COR1023 exhibited a receptors selectivity index (SI = K_iCB1R/K_iCB2R) of 167 and 62, respectively.[10]

Figure 1. General structure of 4-hydroxy-2-quinolone-3-carboxamide derivatives **1** and 7-hydroxy-5-oxopyrazolo[4,3-*b*]pyridine-6-carboxamide derivatives **2** along with structure of representative compounds **2a** and **2b**.



Compounds **2** had been prepared through a multistep synthesis,[10] which involved the early introduction of R^1 on the pyrazole ring and offered the possibility to mainly investigate the influence of the R^3 substituent, *i.e.* the amide portion of the molecules, on biological activity. However, this synthetic approach does not seem to be flexible enough if we want to study the pharmacophoric role of the other substituent R^1, as the alkylation of the pyrazole nitrogen at an early stage gives predominantly the N2-substituted isomer and, not less importantly, chemical diversity on the pyrazole moiety can only be obtained by starting a new synthesis every time.

Based on these observations, the aim of this work was to develop a more versatile synthesis of 7-hydroxy-5-oxopyrazole [4,3-*b*]pyridine-6-carboxamide derivatives (**2**) that would allow to explore the chemical space around the pyrazole nucleus by varying the substituent R^1, keeping the central core and the amide functionality unchanged. Consequently, this work

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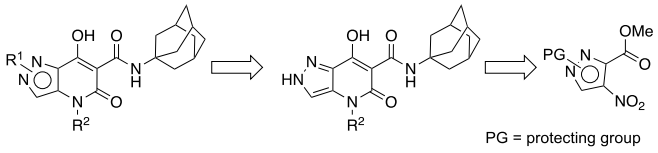
involved the selection of a protecting group for the pyrazole ring which can be easily inserted at the beginning and removed at an advanced stage of the synthetic sequence. This approach would offer the possibility of increasing the chemical diversity at the level of this ring through the introduction of a variety of R^1 substituents, a result that cannot be pursued with a chemical synthesis that starts from a pyrazole irreversibly alkylated at the nitrogen atom (Scheme 1).

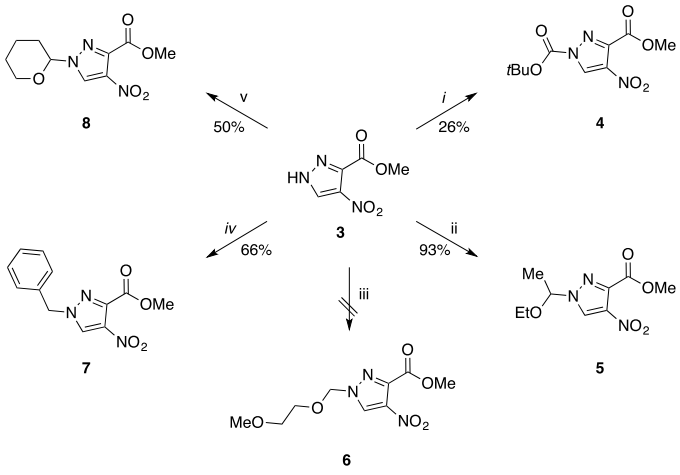
Scheme 1. Retrosynthetic analysis for the preparation of 7-hydroxy-5-oxopyrazole[4,3-*b*]pyridine-6-carboxamide scaffold variously functionalized at N1 and N2.



Results and Discussion

The first point we addressed was the selection of a suitable protecting group (PG) for the pyrazole nitrogen of compound **3** (Scheme 2: for sake of simplicity, only the predominant N2-regiosomers are shown).

Scheme 2. Selection of possible protected precursors.



Reagents and conditions: i) Boc_2O, Et_3N, dry THF, RT, overnight; ii) ethyl vinyl ether, *p*-toluenesulfonic acid, dry DCM, r. t., 2 h; iii) MEM chloride, K_2CO_3, acetone, reflux, overnight; iv) benzyl *p*-toluenesulfonate, K_2CO_3, acetone, r. t., 5 h; v) 3,4-dihydro-2*H*-pyran, *p*-toluenesulfonic acid, DCM, r. t., 2 h. For sake of simplicity, only the main N2-regiosomers are shown.

In particular, we were looking for a PG that could tolerate all the experimental conditions employed during the whole synthetic sequence and be easily removed at the end, so as to give us the possibility to introduce a variety of alkyl chains as replacement of the methyl group present in our prototypes **2a** and **2b**. The first PG we tried was the tert-butoxycarbonyl (BOC) group, which was inserted in position 2 of the pyrazole ring through the reaction of **3** with *di-tert*-butyl dicarbonate (Boc_2O) and Et_3N in dry THF. However, this reaction did not go to completion and the desired product **4** was isolated in low yield (25%) after trituration with petroleum ether.

In a second attempt, we used ethyl vinyl ether to obtain compound 5. The reaction was conducted in dry DCM with ethyl vinyl ether and *p*-toluenesulfonic acid and **5** (racemic) was obtained in high yield (94%) but it looked like a dark oil which underwent rapid degradation.

Another PG we considered was the 2-methoxyethoxymethyl (MEM) group, by alkylating compound **3** with MEM chloride and K_2CO_3 in acetone, but the reaction did not lead to the expected result, giving rise to a complex mixture that was not possible to purify with the available purification methods and therefore the formed compound **6** could not be isolated.

After these discouraging results, other routes that might prove to be more practical were explored. Thus, the benzyl group was considered as a possible PG for pyrazole. When **3** was reacted with benzyl *p*-toluenesulfonate in the presence of K_2CO_3 in acetone, compound **7** (racemic) was obtained as a light yellow solid in good yield (66%) after chromatographic purification. To test a further possibility, 3,4-dihydro-2*H*-pyran (DHP) was taken into consideration. By treating **3** with DHP and *p*-toluenesulfonic acid in DCM, the reaction was complete in 2 h providing **8** as a colorless stable oil in 50% yield after purification by flash column chromatography. Although the alkylation reactions on the pyrazole nitrogen often gives rise to mixtures of regioisomers,[10,11] the THP-protected compound was obtained as a single isomer, which was assigned the structure of N2-substituted isomer **8** on the basis of 2D-NOESY experiments, that showed NOE correlations between H1 proton of the THP ring and the aromatic proton of the pyrazole (Figures 2).

In order to test which of the protected compounds **7** and **8** would be the most reliable for the whole synthetic sequence, we designed simplified compounds which could serve as models for the critical deprotection step. To this end, **7** and **8** were both reduced to the corresponding amines **9** and **10** and then converted into the corresponding amides **11** and **12**, respectively, with *p*-toluoyl chloride in dry DCM (Scheme 3).

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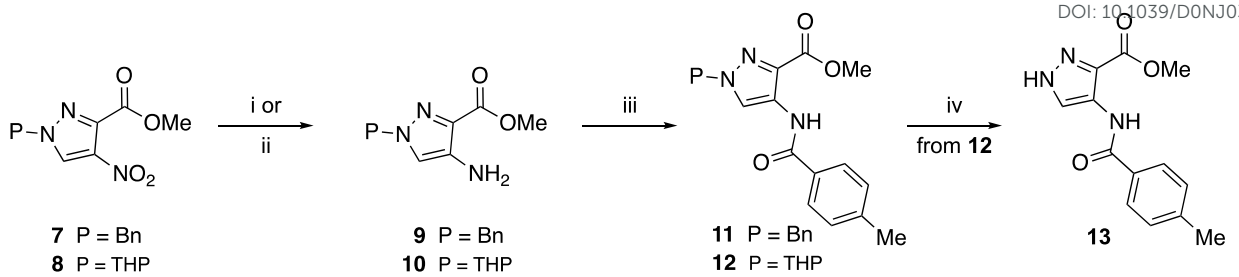
Scheme 3. Synthesis and evaluation of the deprotection procedure of the model compounds **11** and **12.**



7 P = Bn
8 P = THP
9 P = Bn
10 P = THP
11 P = Bn
12 P = THP
13

Reagents and conditions: i) for **7**: Fe^0 powder, $CaCl_2$, EtOH, H_2O, 60 °C, 2 h; ii) for **8**: 10% Pd/C, ammonium formate, EtOH, H_2O, 50 °C, 1 h; iii) *p*-toluoyl chloride, Et_3N, DMAP, dry DCM, r. t., 50 min; iv) *p*-toluenesulfonic acid, MeOH, r. t., overnight.

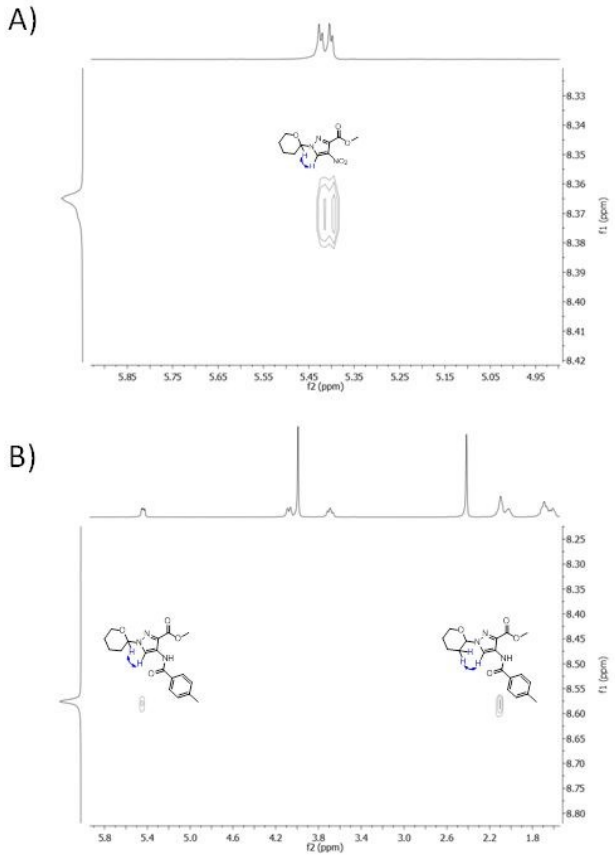


Figure 2. $^1H–^1H$ NOESY spectra of A) compound **8** and B) compound **12** registered in $CDCl_3$.

As a result, **11** appeared as a white solid, insoluble in most organic solvents, thus hampering the execution of deprotection procedures, whereas compound **12** was easily deprotected with *p*-toluenesulfonic acid in MeOH so as to get **13** in 93% yield and with no need of purification. In agreement with what observed for compound **8**, the presence of THP group on the N2 was confirmed by 2D NOESY spectra also on compound **12** (Figure 2). Accordingly, we selected the THP-protected compound **10** as the starting point for the preparation of the desired N1- and N2-substituted compounds.

The target 7-hydroxy-5-oxopyrazolo[4,3-*b*]pyridine-6-carboxamide derivatives were prepared through a multistep synthesis, starting with an *N*-alkylation reaction of compound **10** (Scheme 4). The insertion of an *N*-alkyl chain on the amine in position 4, either by direct alkylation or reductive amination procedure resulted unsuccessful, due to the exclusive or predominant formation of the *N,N*-dialkylated product, likely due to the higher nucleophilic reactivity of secondary amines (generated in the reaction mixture by the first *N*-alkylation) compared to primary ones. For the preparation of compounds **2a**,**b**, [10] this alkylation reaction was best performed in DMF as the solvent and in the absence of any added base, because the initially formed monoalkylated compound, being also the most basic species present in solution, preferentially acted as scavenger for the produced HX acid. As a result, protonation made the monoalkylated compound less nucleophilic and allowed a more selective conversion of the primary amine into the corresponding secondary amine, by reducing the possibility of formation of the dialkylated product. On the other hand, the alkylation reaction of **10**, protected with the acid-sensitive THP group, was not possible in the absence of a base. Thus, assuming that the use of a secondary alkyl halide would avoid the formation of dialkylated compounds for steric reasons, a modified procedure was adopted, using 2-iodopropane as alkylating agent, propionitrile as solvent, and K_2CO_3 as base to neutralize the hydrogen iodide which formed during the reaction, and hence prevent the THP removal. Under these conditions, compound **14** could be isolated in satisfactory 64% yield, while tertiary alkylating agents - as expected - proved to be completely unreactive. Accordingly, we put aside the idea of making structural changes in position 4 and limited ourselves to introduce an isopropyl chain on the nitrogen atom. By reaction with methyl 3-chloro-3-oxopropionate and Et_3N in dry DCM, **14** was converted into the amide derivative **15**, that was subjected to Dieckmann condensation by reaction with NaH and dry MeOH (catalytic amount) in dry THF. The bicyclic 4-hydroxypyrazolo[4,3-*b*]pyridine-2-one derivative **16** thus obtained was treated with 1-aminoadamantane in toluene/THF as solvent to afford **17**. Finally, the amide **17** was treated with *p*-toluenesulfonic acid in MeOH to deprotect the pyrazole nitrogen, leading to the compound **18** with a 67% yield after purification by flash column chromatography (Scheme 4).

The deprotected product **18** was the starting point for studying the substitution of the pyrazole ring with the introduction of a variety of alkyl/aralkyl chains (Scheme 4 and Table 1). Compounds **19-22** were prepared in good to excellent overall yield (60-99%) starting from **18** by alkylation reactions

performed by using the appropriate alkylating agent, K_2CO_3 as base, and acetone as solvent. To test a different alkylation procedure, compounds **23** and **24** were obtained by phase-transfer catalyzed reactions, using 50% NaOH/DCM and tetrabutylammonium bromide as catalyst. The reaction was complete in 2-3 hours, but compounds **23** and **24** were obtained in low yield, due to the formation of degradation products. In addition, all the alkylation reactions led to a mixture of N1- and N2-substituted regioisomers, which were separated by flash column chromatography, with the exception of compound **21** for which only the regioisomer **21A** was identified.

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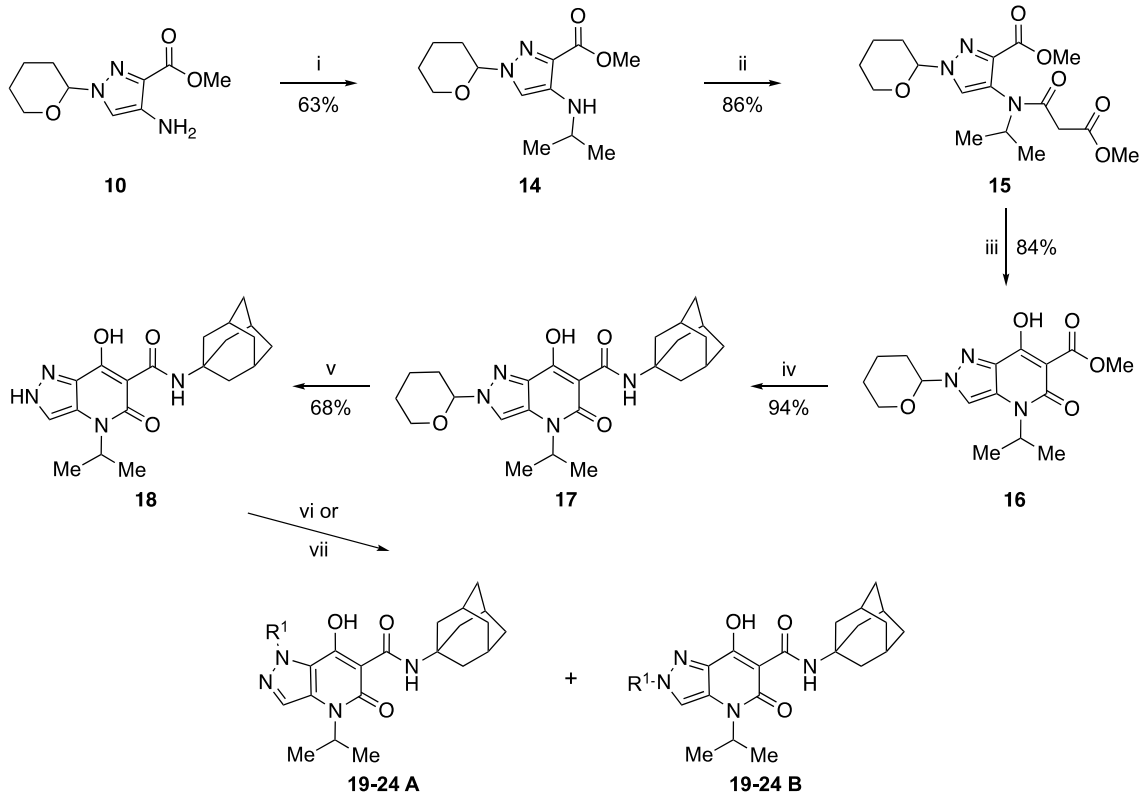
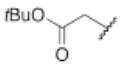
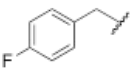
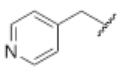
Scheme 4. Synthesis of the N1- and N2-substituted compounds.



Reagents and conditions: i) 2-iodopropane, K_2CO_3, propionitrile, 95 °C, 7-8 h; ii) methyl 3-chloro-3-oxopropionate, Et_3N, dry DCM, r. t., 2 h; iii) NaH, dry MeOH (cat), dry THF, 60 °C, 3 h; iv) 1-aminoadamantane, THF, toluene, 140 °C, 1 h; v) *p*-toluenesulfonic acid, MeOH, r. t., overnight; vi) for **19-22**: appropriate alkylating agent, K_2CO_3, acetone, r. t., 1-18 h; vii) for **23** and **24**: alkylating agent, tetrabutylammonium bromide, 50% NaOH, DCM, r. t., 2-3 h.

Table 1. 7-Hydroxy-5-oxopyrazolo[4,3-*b*]pyridine-6-carboxamide derivatives.

Compd	R^1	Yield %	
		A isomer	B isomer
19	Me	80	17
20		39	60
21		58	–
22		18	61
23		12	27
24		12	16

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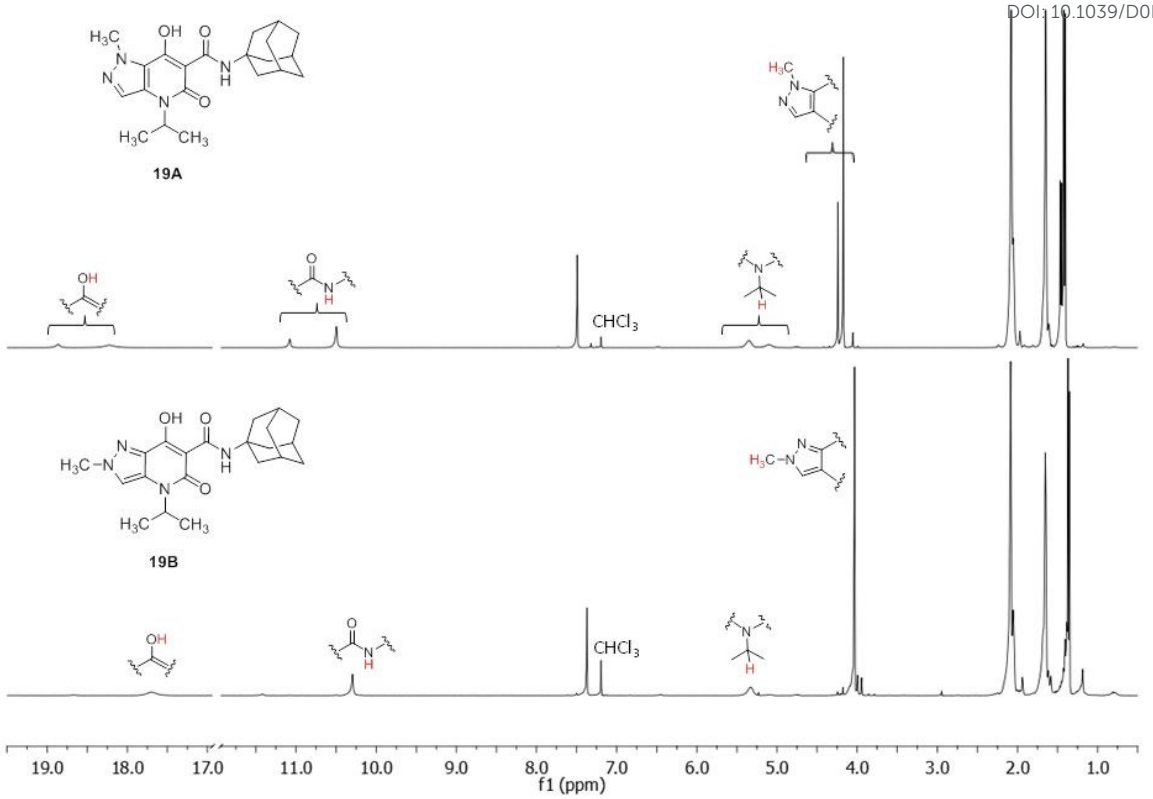
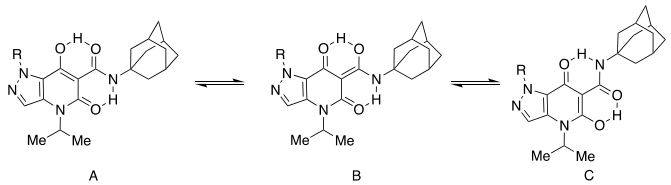


Figure 3. ^{1}H NMR spectrum of compounds **19A** (top) and **19B** (bottom).

Interestingly, the ^{1}H NMR spectra of the two isolated regioisomers show significant differences, as exemplified by the spectra of compounds **19A** and **19B** in Figure 3: a) the derivatives of the A series (*e.g.* **19A** in Figure 3) show a splitting of the signals, that is not equally evident in the NMR spectra of the B derivatives (*e.g.* **19B** in Figure 3), and b) the derivatives of A series show a downfield shift of the signals compared to the chemical shift values for the same protons in the regioisomers of the B series. These observations, together with the comparison with spectral data of COR1022 and COR1023,[10] allowed to assign the N1-substituted structure to the compounds of the A series and the N2-substituted structure to those of the B series.

Scheme 5. Tautomeric equilibria that have been hypothesized for the N1-substituted compounds.



These findings have been tentatively explained by assuming that: i) the compounds can give rise to tautomeric equilibria in solution (Scheme 5), with tautomer A surmised to be the most abundant although no attempt to compute the relative stability of the putative tautomers has been made yet; ii) the substituent at N1 favors tautomers B and C much more than the substituent at N2 does; iii) the ratio between tautomers is affected by the type of substituent present on the nitrogen atom.

Conclusions

In summary, with the aim to explore the chemical space around the 7-hydroxy-5-oxopyrazolo[4,3-*b*]pyridine-6-carboxamide scaffold, keeping the central core and the amide functionality unchanged, twelve new compounds have been synthesized as potential CB2 ligands. The here described alternative approach to the synthesis of 7-hydroxy-5-oxopyrazolo[4,3-*b*]pyridine-6-carboxamide derivatives, despite more lengthy for two more (protection-deprotection) steps, has shown to be more versatile compared to the previously reported synthesis. The protecting group approach allowed to insert a variety of substituents on the pyrazole ring as last step and hence to enhance the chemical diversity on this moiety, a result that could not be easily achieved according to the previously adopted multistep synthesis.

On the other hand, this approach has limited the variety of substituents to be installed at position 4, due to the widely different reactivity between primary, secondary, and tertiary alkylating agents. Last but not least, this synthesis allowed to obtain in most cases either N1- or N2-substituted analogs, thus opening the door to wider exploration of structure-activity relationship for both CB2R agonists and inverse agonists/antagonists with potential in diverse fields of therapeutic relevance.

Experimental

General. All commercially available reagents were used as received unless otherwise specified. Solvents were treated before use with suitable drying agents and used after distillation in an atmosphere of N_2. THF and toluene were distilled from sodiun/benzophenone ketyl; DCM, acetonitrile, and propionitrile from CaH_2; MeOH from Mg/I_2. Reactions requiring anhydrous conditions were performed under N_2. Melting points were determined on a Gallenkamp apparatus and are uncorrected. For flash chromatography 60 Merck Kieselgel 60 (0.040-0.063 mm) was used. Thin layer chromatography (TLC) was performed on silica gel plates (Merck 60 F254) eluting with solvents indicated, visualized by a 254 nm UV lamp (λ = 254 nm) and stained with aqueous potassium permanganate, Pancaldi and phosphomolybdic acid solutions. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker Avance DPX-400 NMR spectrometer at 400 MHz (^{1}H) or 100 MHz (^{13}C). Chemical shifts (δ) and coupling constants (*J*) are reported in parts per million (ppm) and hertz (Hz), respectively. Mass spectra were recorded with an LC-MSD 110 series AGILENT instrument, with electrospray interface and with a 0.4 mL/min flow rate using a binary solvent system of 95:5 methanol/water. The UV detector was set at 254 nm and the mass spectra were acquired either in positive or in negative mode scanning over the mass range of 105-1500.

(*tert*-Butyl) 3-Methoxycarbonyl-4-nitro-1*H*-pyrazole-1-carboxylate (**4**).
TEA (0.37 mL; 2.63 mmol) and Boc_2O (0.57 g; 2.63 mmol) were added to a solution of methyl 4-nitro-1*H*-pyrazole-3-carboxylate (**3**)[11] (0.30 g; 1.75 mmol) in dry THF (10 mL) under a nitrogen atmosphere and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was diluted with H_2O (50 mL) and the aqueous phase was extracted with EtOAc. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The oily residue was purified by trituration with PE to give **4** as a pink solid (0.12 g; 25% yield). Mp: 98.6-100.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 1H), 3.94 (s, 3H), 1.61 (s, 9H). MS (ESI): *m/z* 294 $[M+Na]^+$.

Methyl 1-(1-Ethoxyethyl)-4-nitro-1*H*-pyrazole-3-carboxylate (**5**).
Ethyl vinyl ether (0.32 mL; 3.33 mmol) was added to a suspension of methyl 4-nitro-1*H*-pyrazole-3carboxylate (**3**)[11] (0.30 g; 1.75 mmol) and *p*-toluenesulfonic acid (0.031 g; 0.18 mmol) in dry DCM (60 mL). The green solution which formed was stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with DCM. The organic phase was washed with $NaHCO_3$ solution, then with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The oily residue was purified by flash column chromatography on silica gel (PE:EtOAc 2:1) to afford 0.40 g (94% yield) of **5** as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 5.48 (q, *J* = 5.9 Hz, 1H), 3.91 (s, 3H), 3.43 (m, 2H), 1.60 (d, *J* = 6.0 Hz, 3H), 1.13 (t, *J* = 7.0 Hz, 3H). MS (ESI): *m/z* 266 $[M+Na]^+$.

Methyl 1-Benzyl-4-nitro-1*H*-pyrazole-3-carboxylate (**7**).
To a solution of methyl 4-nitro-1*H*-pyrazole-3-carboxylate (**3**)[11] (2.06 g; 12.04 mmol) in acetone (150 mL), K_2CO_3 (1.84 g; 13.31 mmol) and benzyl *p*-toluenesulfonate (3.50 g; 13.34 mmol) were added. The reaction mixture was stirred at room temperature for 5 h, then it was poured into H_2O (100 mL). The aqueous phase was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The colorless oily residue was purified by flash column chromatography on silica gel, using PE:EtOAc 8:1 as eluent to afford **7** (2.07 g; 66% yield) as a light yellow solid. Mp: 75.9-79.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.35 (m, 3H), 7.25 (m, 2H), 5.27 (s, 2H), 3.94 (s, 3H). MS (ESI): *m/z* 284 $[M+Na]^+$.

Methyl 4-Nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carboxylate (**8**).
A solution of 3,4-dihydro-2*H*-pyran (0.16 mL; 1.75 mmol) in DCM (5 mL) was added dropwise to a suspension of methyl 4-nitro-1*H*-pyrazole-3-carboxylate (**3**)[11] (0.20 g; 1.17 mmol) and *p*-toluenesulfonic acid (0.021 g; 0.12 mmol) in DCM (15 mL), maintained at the temperature of 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for further 2 h. After addition of Et_2O, the solution was washed with a saturated solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent under reduced pressure gave a yellow oil which was purified by flash column chromatography on silica gel, eluting with EtOAc:PE 2:1 to provide **8** (0.15 g; 50% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 5.35 (dd, *J* = 9.1 and 2.7 Hz, 1H), 4.02 (m, 1H), 3.92 (s, 3H), 3.67 (m, 1H), 2.15 (m, 2H), 2.00-1.78 (m, 2H), 1.75-1.47 (m, 2H). MS (ESI): *m/z* 278 $[M+Na]^+$.

Methyl 4-Amino-1-benzyl-1*H*-pyrazole-3-carboxylate (**9**).
Iron powder (1.71 g; 30.62 mmol), anhydrous $CaCl_2$ (0.85 g; 7.66 mmol) and H_2O (5 mL) were added successively to a solution of methyl 1-benzyl-4-nitro-1*H*-pyrazole-3-carboxylate (**7**) (2.00 g; 7.66 mmol) in EtOH (50 mL), warmed at 60 °C and the reaction mixture was vigorously stirred at this temperature for 2 h. After cooling to room temperature, the suspension was filtered through a pad of celite, concentrated in vacuo and brought to pH 9 with 5% Na_2CO_3 solution. The white precipitate of iron hydroxide which formed was filtered out. The aqueous phase was extracted with EtOAc, and the organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The oily residue was purified by flash column chromatography on silica gel (PE:EtOAc 1:2) and by trituration with PE to give **9** (1.01 g; 57% yield) as a white solid. Mp: 110.1-113.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 4H), 7.18-7.12 (m, 1H), 6.87 (s, 1H), 5.17 (s, 2H), 4.08 (s, 2H), 3.85 (s, 3H). MS (ESI): *m/z* 254 $[M+Na]^+$.

Methyl 4-Amino-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carboxylate (**10**).
To a solution of methyl 4-nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carboxylate (**8**) (0.84 g; 3.29 mmol) in EtOH (10 mL) and H_2O (1 mL), ammonium formate (2.06 g; 32.67 mmol) and 10% Pd/C (0.042 g; 0.39 mmol) were added under a nitrogen atmosphere. The reaction mixture was stirred at 50 °C for 1 h. After cooling to room temperature, the mixture was filtered through a pad of celite and the filtrate was diluted with H_2O. The aqueous phase was extracted with EtOAc and the organic layer was dried over anhydrous Na_2SO_4, filtered

and evaporated under reduced pressure to give **10** (0.72 g; 97% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (s, 1H), 5.17 (dd, *J* = 9.0 and 2.8 Hz, 1H), 3.88 (m, 1H), 3.70 (s, 3H), 3.51 (m, 1H), 1.85 (m, 3H), 1.60-1.32 (m, 3H). MS (ESI): *m/z* 248 $[M+Na]^+$.

General procedure for the preparation of compounds **11** and **12**.
To a solution of amine **9** or **10** (1.78 mmol) in dry DCM (20 mL), Et_3N (0.38 mL; 2.66 mmol) and a catalytic amount of DMAP were added under a nitrogen atmosphere. Afterwards a solution of *p*-toluoyl chloride (0.28 mL; 2.13 mmol) in dry DCM (10 mL) was added dropwise and the reaction mixture was stirred at room temperature for 50 min. Then a saturated solution of $NaHCO_3$ (20 mL) was added and the mixture was stirred for further 15 min. The organic phase was washed successively with a saturated solution of $NaHCO_3$, 1 N HCl, H_2O and brine, dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent under reduced pressure left a residue which was purified by flash column chromatography on silica gel to yield the title products.

Methyl 1-Benzyl-4-[(4-methylbenzoyl)amino]-1*H*-pyrazole-3-carboxylate (**11**).
Prepared from **9** according to the general procedure. Eluent: DCM:PE (2:1). White solid (0.48 g; yield 77%). Mp: 157.9-160.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 8.26 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.39-7.16 (m, 7H), 5.30 (s, 2H), 3.96 (s, 3H), 2.35 (s, 3H). MS (ESI): *m/z* 372 $[M+Na]^+$.

Methyl 4-[(4-Methylbenzoyl)amino]-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carboxylate (**12**).
Prepared from **10** according to the general procedure. Eluent: PE:EtOAc (2:1). White solid (0.37 g; yield 60%. Mp: 139.4-140.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (s, 1H), 8.51 (s, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.38 (m, 1H), 4.02 (m, 1H), 3.95 (s, 3H), 3.64 (m, 1H), 2.36 (s, 3H), 2.15-1.89 (m, 3H), 1.79-1.48 (m, 3H). MS (ESI): *m/z* 366 $[M+Na]^+$.

Methyl 4-[(4-Methylbenzoyl)amino]-1*H*-pyrazole-3-carboxylate (**13**).
p-Toluenesulfonic acid (0.009 g; 0.07 mmol) was added to a solution of methyl 4-[(4-methylbenzoyl)amino]-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carboxylate (**12**) (0.050 g; 0.15 mmol) in MeOH (10 mL) and the reaction mixture was stirred at room temperature for 16 h. Then, the solution was concentrated under reduced pressure and the residue obtained was diluted into EtOAc. The organic layer was washed with a saturated solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and evaporated to afford **13** (0.036 g; 93% yield) as a white solid. Mp 229.3-230.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.55 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.13 (s, 1H), 4.04 (s, 3H), 2.37 (s, 3H). MS (ESI): *m/z* 282 $[M+Na]^+$.

Methyl 4-(Isopropylamino)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carboxylate (**14**).
To a solution of methyl 4-amino-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carboxylate (**10**) (0.225 g, 1.00 mmol) in propionitrile (15 mL), K_2CO_3 (0.28 g, 2.02 mmol) and 2-iodopropane (0.20 mL, 2.00 mmol) were added. The reaction mixture was stirred at 95 °C for 7 h. During the first two hours, two further additions of K_2CO_3 (0.28 g; 2.02 mmol) and 2-iodopropane (0.20 mL; 2.00 mmol) were made. Then the mixture was concentrated under reduce pressure, diluted with H_2O (30 mL), and extracted with EtOAc. The organic layer was washed with a saturated solution of $Na_2S_2O_3$ and brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The oily residue was purified by flash column chromatography on silica gel eluting with PE:EtOAc (2:1) to give the title product **14** (0.17 g, 64% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (s, 1H), 5.22 (dd, *J* = 8.9 and 3.3 Hz), 3.94 (m, 1H), 3.77 (s, 3H), 3.54 (m, 1H), 3.15 (m, 1H), 1.97-1.81 (m, 3H), 1.60-1.41 (m, 3H), 1.08 (dd, *J* = 6.3 and 3.6 Hz). MS (ESI): *m/z* 290 $[M+Na]^+$.

Methyl 4-(*N*-Isopropyl-3-methoxy-3-oxopropanamido)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carboxylate (**15**). A solution of methyl 3-chloro-3-oxopropionate (1.00 mL; 9.31 mmol) in dry DCM (5 mL) was added dropwise under a nitrogen atmosphere to a solution of methyl 4-(isopropylamino)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carboxylate (**14**) (1.66 g; 6.21 mmol) and Et_3N (1.30 mL; 9.31 mmol) in dry DCM (35 mL). The reaction mixture was stirred at room temperature for 2 h and then was quenched with a saturated solution of $NaHCO_3$. The mixture was extracted with DCM and the organic phase was washed with 1 N HCl and H_2O, dried over anhydrous Na_2SO_4, filtered and evaporated. The orange oil obtained was purified by flash column chromatography on silica gel, with PE:EtOAc (2:1) as eluent, to afford **15** (1.97 g; 86% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 1H), 5.37 (d, *J* = 9.6 Hz, 1H), 4.91 (m, 1H), 4.01 (m, 1H), 3.83 (s, 3H), 3.72-3.53 (m, 4H), 3.14 (m, 2H), 2.18-2.05 (m, 1H), 2.03-1.70 (m, 2H), 1.69-1.51 (m, 3H), 1.02 (dd, *J* = 6.4 and 4.0 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H). MS (ESI): *m/z* 390 $[M+Na]^+$.

Methyl 7-Hydroxy-4-isopropyl-5-oxo-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylate (**16**).
To a suspension of NaH (0.24 g; 10.0 mmol) in dry THF (50 mL), dry MeOH (0.066 mL) was added under a nitrogen atmosphere. The reaction mixture was stirred at 60 °C for 10 min, then a solution of methyl 4-(*N*-isopropyl-3-methoxy-3-oxopropanamido)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carboxylate (**15**) (1.21 g; 3.29 mmol) in dry THF (20 mL) was added dropwise. The suspension obtained was stirred at 60 °C for 3 h. After cooling to room temperature, THF was removed under nitrogen atmosphere. The reaction mixture was brought to pH 9 with 10% NaOH solution, diluted with H_2O (10 mL) and extracted with EtOAc. The aqueous phase was acidified with 12 N HCl and then extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent under reduce pressure gave a yellow oily residue, which was purified by flash column chromatography on silica gel, eluting with PE:EtOAc (1:9) to afford **16** (0.93 g; 84% yield) as a colorless oil. ^{1}H NMR (400 MHz, acetone-d_6): δ 13.54 (br s, 1H), 8.00 (s, 1H), 5.54 (d, *J* = 9.2 Hz, 1H), 5.08 (m, 1H), 3.95 (m, 1H), 3.83 (s, 3H), 3.67 (m, 1H), 2.24-2.07 (m, 1H), 2.06-1.88 (m, 2H), 1.79 -1.65 (m, 1H), 1.59 (m, 2H), 1.36 (d, *J* = 9.2 Hz, 6H). MS (ESI): *m/z* 358 $[M+Na]^+$.

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N-(Adamantan-1-yl)-7-hydroxy-4-isopropyl-5-oxo-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxamide (**17**).
A mixture of methyl 7-hydroxy-4-isopropyl-5-oxo-2-(tetrahydro-2H-pyran-2-yl)-4,5-dihydro-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylate (**16**) (0.13 g; 0.39 mmol), 1-aminoadamantane (0.11 g; 0.73 mmol), THF (1.5 mL), and toluene (10 mL) was stirred at 140 °C for 1 h. During this time further toluene was added dropwise while the azeotropic mixture MeOH/toluene was distilled out. Once the reaction was complete, the solvent was removed by a nitrogen flow. The residue was taken up into EtOAc (20 mL) and the organic phase was washed with 1 N HCl, H_2O and brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The oily residue was purified by flash column chromatography on silica gel, eluting with PE:EtOAc (2:1) to furnish **17** (0.16 g; 90% yield) as a glassy white solid. Mp 122.1-124.9 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 10.39 (s, 1H), 8.09 (s, 1H), 7.82 (s, 1H), 5.52 (dd, *J* = 9.6 and 2.4 Hz), 5.12 (m, 1H), 4.10-3.95 (m, 1H), 3.74-3.67 (m, 1H), 2.25-1.86 (m, 12H), 1.83.1.53 (m, 9H), 1.42 (d, *J* = 5.9 Hz, 6H). MS (ESI): *m/z* 931 $[2M+Na]^+$.

N-(Adamantan-1-yl)-7-hydroxy-4-isopropyl-5-oxo-4,5-dihydro-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxamide (**18**).
A solution of *N*-(adamantan-1-yl)-7-hydroxy-4-isopropyl-5-oxo-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-dihydro-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxamide (**17**) (0.82 g; 1.80 mmol) and *p*-toluenesulfonic acid (0.11 g; 0.64 mmol) in MeOH (50 mL) was stirred at room temperature overnight, then concentrated under reduce pressure to a small volume. EtOAc (20 mL) and a saturated solution of $NaHCO_3$ (5 mL) and H_2O (10 mL) were added to the solid residue obtained and the aqueous phase was extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent under reduce pressure yielded a white solid residue, which was purified by flash column chromatography on silica gel, using DCM:MeOH (98:2) to obtain **18** (0.45 g; 67% yield) as a white glassy solid (mixture of tautomers in solution). Mp 183.5-185.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 18.93 and 18.08 (s, 1H overall), 10.95 and 10.50 (s, 1H overall), 8.77 (br s, 1H), 7.75 (s, 1H), 5.38 and 5.18 (m, 1H overall), 2.22-1.89 (m, 9H), 1.78-1.60 (m, 6H), 1.49 and 1.44 (d, *J* = 6.8 Hz, 6H overall). MS (ESI): *m/z* 371 $[M+Na]^+$.

General procedure for the preparation of compounds **19-22**.
To a solution of *N*-(adamantan-1-yl)-7-hydroxy-4-isopropyl-5-oxo-4,5-dihydro-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxamide (**18**) (0.14 g; 0.38 mmol) in acetone (20 mL), maintained under a nitrogen atmosphere, anhydrous K_2CO_3 (0.11 g; 0.80 mmol) and the appropriate alkylating agent (0.80 mmol) were added. The reaction mixture was stirred at room temperature for 2-16 h. The mixture was concentrated under reduced pressure and the solid residue was partitioned between H_2O and EtOAc. The aqueous phase was extracted with EtOA and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The residue obtained was purified by flash column chromatography on silica gel.

N-(Adamantan-1-yl)-7-hydroxy-4-isopropyl-1-methyl-5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxamide (**19A**) and *N*-(adamantan-1-yl)-7-hydroxy-4-isopropyl-2-methyl-5-oxo-4,5-dihydro-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxamide (**19B**).
Prepared from **18** by reaction with dimethyl sulfate. Elution with PE:EtOAc (2:1) gave the first regioisomer **19A** as a solid residue that was recrystallized from MeOH to afford a white solid (mixture of tautomers in solution); yield, 80%. Mp 193.6-194.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 18.92 and 18.30 (s, 1H overall), 11.14 and 10.57 (s, 1H overall), 7.56 (s, 1H), 5.42 and 5.16 (m, 1H overall), 4.30 and 4.23 (s, 3H overall), 2.13 (m, 9H), 1.70 (m, 6H), 1.51 and 1.47 (d, *J* = 7.0 Hz, 6H overall). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 165.7, 162.2, 124.1, 123.8, 122.2, 95.6, 52.6, 45.4, 41.5, 39.3, 36.4, 29.4, 19.8. MS (ESI): *m/z* 383 $[M-H]^-$.
Further elution with EtOAc furnished the second isomer **19B** as a white solid; yield, 17%. Mp 263.9-266.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 17.70 (s, 1H), 10.30 (s, 1H), 7.37 (s, 1H), 5.32 (m, 1H), 4.03 (s, 3H), 2.08 (m, 9H), 1.65 (m, 6H), 1.36 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 168.2, 162.9, 132.9, 125.6, 114.5, 96.7, 52.4, 45.4, 41.2, 40.9, 36.8, 30.0, 19.3. MS (ESI): *m/z* 407 $[M+Na]^+$.

N-(Adamantan-1-yl)-7-hydroxy-4-isopropyl-5-oxo-1-(prop-2-yn-1-yl)-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxamide (**20A**) and *N*-(Adamantan-1-yl)-7-hydroxy-4-isopropyl-5-oxo-2-(prop-2-yn-1-yl)-4,5-dihydro-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxamide (**20B**).
Prepared from **18** by reaction with propargyl bromide. Elution with PE:EtOAc (5:1) afforded the first regioisomer **20A** as a colorless oil (mixture of tautomers in solution); yield, 39%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 18.83 and 18.39 (br s, 1H overall), 11.01 and 10.48 (s, 1H overall), 7.59 (s, 1H), 5.51 and 5.34 (s, 2H overall), 5.10 (m, 1H), 2.34 (s, 1H), 2.06 (m, 9H), 1.62 (m, 6H), 1.45 and 1.41 (d, *J* = 7.0 Hz, 6H overall). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 166.3, 162.2, 127.9, 125.6, 125.4, 95.8, 73.7, 73.4, 53.2, 52.8, 45.5, 41.4, 36.3, 29.4, 19.9. MS (ESI): *m/z* 407 $[M-H]^-$.
Further elution with PE:EtOAc (4:1 to 1:1) gave **20B** as a light yellow oil; yield, 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 17.75 (br s, 1H), 10.25 (s, 1H), 7.64 (s, 1H), 5.26 (m, 1H), 5.05 (s, 2H), 2.55 (s, 1H), 2.03 (m, 9H), 1.62 (m, 6H), 1.35 (d, *J* = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 168.9, 162.8, 133.5, 125.5, 113.5, 97.1, 76.2, 75.6, 52.5, 45.6, 43.7, 41.5, 36.4, 29.4, 19.3. MS (ESI): *m/z* 407 $[M-H]^-$.

N-(Adamantan-1-yl)-1-(cyanomethyl)-7-hydroxy-4-isopropyl-5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxamide (**21A**).
Prepared from **18** using chloroacetonitrile as alkylating agent. Eluent: PE:EtOAc (3:1). Glassy white solid (mixture of tautomers in solution); yield, 58%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 18.78 and 18.52 (s, 1H overall), 10.91 and 10.47 (s, 1H overall), 7.65 (s, 1H), 5.67 and 5.49 (s, 2H overall), 5.33 and 5.13 (m, 1H overall), 2.07 (m, 9H), 1.65 (m, 6H), 1.46 and 1.42 (d, *J* = 7.0 Hz, 6H overall). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 171.4, 168.3, 166.6, 165.7, 162.2, 127.2, 126.9, 126.8, 122.0, 114.2, 113.9, 95.9, 93.0, 53.4, 53.1, 45.6, 41.5, 41.4, 39.3, 38.7, 36.3, 36.2, 29.4, 20.0, 19.9. MS (ESI): *m/z* 432 $[M+Na]^+$.

tert-Butyl 2-[6-[(Adamantan-1-yl)carbamoyl]-7-hydroxy-4-isopropyl-5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridin-1-yl]acetate (**22A**) and *tert*-Butyl 2-[6-[(Adamantan-1-

yl)carbamoyl]-7-hydroxy-4-isopropyl-5-oxo-4,5-dihydro-2*H*-pyrazolo[4,3-*b*]pyridin-2-yl]acetate (**22B**).
Obtained from **18** by reaction with *tert*-butyl bromoacetate. Elution with PE:EtOAc (4:1) afforded the first isomer **22A** as a colorless oil (mixture of tautomers in solution); yield, 18%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 18.81 and 18.16 (s, 1H overall), 11.00 and 10.47 (s, 1H overall), 7.58 (s, 1H), 5.34 (m, 1H), 5.27 and 5.14 (s, 2H overall), 2.06 (m, 9H), 1.64 (m, 6H), 1.48-1.38 (m, 15H). MS (ESI): *m/z* 507 $[M+Na]^+$. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 167.1, 165.3, 162.3, 125.5, 125.1, 122.5, 96.0, 82.9, 53.7, 52.6, 45.6, 41.6, 36.3, 29.4, 28.0, 19.9.
Further elution with PE:EtOAc (3:1) gave **22B** as a white solid; yield, 61%. Mp 199.1-200.0 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 17.72 (s, 1H), 10.28 (s, 1H), 7.50 (s, 1H), 5.28 (m, 1H), 4.90 (s, 2H), 2.24-1.99 (m, 9H), 1.71-1.57 (m, 6H), 1.49.1.27 (m, 15H). MS (ESI): *m/z* 485 $[M+H]^+$. ^{13}C NMR (100 MHz, $CDCl_3$): 171.4, 169.0, 165.8, 162.9, 133.6, 125.6, 115.6, 97.2, 83.5, 55.4, 52.5, 45.6, 41.6, 36.4, 29.4, 28.0, 19.3.

General procedure for the preparation of compounds **23** and **24**.
A solution of *N*-(adamantan-1-yl)-7-hydroxy-4-isopropyl-5-oxo-4,5-dihydro-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxamide (**18**) (0.14 g; 0.38 mmol) and the appropriate alkylating agent (0.40 mmol) in CH_2Cl_2 (5 mL) was added to a suspension of 50% NaOH solution (3 mL) and tetrabutylammonium bromide (0.13 g; 0.40 mmol). The reaction mixture was stirred vigorously at room temperature for 2-3 h, then it was diluted with H_2O (20 mL) and CH_2Cl_2 (30 mL). The organic phase was separated and the aqueous phase was extracted again with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel.

N-(Adamantan-1-yl)-1-(4-fluorobenzyl)-7-hydroxy-4-isopropyl-5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxamide (**23A**) and *N*-(Adamantan-1-yl)-2-(4-fluorobenzyl)-7-hydroxy-4-isopropyl-5-oxo-4,5-dihydro-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxamide (**23B**).
Prepared from **18** by reaction with 4-fluorobenzyl chloride. Elution with PE:EtOAc (4:1) provided the first regioisomer **23A** as a colorless oil (mixture of tautomers in solution); yield, 12%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 18.86 and 18.43 (s, 1H overall), 11.12 and 10.52 (s, 1H overall), 7.55 and 7.54 (s, 1H overall), 7.33 (m, 2H), 6.92 (m, 2H), 5.80 and 5.64 (s, 2H overall), 5.33 and 5.09 (m, 1H overall), 2.08 (m, 9H), 1.66 (m, 6H), 1.45 and 1.42 (d, *J* = 7.1 Hz, 6H overall). MS (ESI): *m/z* 501 $[M+Na]^+$.
The second isomer **23B** was isolated by further elution with PE:EtOAc (3:1 to 1:1). Light yellow oil; yield, 27%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 17.79 (s, 1H), 10.28 (s, 1H), 7.31 (s, 1H), 7.23 (m, 2H), 6.99 (m, 2H), 5.36 (s, 2H), 5.22 (m, 1H), 2.07 (m, 9H) 1.64 (m, 6H), 1.30 (d, *J* = 7.0 Hz, 6H). MS (ESI): *m/z* 479 $[M+H]^+$.

N-(Adamantan-1-yl)-7-hydroxy-4-isopropyl-5-oxo-1-(pyridin-4-ylmethyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxamide (**24A**) and *N*-(Adamantan-1-yl)-7-hydroxy-4-isopropyl-5-oxo-2-(pyridin-4-ylmethyl)-4,5-dihydro-2*H*-pyrazolo[4,3-*b*]pyridine-6-carboxamide (**24B**).
Obtained from **18** by reaction with 4-(bromomethyl)pyridine hydrobromide. Elution with EtOAc:PE (3:1) furnished the first regioisomer **24A** as an orange oil (mixture of tautomers in solution); yield, 12%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 18.84 and 18.41 (s, 1H overall), 11.01 and 10.50 (s, 1H overall), 8.48 (m, 2H), 7.60 (s, 1H), 7.13 (m, 2H), 5.85 and 5.69 (s, 2H overall), 5.37 and 5.12 (m, 1H overall), 2.06 and 1.92 (m, 9H overall), 1.65-1.60 (m, 6H overall), 1.47 and 1.43 (d, *J* = 7.0 Hz, 6H, overall). MS (ESI): *m/z* 484 $[M+Na]^+$.
Further elution with EtOAc:PE (4:1) to EtOAc:MeOH (99:1) gave **24B** as a yellow oil; yield, 16%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 17.86 (s, 1H), 10.27 (s, 1H), 8.53 (m, 2H), 7.39 (s, 1H), 7.06 (m, 2H), 5.42 (s, 2H), 5.26 (m, 1H), 2.08 (m, 9H), 1.64 (m, 6H), 1.33 (d, *J* = 7.1 Hz, 6H). MS (ESI): *m/z* 462 $[M+H]^+$.

Conflicts of interest

There are no conflicts to declare.

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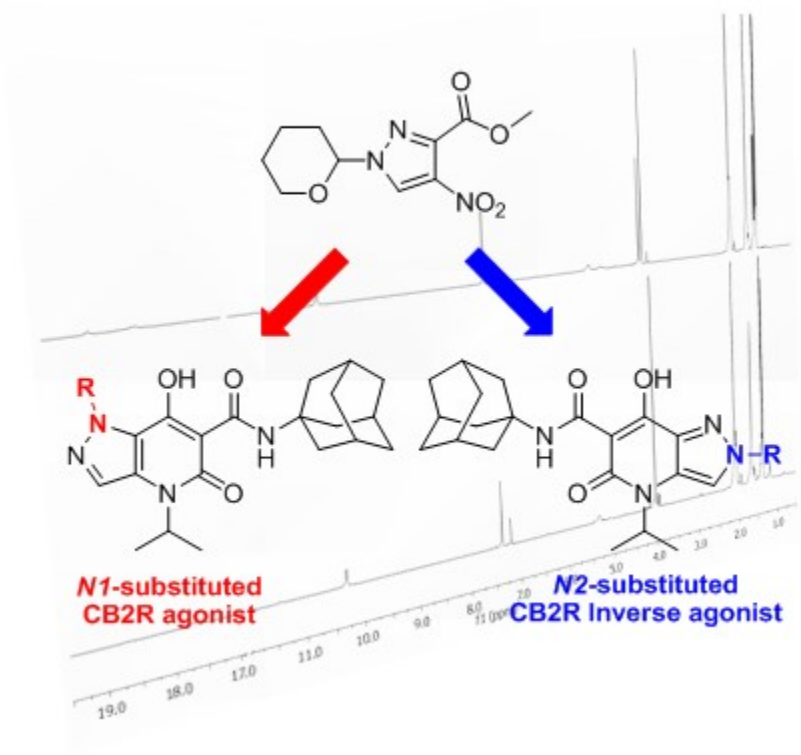

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