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# Structure–Activity Studies of a Series of Dipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3-ones Binding to the Immune Regulatory Protein B7.1

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**Abstract**—The interaction of co-stimulatory molecules on T cells with B7 molecules on antigen presenting cells plays an important role in the activation of naive T cells. Consequently, agents that disrupt these interactions should have applications in treatment of transplant rejection as well as autoimmune diseases. To this end, specific small molecule inhibitors of human B7.1 were identified and characterized. Herein, we report the identification of potent small molecule inhibitors of the B7.1–CD28 interaction. In a high-throughput screen we identified several leads that prevented the interaction of B7.1 with CD28 with activities in the nanomolar to low micromolar range. One of these, the dihydrodipyrazolopyridinone **1**, was subsequently shown to bind the V-like domain of human B7.1 at equimolar stoichiometry. With this as a starting point, we report here the synthesis and initial in vitro structure–activity relationships of a series of these compounds.


## Introduction

Regulation of T cell responses plays a primary role in determining the outcome of auto-immune disease, the development of tumor immunity, and graft survival following transplantation.[1–4] These immune responses are controlled by interaction of molecules on T cell and antigen presenting cell (APC) surfaces. Activation of T cells requires two signals, an antigen-specific signal delivered through T cell antigen receptor (TcR), and a second co-stimulatory signal. This co-stimulatory signal dictates the outcome for T cells through the binding of B7.1 and B7.2 expressed on antigen presenting cells to CD28 and CTLA-4 on T cells.[1,2] CD28 engagement by B7′s amplifies T cell receptor signaling and stimulates production of cytokines required for T-cell proliferation. On the other hand, CTLA-4 engagement by B7′s down regulates the immune response.[5–7] This amplification or attenuation of TcR signaling occurs at a specialized contact area between T cell and APC membranes known as the immunolgical synapse.[8,9] For CD28-dependent amplification, this involves bulk recruitment of cell surface molecules and kinase-rich rafts to the synapse, thereby increasing receptor phosphorylation and signaling.[10,11] CTLA-4-dependent attenuation involves recruitment of tyrosine phosphatases (such as SHP-2) to the synapse, resulting in dephosphorylation.[12,13] In experimental disease models, altering these co-stimulatory signals has profound effects on immunity. Blocking B7/CD28 interactions with monoclonal antibodies or soluble receptors results in immunosuppression and enhanced allograft survival, while B7/CTLA-4 blockade results in enhanced anti-tumor immune responses.[14–16]

In recent clinical trials, co-stimulatory blockade has shown considerable therapeutic potential for immunotherapy in both allograft transplantation and psoriasis.[3,4] To date, co-stimulatory modifiers in the clinic are either monoclonal antibodies or fusion proteins of the CTLA4 receptor. Herein, we report the identification of potent small molecule inhibitors of the B7.1–CD28 interaction. In a high-throughput screen we

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identified several leads that prevented the interaction of B7.1 with CD28 with activities in the nanomolar to low micromolar range. One of these, the dihydrodipyrazolopyridinone **1**, was subsequently shown to bind the V-like domain of human B7.1 at equimolar stoichiometry.[17] With this as a starting point, we report here the synthesis and initial in vitro structure–activity relationships of a series of these compounds. Target compounds were synthesized by several routes in order to systematically modify peripheral substituents, as well as the heterocyclic framework of **1**. Of these compounds, several tight-binding analogues were identified and shown to block CD28 signaling in a cell-based assay.

## Chemistry

In the structure–activity study reported here, we attempted to make only single-point changes to the lead compound **1** (Fig. 1), with a few exceptions. Modifications to the *N*-aryl ring on the dihydropyrazole portion of **1** was performed with chemistry that allowed the 6-methyl-4-(3-[trifluoromethyl]phenyl) - dihydrodipyrazolopyridinone core to remain constant, while variations on the 4-(3-[trifluoromethyl]phenyl) group were performed utilizing either the 2-substituted 4′-chlorophenyl-, 4′-fluorophenyl-, or 3′-fluorophenyl-6-methyl-dihydrodipyrazolopyridinone core of **1a**. In a similar fashion, analogues with changes to the pyrazole ring (**1c**) contained either a 2-(4′-chlorophenyl)-, 2-(4′-fluorophenyl)-, or 2-(3′-fluorophenyl)- group in the 'northern' section, and a 4-[3-(trifluoromethyl)phenyl]- ring in the 'southern' section. The chemistry depicted in Scheme 1 was utilized to prepare derivatives represented by the structure **1a**. Intermediates **2a–h** were prepared by reaction of an aryl or heteroaryl ester with sodium hydride and ethyl acetate, followed by methylation with (trimethylsilyl)diazomethane. Condensation with either ethyl 5-amino-1-methylpyrazole-4-carboxylate or ethyl 2-aminothiophene-3-carboxylate using sodium hydride in refluxing dioxane gave the 4-hydroxy-1-methyl-pyrazolopyridine or 4-hydroxy-thienylpyridine esters respectively.[18] After conversion of the hydroxypyridines to the chloropyridines **3a–h** and **4** with phosphorus oxychloride, annelation of the pyrazolone ring was accomplished by heating with an excess of the desired hydrazine in refluxing ethanol, followed by cyclization with either hot acetic acid or with sodium methoxide.[19] The resulting products **6a–y** (with the exception of **6n**, **6r**, **6s**, **6v**, and **7a**) were isolated in moderate yields (40–80%).[21] Other analogues were prepared by the following conversions: Methylation on the remaining free nitrogen atom of **1** was accomplished with NaH, MeOTf in DMF to give **7a**.[20] Saponification of the nitrile group of **6p** with sodium hydroxide in hot ethylene glycol gave the carboxylic acid **6s** in 95% yield. Nitrile **6p** was also subjected to basic hydrolysis in the presence of hydrogen peroxide to afford the amide derivative **6t** in a respectable 40% yield. The nitro analogue, **6v** was reduced by hydrogen and catalytic palladium on carbon to give the amine **6w**. Finally, reaction of **4a** with alkylhydrazines resulted in regioisomeric mixtures of addition products, with the product of the terminal nitrogen atom addition to the ester group predominating. To avoid this and in order to prepare the *N*-benzyl-pyr-

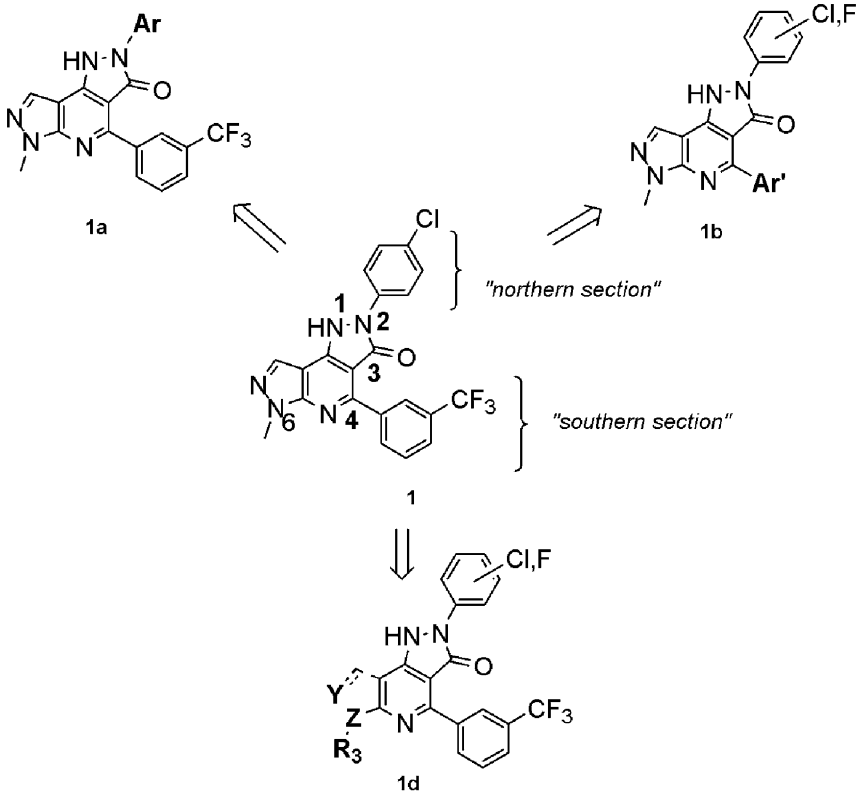
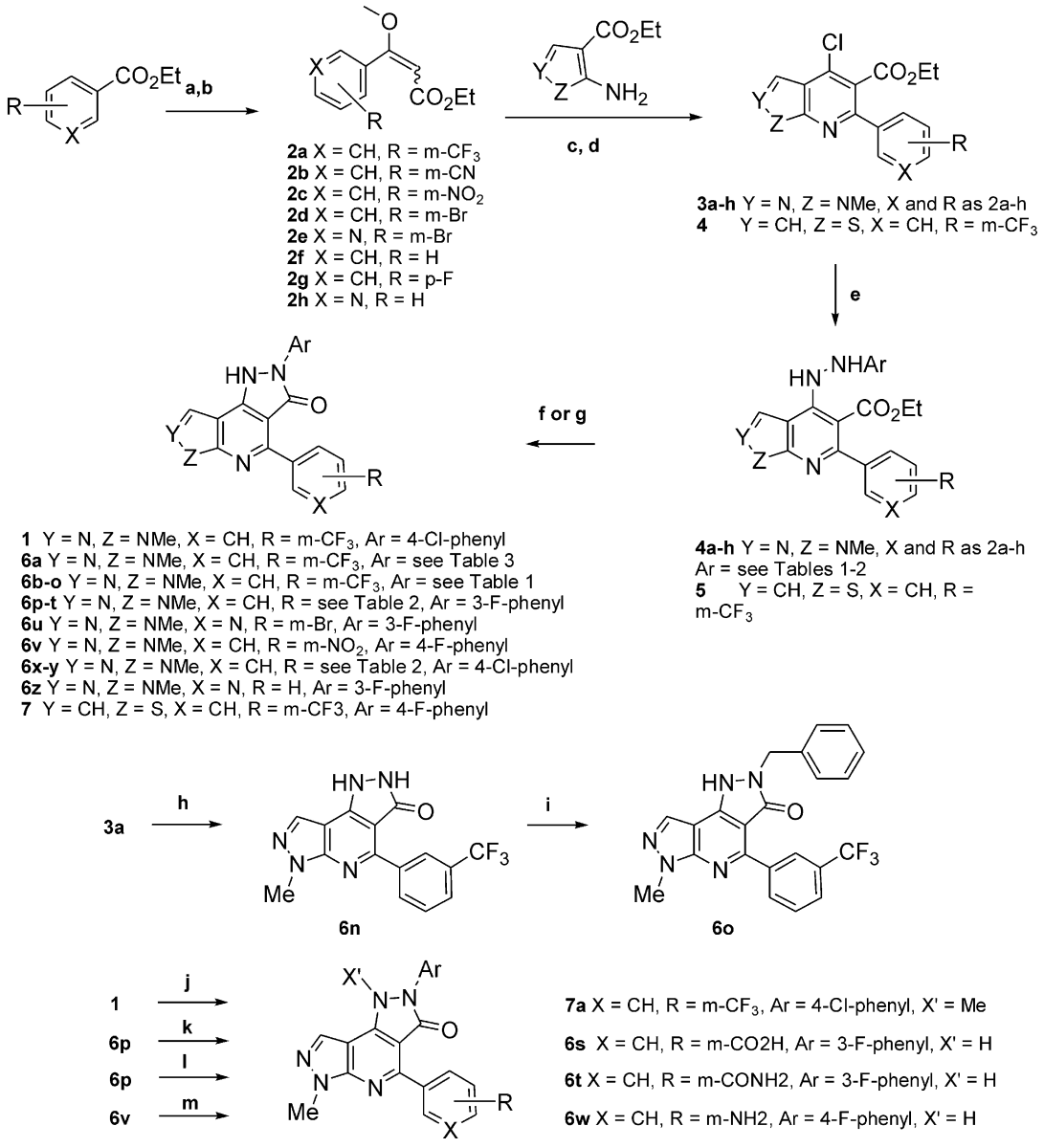


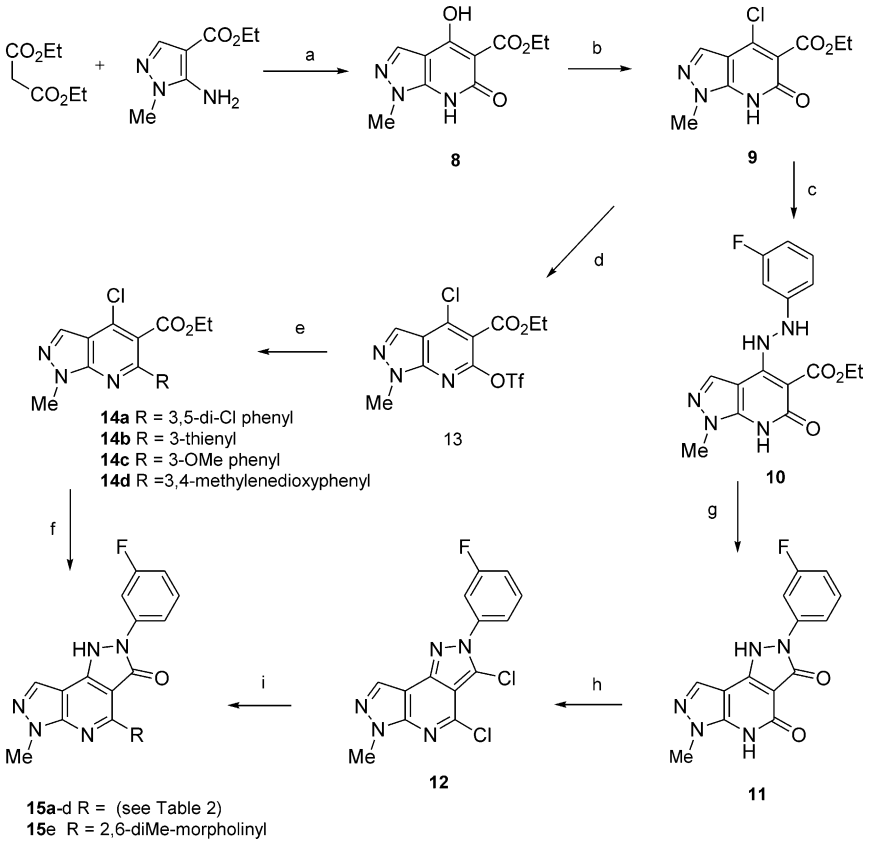

**Figure 1.**




**Scheme 1.** Synthesis of dihydrodipyrazolo- and dihydropyrazolo thienylpyridinone derivatives. Reagents: (a) EtOAc or MeOAc, NaH, rt to reflux, 60–95%; (b) $TMSCHN_2$, 95%; (c) NaH, dioxane, reflux overnight 60–80%; (d) $POCl_3$ reflux, 6 h, 75–85%; (e) arylhydrazine, ethanol, reflux, 50–70%; (f) acetic acid, 100 °C; (g) NaOMe, methanol, reflux, 40–80%; (h) anhydrous hydrazine, ethanol, reflux, 90%; (i) (1) $(Boc)_2O$; (2) PS-$PPh_3$, $PhCH_2OH$, DIAD, THF 0 °C to rt; (3) TFA, 0 °C to rt, 55%; (j) NaH, MeOTf, DMF, 90%; (k) NaOH, ethylene glycol, DMSO, 30% $H_2O_2$, $K_2CO_3$, $H_2O$, 4 h, 40%; (m) EtOAc, MeOH, $H_2$–Pd/C, 20 psi, 3 h, 67%.

azolone analogue **6o**, the chloropyrazolopyridine **3a** was reacted with anhydrous hydrazine, which directly afforded the unsubstituted dihydrodipyrazolopyridinone **6n**. Deprotonation of **6n** with NaH in DMF and alkylation with benzyl bromide gave **6o**, after chromatographic isolation.

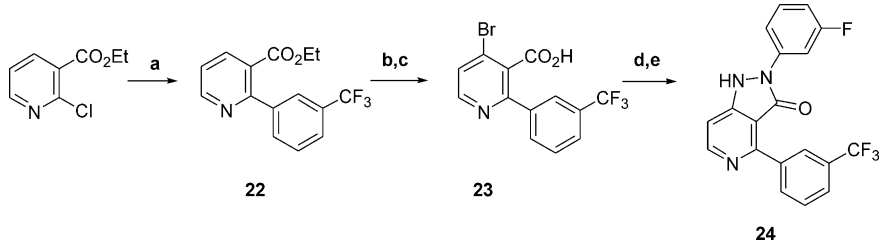
We also developed an alternative route for the synthesis of 4-substituted 2-(3-fluorophenyl)-6-methyl-dihydrodipyrazolopyridinones (Scheme 2). Condensation of diethylmalonate and ethyl-5-amino-1-methylpyrazole-4-carboxylate with sodium methoxide in methanol provided the hydroxypyridinone **8** in good yield.[22] Conversion **8** to the chloropyridinone **9** was accomplished with $POCl_3$ and $BnEt_3NCl$ in acetonitrile.[23] The hydrazine moiety was added as described in Scheme 1 to afford **10**, which was cyclized in hot acetic acid to give **11**. Treatment of **11** with phosphorus oxychloride gave the dichlorodipyrazolopyridine **12**. Compound **12** underwent a smooth regioselective substitution at the 4-Cl position with 2,6-dimethylmorpholine to provide the 3-chloro-4-morpholinyl-dipyrazolopyridine,[24] which was converted to the dihydrodipyrazolopyridinone **15e** with sodium methoxide followed by acidic hydrolysis. A few selected 4-aryl 2-(3-fluorophenyl)-6-methyl-dihydrodipyrazolopyridinones were prepared via the triflate **13**, which underwent Suzuki coupling with several arylboronic acids to give the corresponding aryl substituted chloropyridines **14a–d**.[25,26] Compounds **14a–d** were converted to the desired analogues **15a–d** according to chemistry described in Scheme 1.



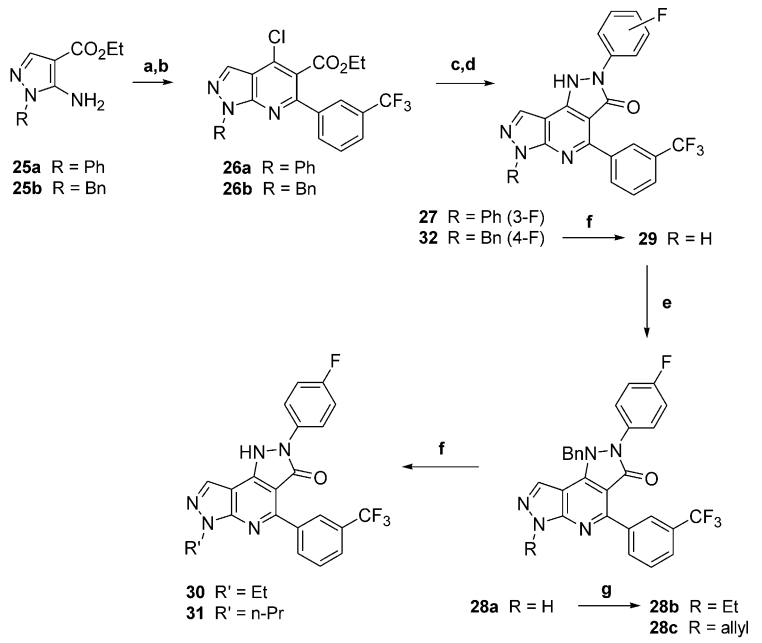

**Scheme 2.** Representative synthesis of 4-substituted- (2-(3-fluorophenyl)-dihydrodipyrazolopyridinone derivatives. Reagents: (a) Na, ethanol, reflux 72 h, 82%; (b) $POCl_3$, $BnEt_3NCl$, $CH_3CN$, 40 °C to reflux, 3 h, 73%; (c) 3-fluorophenylhydrazine, ethanol, reflux, 12 h, 88%; (d) $TfO_2$, 2,6-di-*tert*-butyl-4-methylpyridine, $CH_2Cl_2$, 0 °C, 18 h, 92%; (e) $Pd(OAc)_2$, $2PPh_3$, $K_3PO_4$, $BnEt_3NCl$, DME, $H_2O$, $Ar'B(OH)_2$, 2 h, 40–50%; (f) 3-fluorophenylhydrazine, THF, reflux then acetic acid, 100 °C, overnight, 40–55%; (g) acetic acid, 100 °C, 6 h, 80%; (h) $POCl_3$, reflux, 2 h, 75%; (i) 2,6-dimethylmorpholine, DMF, 140 °C, 4 h then NaOH, MeOH, THF, 16 h, 60% for two steps.

The monopyrazolopyridinone **24** was prepared via a five step sequence shown in Scheme 3. Ethyl 2-chloropyridine-3-carboxylate underwent a smooth Suzuki coupling reaction with 3-(trifluoromethyl)phenylboronic acid to give **22** in excellent yield. Ortholithiation and subsequent lithium–halogen exchange was best accomplished with the corresponding carboxylic acid of **22** using s-BuLi and phenyltrimethylammonium tribromide in THF.[27] Alternative ortholithiation directing groups resulted in dibromination products that could not be separated from each other and/or characterized. Following esterification of the carboxylic acid function of **23**, aromatic substitution with 3-fluorophenylhydrazine in refluxing ethanol resulted in concommitant cyclization to give **24** directly.

For variations on the pyrazole ring of **1**, the chemistry in Scheme 4 was employed. Starting from either **25a** or **25b** and following the same chemistry as depicted in Scheme 1, the 6-phenyl and 6-benzyl dihydrodipyrazolopyridinones **27** and **32** were obtained via the phenyl and benzyl chloropyridine intermediates **26a** and **26b**, respectively. Hydrogenolysis of **32** afforded the unsubstituted pyrazole analogue **29** in very good yield. Attempted regioselective alkylation of the N-6 pyrazole nitrogen atom over the N-3 dihydropyrazole atom of **29** with various alkyl halides gave a complicated mixture of products. Alternatively, protection of the nitrogen atom in the dihydropyrazole ring of **29** with diisopropylethylamine gave the monobenzylated derivative **28a**. Alkylation via sodium hydride in DMF with ethyl



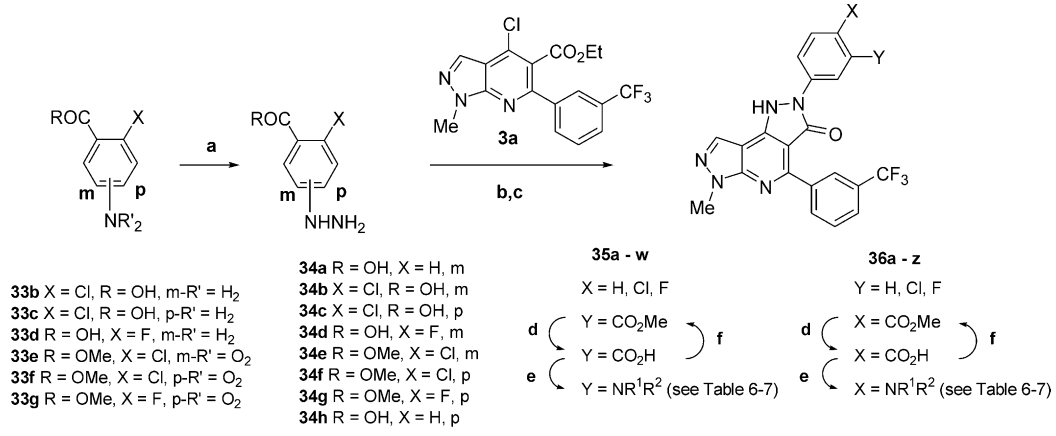
**Scheme 3.** Synthesis of 2,4 substituted (monopyrazolo)pyridinones. Reagents: (a) 3-(trifluoromethyl)phenylboronic acid, $Pd(PPh_3)_4$, $Na_2CO_3$, $H_2O$, DME 85 °C, 95%; (b) NaOH, $H_2O$ 84%; (c) s-BuLi, THF, $PhMe_3NBr_3$, 45%; (d) $TMSCHN_2$ 73%; (e) 3-F phenylhydrazine, ethanol, reflux 33%.




**Scheme 4.** Synthesis of 6-substituted dipyrazolopyridinones. Reagents: (a) 2NaH, dioxane, reflux overnight 60–80%; (b) $POCl_3$ reflux, 6 h, 75–85%; (c) 4-fluorophenylhydrazine, ethanol, reflux, 50–70%; (d) acetic acid, 100 °C, 40–80%; (e) *i*-PrNEt$_2$, BnBr, DMF 78%; (f) $H_2$, Pd/C 80–92%; (g) EtBr, or *n*-PrBr, NaH, DMF, 40–65%.

iodide or allyl bromide gave the ethyl and allyl derivatives **28b** and **28c**, respectively. Hydrogenolysis then afforded the ethyl-substituted pyrazole analogue **30** and propyl-substituted pyrazole analogue **31**.

In parallel with characterizing the pharmacophore binding requirements of **1** and analogues for in vitro B7.1–CD28 inhibition, we also attempted to gain increased potency through additional interactions beyond the pyrazolopyridinone core. The extension of functionality was facilitated through preparation of carboxylic acid and amide derivatives (Scheme 5). These derivatives were synthesized by addition of the desired hydrazinobenzoic acids or esters to the chloro intermediate **3a** and in the case of amides by subsequent acylation with a variety of amines. While 4-hydrazinobenzoic acid (**34h**) and 3-hydrazinobenzoic acid (**34a**) were commercially available, the halogen-substituted methyl hydrazinobenzoic acids and esters **34b–g** were obtained from commercially available halo-substituted amino- or nitro-benzoates. Starting from the nitrobenzoates **33e–g**, the sequence included reduction of the nitro group with tin chloride dihydrate, diazotization of the isolated amine with sodium nitrite in aqueous hydrochloric acid and finally in situ reduction, to afford the hydrazines **34e–g** as hydrochloride salts. The hydrazines **34b–d** were prepared from the aminobenzoates **33b–d**, starting from the diazotization step. The resulting hydrazino salts were neutralized with aqueous NaOH. This neutralization step was necessary to facilitate clean addition to the chloropyrazolopyridine **3a**. The addition to **3a** was accomplished by treating a warm ethylene glycol solution of the hydrazines with sodium *tert*-butoxide, followed by slow introduction of **3a**. By this




**Scheme 5.** General synthesis of 6-methyl-4-[3-(trifluoromethyl)phenyl]-dihydrodipyrazolopyridinyl-benzoates and benzamides. Reagents: (a) for **33b–d**: (1) $NaNO_2$, HCl; (2) $SnCl_2$, HCl/$H_2O$ 30–50%; (a) for **33e–g**: (1) $SnCl_2$, HCl/$H_2O$; (2) $NaNO_2$, HCl; (3) $SnCl_2$, HCl/$H_2O$ 30–50%; (b) NaOtBu, ethylene glycol 100 °C, 24 h, 50–60%; (c) NaH, DMF, 100 °C, 70%; (d) for **36e**,**f**: LiOH, THF, MeOH 99%; (e) EDCI, DMF, *i*PrNEt$_2$, heat 60–95%; (f) for **35a**,**b** and **c**: MeOH, HCl 99%.

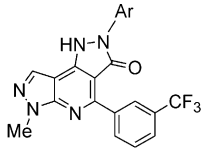
method, analogues **35a–c**, **35f**, **36a**, and **36e–f** were obtained directly. The ester analogues **35d** (X = H, Y = $CO_2Me$), **35e** (X = Cl, Y = $CO_2Me$), **36d** (Y = $CO_2Me$, X = H) were prepared from the corresponding acids **35a**, **35b**, and **36a**, respectively by acid-catalyzed esterification. The acid analogues **36b** (X = $CO_2H$, Y = Cl) and **36c** (X = $CO_2H$, Y = F) were prepared by saponication of the esters **36e** and **36f**, respectively. Conversions to amide derivatives **35g–w** and **36g–z** (see Tables 6 and 7) via the known water-soluble carbodiimide protocol (EDCI).

## Structure–Activity Relationships

Compounds were first evaluated for inhibition of human B7.1 binding to CD28 using a kinetic ELISA as previously described.[17] Briefly, this involved coating wells with a CD28–Fc fusion protein and blocking remaining sites with albumin. A preformed detection complex of B7.1 coupled to alkaline phosphatase was then incubated with inhibitors for 30 min. This mixture was then added to the CD28–Fc coated wells, incubated 25 min and washed. Binding was then quantified using the colourimetric substrate *para*-nitro phenyl phosphate and measuring the optical density at 405 nm. Inhibition constants ($IC_{50}$'s) were then calculated by subtracting background binding and comparing to uninhibited (DMSO alone) controls. Data for the lead compound **1** or the structurally similar analogue **6c** are included in Tables 1–4 for the purposes of comparison.

Our first goal was to investigate the role of the two peripheral aromatic rings on the dihydrodipyrazolopyridinone core for inhibitory activity (see Fig. 1 for 'northern' and 'southern' rings). We sought to test steric, electronic and conformational requirements at these two positions while maintaining a reasonable molecular weight range and drug-like profile.[30,31] For the northern ring system the data indicated a general trend that favored increased binding affinity with electron deficient *meta*- and *para*-substituted phenyl rings. Substantially decreased affinity with *ortho*-substituted phenyl rings and a tolerance for steric bulk in the *para* position was seen when this ring substituent provided hydrogen bond donor–acceptor properties (Table 1). In

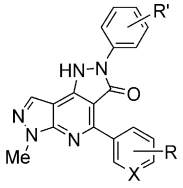
**Table 1.** In vitro B7.1–CD28 binding inhibition for 2-substituted-4-(3-(trifluoromethyl)phenyl)-dipyrazolopyridinones




| Compd | Ar = | B7.1–CD28 inhibition $IC_{50}$ (nM)[a] |
|---|---|---|
| **1** | 4-Chlorophenyl | 60 ± 17 |
| **6b** | 4-Fluorophenyl | 50 ± 3 |
| **6c** | 3-Fluorophenyl | 20 ± 3 |
| **6d** | 3-Chloro-4-fluorophenyl | 42 ± 5 |
| **6e** | 2-Fluorophenyl | 300 ± 80 |
| **6f** | 2,4-Difluorophenyl | 1000 ± 250 |
| **6g** | 2′-Carboxy-5′-methyl-3-thienyl | > 3000 |
| **6h** | 2-Pyridizone | 70 ± 12 |
| **6i** | 1-*tert*-Butylphenyl | 900 ± 250 |
| **6j** | 4-Aminosulfonylphenyl | 150 ± 25 |
| **6k** | 4-Benzyloxyphenyl | 25 ± 3 |
| **6l** | 4-Biphenyl | 39 ± 9 |
| **6m** | 4-Hydroxymethylphenyl | 33 ± 7 |
| **6n** | H | > 3000 |
| **6o** | Benzyl | > 3000 |

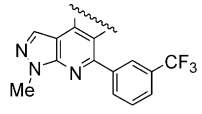
[a]See Experimental for assay protocol. Determinations were done in triplicate. Dose–response curves were done at five concentrations.

**Table 2.** In vitro B7.1–CD28 binding inhibition for 4-substituted-2-(halophenyl)-dipyrazolo(3,4*b*:3:4′*d*)pyridinones




| Compd | R′ | X | R | B7.1–CD28 inhibition $IC_{50}$ (nM) |
|---|---|---|---|---|
| **1** | 4-Cl | CH | 3-$CF_3$ | 60 ± 17 |
| **6c** | 3-F | CH | 3-$CF_3$ | 20 ± 3 |
| **6p** | 3-F | CH | 3-CN | 50 ± 10 |
| **6q** | 3-F | CH | 3-$NO_2$ | 4 ± 1 |
| **6r** | 3-F | CH | 3-Br | 22 ± 3 |
| **6s** | 3-F | CH | 3-$CO_2H$ | 72 ± 13 |
| **6t** | 3-F | CH | 3-$CONH_2$ | 1500 ± 300 |
| **6u** | 3-F | N | 3-Br | 20 ± 3 |
| **6v** | 4-F | CH | 3-$NO_2$ | 50 ± 13 |
| **6w** | 4-F | CH | 3-$NH_2$ | 400 ± 100 |
| **6x** | 4-Cl | CH | H | 1800 ± 200 |
| **6y** | 4-Cl | CH | 3-F | > 3000 |
| **6z** | 3-F | N | H | > 3000 |
| **15a** | 3-F | CH | 3,5-di-Cl | 40 ± 5 |
| **15b** | 3-F | 3-Thienyl | | 105 ± 25 |
| **15c** | 3-F | CH | 3-OMe | 82 ± 9 |
| **15d** | 3-F | CH | 3,4-Methylenedioxy | 295 ± 50 |
| **15e** | | 2,6-Dimethylmorpholine | | 188 ± 54 |

**Table 3.** In vitro B7.1–CD28 binding inhibition for (3,4′*d*)-substituted-4-(3-(trifluoromethyl)phenyl)-pyrazolo(3,4*b*)pyridines



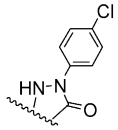
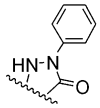
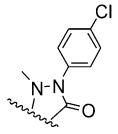
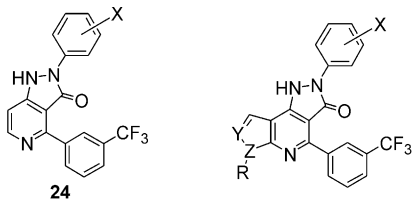

| Compd | 3,4 d Group | B7.1–CD28 inhibition $IC_{50}$ (nM) |
|---|---|---|
| **1** |  | 60 ± 17 |
| **6a** |  | 200 ± 70 |
| **7a** |  | > 3000 |

**Table 4.** In vitro B7.1–CD28 binding inhibition for substituted-fluorophenyl-(3-(trifluoromethyl)phenyl)-pyrazolopyridinones



**24**

| Compd | X | Y | Z | R | B7.1–CD28 inhibition $IC_{50}$ (nM) |
|---|---|---|---|---|---|
| **24** | 3-F | — | — | — | 1300 ± 100 |
| **6b** | 3-F | N | N | $CH_3$ | 20 ± 3 |
| **6a** | 4-F | N | N | $CH_3$ | 50 ± 3 |
| **30** | 4-F | N | N | Ethyl | 1500 ± 60 |
| **27** | 3-F | N | N | Phenyl | 750 ± 90 |
| **32** | 4-F | N | N | Benzyl | 70 ± 20 |
| **31** | 4-F | N | N | Propyl | 90 ± 8 |
| **29** | 4-F | N | N | H | 100 ± 20 |
| **7** | 4-F | CH | S | — | 600 ± 100 |

addition, it appeared that six-membered aromatic rings where preferred to five-membered heteroaromatics. Removal of the northern aromatic ring, or replacement of the ring with alkyl groups completely abolished activity (**6n**). The analogue with an unsubstituted phenyl ring (**6a**, see Table 3) gave slightly diminished activity compared to the lead compound **1**. Electron-withdrawing halogen groups in the 3- and/or 4-positions gave compounds with similar inhibitory activity (**6b**, **6c**, and **6d**), with the 3-fluorophenyl analogue **6c** the most active. *Ortho*-substituted ring systems such as **6e**, and **6f**, were less active than **1,** indicating a possible preference for the ring to be nearly planar to the dihydrodipyrazolopyridinone core. Replacement of the 2-phenyl moiety with a substituted thienyl ring as in **6g** led to significantly reduced activity. In contrast, six-membered heteroaromatic ring systems led to compounds with inhibitory activity comparable to **1** as in the 2-pyridizone (**6h**) analogue. One notable trend was seen with *para*-substituted phenyl ring analogues. The electron-donating and bulky 4-*tert*-butyl group of **6i** gave weak activity; however, the isosteric but polar sulfonamide group of **6j** was only 2.5 times less active than **1**. Other groups in the *para* position such as the benzyloxy group **6k**, the hydroxymethyl group **6m** and the 4-biphenyl ring system **6l**, were comparable or more potent than **1**. Finally, increasing the freedom of rotation and distance of the aromatic ring from the dihydrodipyrazolopyridinone core, as in the benzyl analogue **6o**, led to reduced activity.

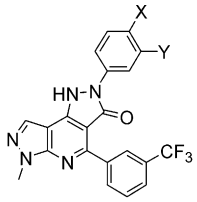
In contrast to the ability of the northern-position to accept a fair amount of functional group changes, large changes from the 3-trifluoromethylphenyl group in the southern aromatic ring were less well tolerated. In general, electron-withdrawing groups in the *meta* position of a six-membered aromatic ring led to potent inhibition; several analogues gave $IC_{50's} \leq 25$ nM (Table 2) with the electron-deficient nitro derivative **6q** as the most potent. This electrostatic trend was also seen with the 3-methoxy analogue **15c** (inductively withdrawing–resonance donating, $IC_{50} = 82$ nM), while the electron-rich 3-amino analogue (**6w**) was only weakly active. Two standouts from this trend were the electron deficient 3-carboxamido analogue **6t** which was only weakly active (1500 nM), and the electronically neutral 3-carboxy analogue **6s** (72 nM), which gave inhibitory activity comparable to **1**. The disubstituted ring systems in **15a** and **15d** were weakly active and the 2,6-dimethylmorpholinyl derivative (**15e**) which contains a nonaromatic ring at the 4-position, was moderately active at 190 nM. The moderate binding affinity of (**15e**) is not easily explained, by electrostatic contributions alone, but may include the hydrogen bond acceptor properties of the morpholine oxygen atom. Analogues lacking moderately sized *meta*-substitution feature such as **6x**, **6y** and particularly the 4-(3-pyridyl) analogue **6z**, were weak inhibitors.

Variations to the pyrazolone ring system were studied (Table 3). As with the southern ring system, this portion of the lead series also showed very tight SAR. A requirement for hydrogen bond donation at the pyrazolone binding site along with proper steric volume and northern ring orientation appeared to play an important role for binding. Methylation of the free nitrogen atom on this ring led to inactivity (**7a**).

A preference for specific Van der Waals interactions at the pyrazole binding site was noted when several N1 substituted pyrazole analogues and a thienyl analogue were tested in the binding assay (Table 4). While the unsubstituted pyrazole compound **29** was only half as active as the lead **1**, the thienyl ring analogue **7** was considerably less active. The pyridine analogue **24** was inactive, illustrating an essential role for a more fully substituted pyridine nucleus. The ethyl-substituted compound **30** and the phenyl analogue **27** were weak inhibitors; however, the propyl and benzyl analogues **31** and **28** retained inhibitory activity comparable to **6a**.

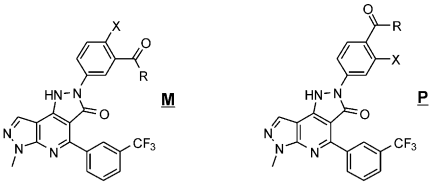
Crystallographic studies of protein–protein complexes most frequently show that rather large surface area contacts (>1600 angstroms$^2$) exist between the two interacting macromolecules.[28] In order to inhibit contacts of this magnitude with a small molecule, hydrophobic interactions over a large area may be necessary. Toward that end, a further goal of this SAR study was to facilitate improved binding with the B7.1 protein beyond the dihydrodipyrazolopyridinone core. Due to a greater tolerance of functionality in the 'northern' region, we decided to focus on this area and first tested the incorporation of a hydrogen bonding group in the form of a non-basic carboxylate at either the *meta*- or *para*-positions (**M** or **P**, Table 5). Due to the tight binding of 'northern' analogues containing halogen substituents, we also studied the corresponding *meta*- or *para*-carboxylates with vicinally substituted fluoro or chloro groups with the possibility that these two groups would operate in a synergistic manner for increased inhibition. The presence of a larger chloro atom but not a smaller fluoro atom adjacent to the carboxylate group led to favorable interactions between the small molecule and the protein. For example, the *meta*-acid analogue

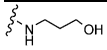
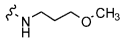
**Table 5.** In vitro B7.1–CD28 binding inhibition for 6-methyl-4-[3-(trifluoromethyl)phenyl]-dihydrodipyrazolopyridinyl benzoates



| Compd | Y | X | B7.1–CD28 inhibition $IC_{50}$ (nM) |
|---|---|---|---|
| **35a** | $CO_2H$ | H | 48±10 |
| **35b** | $CO_2H$ | Cl | 7±3 |
| **35c** | $CO_2H$ | F | 70±14 |
| **35d** | $CO_2Me$ | H | 8±4 |
| **35e** | $CO_2Me$ | Cl | 120±20 |
| **35f** | $CO_2Me$ | F | 98±9 |
| **36a** | H | $CO_2H$ | 190±40 |
| **36b** | Cl | $CO_2H$ | 16±2 |
| **36c** | F | $CO_2H$ | 210±20 |
| **36d** | H | $CO_2Me$ | 31±5 |
| **36e** | Cl | $CO_2Me$ | 41±13 |
| **36f** | F | $CO_2Me$ | 12±2 |

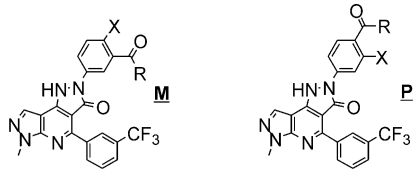
**Table 6.** In vitro B7.1–CD28 binding inhibition for 6-methyl-4-[3-(trifluoromethyl)phenyl]-dihydrodipyrazolopyridinyl benzamides

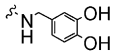
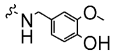
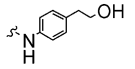
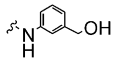
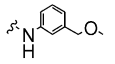
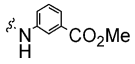
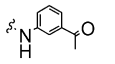
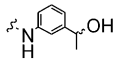


| R | R group position | Compd | X | B7.1–CD28 inhibition $IC_{50}$ (nM) |
|---|---|---|---|---|
|  | P | **36g** | H | 98±12 |
|  | P | **36h** | H | 110±12 |
| | M | **35g** | H | 180±22 |
|  | P | **36i** | H | 500±95 |
|  | P | **36j** | H | 13±4 |
| | P | **36k** | F | 310±60 |
| | M | **35h** | H | 54±24 |
| | M | **35i** | F | 2400±600 |
|  | M | **35k** | H | 44±7 |
| | P | **36n** | H | 110±20 |
|  | M | **35n** | H | 270±44 |
|  | M | **35n** | H | 20±4 |
| | M | **35o** | Cl | 44±4 |
|  | M | **35p** | H | 66±7 |

series **35a–c** showed good activity, with the addition of a *para*-chloro group (**35b**) improving activity 7-fold over **35a** while the 4-fluoro-3-carboxy analogue **35c**, was 10-fold less active than the chloro derivative. The same

**Table 7.** In vitro B7.1–CD28 binding inhibition for 6-methyl-4-[3-(trifluoromethyl)phenyl]dihydrodipyrazolopyridinyl benzamide



| R | R group position | Compd | X | B7.1–CD28 inhibition $IC_{50}$ (nM) |
|---|---|---|---|---|
|  | M | **35q** | H | 120±75 |
| | P | **36p** | H | 79±15 |
|  | M | **35r** | H | 180±30 |
|  | M | **35s** | H | 300±100 |
|  | P | **36q** | H | 36±5 |
| | M | **35t** | H | 9±1 |
| | M | **35u** | Cl | 22±4 |
|  | M | **35v** | H | 55±9 |
|  | P | **36r** | H | 23±7 |
| | P | **36s** | F | 64±11 |
|  | P | **36t** | H | 17±5 |
| | M | **35w** | H | 100±30 |
|  | P | **36u** | H | 110±20 |
|  | P | **36v** | H | 94±32 |
|  | P | **36w** | H | 44±15 |
|  | P | **36x** | H | 3±1 |
| | P | **36y** | Cl | 550±85 |

trend of binding inhibition was seen for the *para*-acid series of analogues **36b**, **36a** and **36c** (Cl > > H > F). The effect of an adjacent halogen atom on the methyl ester series showed a non-linear trend. The unsubstituted *meta*-ester analogue **35d** gave greater inhibition than the 4-Cl analogue **35e** and the 4-F analogue **35f**, while the 3-F *para*-ester **36f** was a tighter binder than either the 3-H or 3-Cl derivatives. It is not understood whether the larger chloro atom favorably effects the rotational orientation of the carboxylate group compared to the corresponding methyl ester, or if steric and/or electrostatic forces are playing a larger role. Presumably the ester analogues would be metabolically converted to the acids in vivo; nontheless, we used this SAR information to guide us in preparing other analogues of the northern ring section, particularly the amide series.

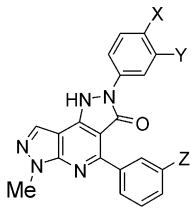
Two separate series of amides corresponding to the *meta*-carboxylic acids **35a–c** and *para*-carboxylic acid

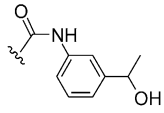
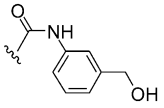
**36a–c** were studied. For the ease of discussion, the groups are further divided into amides derived from alkyl or saturated heterocyclic amines (Table 6) and amides prepared from benzylic or aromatic amines (Table 7). Building on the SAR from the various 2-substituted dihydrodipyrazolopyridinones reviewed in Table 1, we mainly focussed on incorporating functionality with the potential for hydrogen bonding, or groups without large steric volume. The amides we prepared in this study indicated that a cyclic ring system beyond the 'northern' aromatic portion with small substituents capable of accepting a hydrogen bond, or of making a charge–charge interaction were beneficial for tighter binding. The 3-hydroxy propyl amide **36g** (Table 6) gave moderate inhibition and the corresponding methyl ether **36h** was nearly as active, with a preference for this group to be in the *para*-position. The hydroxy ethyl chain was equally as active; however, longer chain derivatives with hydroxy, methoxy, ester, or amide groups were considerably less active (data not shown). Cyclic rings with an ether or hydroxy group showed improved binding over the acyclic analogues. The morpholine derivatives **36j** and **35h** showed notable activity, with the *para*-amides being tighter binders than the *meta*-amides, however; here, the fluoro-substituted analogues **36k** and **35i** showed poor binding compared to the fluoro methyl ester **36f**. The pyrrolidine analogues **35k** and **36n** gave equivalent inhibition with the *meta*-amides again showing tighter binding. The L-proline methyl ester **35m** was a weak inhibitor, however the L-proline acid **35n** at 20 nM was almost 14-fold more active. The D-proline isomer **35p** showed weaker inhibition at 66 nM indicating only slight enantiospecificity for binding in this region. While it was clear that these amide analogues did not show improved binding over the carboxylates **35b**, **35d**, or **36f**, a select group of aniline-based amides shown in Table 7 demonstrated comparable binding.

The SAR study of benzyl and aniline amides indicated some apparent trends (Table 7). The secondary benzyl analogues **35q** and **36p** were better inhibitors than the *N*-methylated and bicyclic systems represented by **35r** and **35s**, respectfully. The presence of hydroxy groups on the aromatic ring of the benzyl analogues gave improved binding over the unsubstituted derivatives as was seen for **36q** and **35t–v**. For the aniline derivatives it was clear that hydroxymethyl and hydroxyethyl groups (**36r–t** and **35w**) offered improved binding over the corresponding ester (**36v**), keto (**36w**) and methoxy (**36u**) aniline amides, with the *N*-[3-(1-hydroxyethyl)phenyl] derivative **36x** giving an $IC_{50}$ of 3 nM. As was the case with the amides in Table 6, the few amides with chloro or fluoro groups ortho to the benzamide carbonyl group were significantly less active.

Some of the more potent compounds were selected for further characterization using a cell-based assay of B7.1 stimulated signaling through CD28. The main objective of this assay was to investigate how these compounds would inhibit B7.1-CD28 signaling in an environment of high avidity. In this assay, Chinese Hamster Ovary cells expressing human B7.1 were used to stimulate the Jurkat $CD28^+$ human T cell line. Signaling through

**Table 8.** In vitro B7.1–CD28 binding inhibition and cell-based inhibition of selected 6-methyl-dihydrodipyrazolopyridinones




| Compd | X = | Y = | Z = | B7.1–CD28 inhibition (nM) | CD28–PIK3 association in Jurkat cells inhibition @ 50 μM (%) |
|---|---|---|---|---|---|
| **6q** | H | F | $NO_2$ | 4 ± 1 | 71 |
| **35b** | Cl | $CO_2H$ | $CF_3$ | 7 ± 3 | 38 |
| **36x** | H |  | $CF_3$ | 3 ± 1 | 42 |
| **35w** | H |  | $CF_3$ | 17 ± 3 | 23 |

CD28 was evaluated by monitoring its association with PI3-kinase. Briefly, CHO-B7.1 cells were pretreated with compounds at a concentration of 50 μM for 30 min on ice. Jurkat cells were added to these at a ratio of 8:1 for 12 min at 37 °C. This reaction was stopped by addition of ice-cold NP-40 lysis buffer, cell debris was removed by centrifugation, and the CD28 in the lysate was immunoprecipitated using an antibody to CD28.

These immunoprecipitates were washed with lysis buffer and resolved by electrophoresis. The CD28-associated PI3-kinase was detected by western blot using an anti-PI3-kinase antibody and quantified by densitometry. Results were then expressed compared to uninhibited controls. It should be noted that CHO-B7.1 and Jurkat cells do not form an immunological synapse. As shown in Table 8, these inhibitors were each able to inhibit PI3-kinase association with CD28 between 23 and 71%, but only at the relatively high concentration of 50 μM.

## Conclusion

Identification of potent, orally active drugs to disrupt co-stimulatory molecule interactions between T cells and antigen presenting cells faces a number of thermodynamic challenges.[17] These derive from the need to develop inhibitors with slow enough off rates to compete effectively with the multiple interactions between two cell surfaces, which result in high avidity interactions. The molecular details of these interactions were first revealed by the recently solved crystal structure of B7.1 bound to CTLA4,[29] in which CTLA4 and B7.1 pack in a strikingly periodic zipper-like arrangement. Bivalent CTLA4 homodimers bridge bivalent B7.1 homodimers to form an unusually stable signaling

complex, which is likely similar to the interactions between CD28 and B7.1 on cells. Because of this, it is not surprising that the compounds identified here, although potent inhibitors of B7.1 binding to CD28 in in vitro cell-free assays, are only weak inhibitors of CD28 signaling in cells.

Although many of the analogues reported here were capable of blocking the activation of CD28 associated PI3 kinase in Jurkat cells following stimulation with CHO-B7.1 cells, high compound concentrations were required to obtain significant levels of inhibition. This requirement for high inhibitor concentrations likely reflects the differences in dissociation rates of the small molecules from B7.1 compared to that of CD28. Since small molecules dissociate much faster from B7.1 than does CD28, therefore a high small molecule concentration is required to maintain a high percentage of occupancy of B7.1. As noted above, this difference is dissociation rates is further amplified by the fact that under physiological conditions the B7.1/CD28 interaction occurs in a specialized cell surface environment, known as the immunological synapse, where the strong multivalent complexes form. In fact, the small molecules presented here are incapable of preventing the adhesion of cells expressing CD28 to those expressing B7.1 due to the strength of these multivalent complexes.[17] Thus, it is likely that the development of suitable antagonists for such interactions will involve the identification of potent compounds with dissociation rates slow enough to effectively compete with the stable complexes formed between immune system cells.[32]

To develop analogues with slower off rates will likely involve the use of co-crystals of these current compounds with B7.1 to guide further improvements. Importantly, previous studies had mapped the binding of the dihydrodipyrazolopyridinone **1** lead compound to a site on the GFCC′C″ face of the N-terminal V-set domain of human B7.1, very near to the site of its interactions with counter receptors.[17] This small molecule binding site is not present in the homologous human B7.2, or even mouse B7.1, thus explaining the exquisite specificity of the compounds described here. Occupancy of this site by inhibitors blocked B7.1 binding not only to CD28, but also to CTLA4, although at much higher concentrations of inhibitors.[17] Therefore, this site on B7.1 may represent a rare 'hot spot' for small molecule antagonist design. To this end, the SAR reported here represent an important initial insight into modifications of this lead structure resulting in analogues with improved potency. Drug candidates from these analogues my then provide a potent means of inhibiting B7.1 mediated co-stimulation, resulting in a novel approach to immune modulation.

## Experimental

### Biology

**CD28/B7.1 ELISA.** Wells were coated with 300 ng CD28-Fc in carbonate buffer (pH 9.4) overnight at 4 °C, blocked with 1% BSA in TBS for 1 h at 22 °C, then washed 3× in TBS prior to assay. The detection complex was formed as follows: B7.1–Fc-biotin, prepared using NHS-LC-biotin (Pierce #21335) according to the manufacturers instructions (4.1 mol biotin/mol Fc), was added at 0.8 μg/mL to streptavidin–alkaline phosphatase (Caltag SA1008) at 1:1000 in TBS. Inhibitors or DMSO (1% final) were added to this complex and incubated 30 min at 22 °C. Detection complex (±inhibitors) was then added to the CD28 coated wells for 25 min at 22 °C, washed 5× with TBS, developed with the colorimetric substrate pNPP (Pierce #34045) in diethanolamine/$MgCl_2$ buffer (pH 9.5) and read at 405 nm.

**Cell-based assay for B7.1 inhibitors (co-immunoprecipitation of CD28 and PI3-kinase).** CHO-B7.1 cells were pretreated with B7.1 compounds (final concentration 50 μM) at 25 °C for 10 min, followed by a 30-min incubation at 4 °C. The cells were then mixed with Jurkat cells (Human T cell line, ATCC) and incubated for an additional 12 min at 37 °C. The ratio of CHO-B7.1 cells to Jurkat Cells in the mixture was 1:8. The reaction was stopped by addition of ice-cold NP-40 lysis buffer and the cells were incubated on ice for 30 min. The cell debris was removed by centrifugation (6 min at 14,000 rpm) and the CD28 in the lysate was immunoprecipitated using anti-CD28 (Clone 3-D10, GI) at 4 °C for 4 h. The immunoprecipitate was washed 4 × with NP-40 lysis buffer and resolved by SDS–PAGE. The CD28-associated PI3-kinase was detected by western blot using anti-PI3-kinase (UBI) and quantified by densitometry.

### Chemistry

$^1$H NMR spectra were determined on a Bruker instrument at 300 MHz unless otherwise stated. Chemical shifts (δ) are expressed in parts per million relative to the internal standard tetramethylsilane. Coupling constants (*J*) are given in Hz. Electrospray and chemical ionization ($NH_3$) mass spectra were recorded on a Hewlett-Packard 1100 series MSD spectrometer. LC spectra were recorded on a Hewlett-Packard 1100 series ALS with a diode array detector at 254 nm. Chromatographic purifications were performed either by flash chromatography using Baker 40 mm silica gel or by Biotage™ silica gel cartridges. Melting points were determined in open capillary tubes and are uncorrected. Compound purity was assessed via the results of two diverse HPLC systems; Method A: MeOH–$H_2O$ (both containing 0.1% $HCO_2H$ and 0.1% *i*PrOH). Gradient: 5% MeOH to 100% MeOH, over 7 min. Method B: $CH_3CN$–$H_2O$ (both containing 0.1% $HCO_2H$ and 0.1% *i*PrOH). Gradient: 5% $CH_3CN$ to 100% $CH_3CN$, over 7 min.

**Methyl 3-methoxy-3-(5-bromo-3-pyridinyl)-2-propenoate (2e).** To a solution of methyl 5-bromonicotinate (15.0 g, 69.4 mmol) in ethyl acetate (500 mL) was added NaH (60% in mineral oil, 2.4 g) and the mixture was gently heated at 40 °C until a mild exotherm occurred. After the solvent ceased from refluxing, additional NaH was added (2.27 g, total of 139 mmol) and the mixture heated at reflux temperature for 16 h. After allowing the

solution to cool to room temperature methylene chloride (300 mL) and water (350 mL) were added. The organic phase was washed with brine, dried over sodium sulfate and concentrated. To this oil was added acetonitrile (240 mL) and methanol (60 mL) followed by a solution of $TMSCHN_2$ in hexanes (70 mL, 2 M, 139 mmol). This solution was stirred for 36 h at which time aq HCl (5%, 50 mL) was added. After nitrogen evolution ceased, the organic layer was separated, washed with brine, dried over sodium sulfate and concentrated. The residue was chromatographed through a plug of silica gel (4:1, hexane/EtOAc) to give **2e** (10.1 g, 53%) as a light-brown solid. $^1$H NMR ($CDCl_3$) δ 8.73 (s, 2H), 8.04 (s, 1H), 5.62 (s, 1H), 3.96 (s, 3H), 3.79 (s, 3H).

**Methyl 3-methoxy-3-(3-cyanophenyl)-2-propenoate (2b).** Yield 8.98 g (64%). $^1$H NMR ($CDCl_3$) δ 7.59 (s, 1H), 7.55 (d, $J$ = 5.6 Hz, 1H), 7.43 (m, 1H), 7.33 (d, $J$ = 4.6 Hz, 1H), 4.9 (s, 1H), 3.95 (s, 3H), 3.78 (s, 3H). MS (ES+) $m/z$ 218 $(M+H)^{+1}$.

**Methyl 3-methoxy-3-(3-nitrophenyl)-2-propenoate (2c).** Yield 8.47 g (75%). $^1$H NMR ($CDCl_3$) δ 8.61 (s, 1H), 8.38 (d, $J$ = 8.6 Hz, 1H), 8.13 (d, $J$ = 8.87 Hz, 1H), 7.60 (dd, $J$ = 8.82, 8.30 Hz, 1H), 5.81 (s, 1H), 3.83 (s, 3H), 3.79 (s, 3H). MS (ES+) $m/z$ 238 $(M+H)^{+1}$.

**Ethyl 3-methoxy-3-(3-bromophenyl)-2-propenoate (2d).** Using ethyl acetate afforded 15.55 g (92%). The crude material was used in the next step and characterized as **3d**.

**Ethyl 3-methoxy-3-(3-trifluoromethylphenyl)-2-propenoate (2a).** Using ethyl acetate afforded 65.5 g (78%). The crude material was used in the next step.

**Ethyl 3-methoxy-3-phenyl-2-propenoate (2f).** Prepared according to the procedure for **2e** from commercially available ethyl benzoylacetate. Yield 2.67 g, 100%. MS (ES+) $m/z$ 207.3 $(M+H)^{+}$.

**Ethyl 3-methoxy-3-(3-fluorophenyl)-2-propenoate (2g).** Prepared according to the procedure for **2e** from commercially available ethyl 3-fluorobenzoylacetate. Yield 2.86 g, 43%. MS (ES+) $m/z$ 225.2 $(M+H)^{+}$.

**Methyl 3-methoxy-3-(3-pyridinyl)-2-propenoate (2h).** Prepared according to the procedure for **2e** from commercially available methyl nicotinoylacetate. Yield 82%. $^1$H NMR ($CDCl_3$) δ 8.82 (s, 1H), 8.64 (d, $J$ = 4.2 Hz, 1H), 7.74 (d, $J$ = 6.3 Hz, 1H), 7.38 (m, 1H), 5.59 (s, 1H), 3.88 (s, 3H), 3.73 (s, 3H); MS (ES+) $m/z$ 194 (90%, $M+H^{+}$).

**Ethyl 4-chloro-6-(5-bromo-3-pyridinyl)-1-methyl-5-pyrazolopyridinecarboxylate (3e).** To a solution of ethyl 5-amino-1-methyl-4-pyrazole carboxylate (5.91 g, 35 mmol) in THF (350 mL) was added NaH (60% in mineral oil, 4.1 g, 122 mmol). After the mixture was stirred for 30 min, **2e** (10 g, 35 mmol) was added and the mixture was heated at reflux temperature for 36 h. The resulting homogeneous solution was cooled to 0 °C and carefully acidified to pH 5 with aq HCl. The mixture was extracted with EtOAc (3 × 100 mL). The organic layer was washed with brine, dried over sodium sulfate and concentrated. The off-white solid was triturated with hexanes to give 9 g of a white solid. $^1$H NMR ($CDCl_3$) δ 8.77 (s, 3H), 8.07 (s, 1H), 5.62 (s, 1H), 3.89 (s, 3H), 3.78 (s, 3H). This solid was dissolved in phosphorus oxychloride (150 mL) and heated to reflux temperature for 2 h. The reaction mixture was concentrated, dissolved in EtOAc (200 mL), cooled to 0 °C and neutralized with aqueous sodium carbonate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. Chromatography on silica gel (3:1 hexane/EtOAc) gave **3e** (7.43 g, 65% for two steps) as a white powder. $^1$H NMR ($CDCl_3$) δ 8.78 (m, 3H), 8.17 (s, 1H), 4.18 (s, 3H), 3.81 (s, 3H); MS (ES+) $m/z$ 381.3, 383.3, 385.3 $(M+H)^{+1}$.

**Ethyl 4-chloro-6-(3-cyanophenyl)-1-methyl-5-pyrazolopyridinecarboxylate (3b).** 95% yield as a white powder. $^1$H NMR ($CDCl_3$) δ 8.21 (s, 1H), 8.04 (s, 1H), 7.91 (m, 1H), 7.79 (d, $J$ = 7.6 Hz, 1H), 7.62 (dd, $J$ = 7.83, 8.10 Hz, 1H), 4.27 (s, 3H), 380 (s, 3H). MS (ES+) $m/z$ 327$(M+H)^{+1}$.

**Ethyl 4-chloro-6-(3-nitrophenyl)-1-methyl-5-pyrazolopyridinecarboxylate (3c).** $^1$H NMR ($CDCl_3$) δ 8.62 (s, 1H), 8.35 (d, $J$ = 7.4 Hz, 1H), 8.21 (s, 1H), 8.04 (d, $J$ = 7.69 Hz, 1H), 7.68 (dd, $J$ = 7.42, 7.63 Hz, 1H), 4.23 (s, 3H), 3.84 (s, 3H). MS (ES+) $m/z$ 347 $(M+H)^{+1}$.

**Ethyl 4-chloro-6-(3-bromophenyl)-1-methyl-5-pyrazolopyridinecarboxylate (3d).** Chromatography on silica gel (5:1 hexane/EtOAc) gave **3d** (12.21 g, 57%) as a white solid. $^1$H NMR ($CDCl_3$) δ 8.09 (s, 1H), 7.76 (s, 1H), 7.51 (m, 2H), 7.24 (m, 1H), 4.31 (q, $J$ = 7.5 Hz, 2H), 4.18 (s, 3H), 1.26 (t, $J$ = 7.5 Hz, 3H).

**Ethyl 4-chloro-6-(3-trifluoromethylphenyl)-1-methyl-5-pyrazolo pyridine carboxylate (3a).** Chromatography on silica gel (3:1 hexane/EtOAc) gave 65 g of a white solid. $^1$H NMR ($CDCl_3$) δ 8.41 (s, 1H), 8.06 (d, $J$ = 0.9 Hz, 1H), 7.91 (dd, $J$ = 7.1, 0.85 Hz, 1H), 7.76 (d, $J$ = 7.1 Hz, 1H), 7.68 (ddd, $J$ = 8.2, 2.2 Hz, 1H) 4.31 (q, $J$ = 7.5 Hz, 2H), overlapping with 4.26 (s, 3H), 1.36 (t, $J$ = 7.5 Hz, 3H).

**Ethyl 4-chloro-6-phenyl-1-methyl-5-pyrazolopyridine carboxylate (3f).** Yield 1.4 g, 60% $^1$H NMR ($CDCl_3$) δ 8.19 (s, 1H), 7.69 (m, 2H), 7.49 (m, 3H), 4.22 (s, 3H), overlapping 4.21 (q, 2H), 1.09 (t, $J$ = 7.2 Hz, 3H).

**Ethyl 4-chloro-6-(3-fluorophenyl)-1-methyl-5-pyrazolopyridine carboxylate (3g).** Yield 1.59 g, 73% $^1$H NMR ($CDCl_3$) δ 8.19 (s, 1H), 7.46 (m, 3H), 7.19 (m, 1H), 4.22 (s, 3H), 3.78 (s, 3H).

**Ethyl 4-chloro-6-(3-pyridinyl)-1-methyl-5-pyrazolopyridine carboxylate (3h).** Yield 44%. $^1$H NMR ($CDCl_3$) 8.73 (d, $J$ = 4.94 Hz, 1H), 8.33 (s, 1H), 8.18 (s, 1H), 7.59 (m, 2H), 4.23 (q, $J$ = 3.8 Hz, 2H), 1.11 (t, $J$ = 3.9 Hz, 3H). MS (ES+) $m/z$ 317 $(M+H)^{+1}$.

**Ethyl 4-chloro-6-[3-(trifluoromethyl)phenyl)-1-phenyl-5-pyrazolopyridine carboxylate (26a).** Yield 1.9 g, 25% $^1$H

NMR ($CDCl_3$) δ 8.39 (s, 1H), 8.24 (d, $J=6.1$ Hz, 2H), 7.96 (s, 1H), 7.92 (d, $J=6.1$ Hz, 1H), 7.75 (d, $J=6.1$ Hz, 1H), 7.62 (m, 1H), 7.48 (m, 2H), 7.39 (m, 1H), 4.23 (q, $J=7.2$ Hz, 2H), 1.15 (t, $J=7.2$ Hz, 3H). MS (ES+) $m/z$ 446.4 $(M+H)^{+1}$.

**Methyl 1-benzyl-4-chloro-6-[3-(trifluoromethyl)phenyl)-5-pyrazolopyridine carboxylate (26b).** Prepared from methyl 5-amino-1-benzyl-1*H*-pyrazole-4-carboxylate and **2a** according to the procedure for **3a**. Purified by flash chromatography on silica gel (10:85:5 EtOAc/hexane/$CHCl_3$) in 72% yield (two steps).

**2-(4-Chlorophenyl)-6-methyl-4-[3-(trifluoromethyl)phenyl]-1,6-dihydro-dipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (1).** A solution of **3a** (0.38 g, 1 mmol) and 4-chlorophenylhydrazine (3 equiv) in anhydrous ethanol (10 mL) was stirred at reflux for 4 h. An additional 3 equiv of the hydrazine was added and the mixture was stirred for an additional 16 h. After evaporating to dryness, the residue was chromatographed over silica gel (heptane/EtOAc, 3:1) to give 357 mg (74%) of **4a** as a light-yellow solid. This material was stirred in AcOH (30 mL) at reflux temperature for 6 h. The AcOH was removed in vacuo, the resulting solid was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$. The organic layer was dried ($Na_2SO_4$), filtered and evaporated to give an orange solid that was recrystallized from EtOH/EtOAc/heptane to give 250 mg (78%) as a pink crystalline solid. $^1$H NMR (acetone-$d_6$) δ 8.55 (d, $J=6.7$ Hz, 1H), 8.48 (d, $J=8.2$ Hz, 1H), 8.32 (d, $J=8.2$ Hz, 2H), 7.91 (s, 1H), 7.67 (dd, $J=7.1$, 0.85 Hz, 1H), 7.59 (ddd, $J=8.2$, 2.2 Hz, 1H), 7.38 (d, $J=8.2$ Hz, 1H), 4.07 (s, 3H). MS (ES+) $m/z$ 444.1 $(M+H)^{+1}$ HPLC Method A: room temperature, 4.06 min, 100%. HPLC Method B: room temperature, 4.27 min, 100%.

**4-Fluorophenyl)-6-methyl-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (6b).** Prepared from 4-fluorophenylhydrazine and **3a** and obtained in 79% yield, mp 275 °C (dec.). $^1$H NMR (DMSO-$d_6$) δ 8.38 (s, 1H), 8.31 (d, $J=7.49$ Hz, 1H), 8.20 (s, 1H), 7.91 (m, 3H), 7.76 (dd, $J=7.75$, 8.73 Hz, 1H), 7.35 (dd, $J=7.71$, 8.76 Hz, 2H), 4.12 (s, 3H). MS (ES+) $m/z$ 428.2 $(M+H)^{+1}$. HPLC Method A: room temperature, 3.93 min, 97.52%. HPLC Method B: room temperature, 4.71 min, 97.32%.

**2-(3-Fluorophenyl)-6-methyl-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (6c).** Prepared from 3-fluorophenylhydrazine and **3a** and obtained in 82% yield, mp 276 °C (dec.). $^1$H NMR (DMSO-$d_6$) δ 8.49 (s, 1H), 8.41 (d, $J=8.75$ Hz, 1H), 8.18 (s, 1H), 7.90 (m, 1H), 7.81 (d, $J=8.43$ Hz, 1H), 7.73 (d, $J=8.42$, 8.71 Hz, 1H), 7.50 (m, 1H), 7.01 (m, 1H), 4.15 (s, 3H). MS (ES+) $m/z$ 428 $(M+H)^{+1}$. HPLC Method A: room temperature, 4.79 min, 98%. HPLC Method B: room temperature, 4.77 min, 98%.

**2-(3-Chloro-4-fluorophenyl)-6-methyl-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]-pyridin-3(2*H*)-one (6d).** Yield: 0.031 g (74%) of a gold-brown solid. $^1$H NMR (acetone-$d_6$) δ 4.05 (s, 3H), 7.32 (m, 1H), 7.5-7.92 (m, 3H), 8.03 (s, 1H), 8.08 (s, 1H), 8.28 (br s, 1H), 8.34 (s, 1H). MS $m/z$ 460 (M−H).

**2-(2-Fluorophenyl)-6-methyl-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (6e).** Prepared from 2-fluorophenylhydrazine and **3a** and obtained in 71% yield, mp 275.9–278.5 °C. $^1$H NMR (DMSO-$d_6$) δ 8.56 (s, 1H), 8.49 (d, $J=8.71$ Hz, 1H), 8.13 (s, 1H), 7.83 (d, $J=8.42$ Hz, 1H), 7.73 (m, 2H), 7.48 (m, 1H), 7.34 (m, 2H), 4.19 (s, 3H). MS (ES+) $m/z$ 428 $(M+H)^{+1}$. HPLC Method A: room temperature, 3.70 min, 98%. HPLC Method B: room temperature, 4.54 min, 98%.

**6-Methyl-4-[3-(trifluoromethyl)phenyl]-2-[4-(trifluoromethyl)-2-pyrimidinyl]-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (6f).** Prepared from 4-trifluoromethyl-2-pyrimidinylhydrazine and **3a** and isolated in 56% yield, mp 265.8–269 °C. $^1$H NMR (DMSO-$d_6$) δ 9.21 (s, 1H), 8.25 (m, 3H), 7.88 (d, $J=8.01$ Hz, 1H), 7.81 (d, $J=7.79$ Hz, 1H), 7.80 (m, 1H), 4.11 (s, 3H). MS (ES+) $m/z$ 480 $(M+H)^{+1}$. HPLC Method A: room temperature, 4.75 min, 98%. HPLC Method Example B: room temperature, 4.77 min, 98%.

**5-Methyl-3-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)-2-thiophenecarboxylic acid (6g).** Prepared from 2-carboxy-5-methyl-3-thiophenohydrazine and **3a** and isolated in 95% yield, mp 275 °C (dec.). $^1$H NMR (DMSO-$d_6$) δ 8.47 (s, 1H), 8.33 (m 1H), 8.25 (s, 1H), 7.89 (m, 1H), 7.67 (m, 2H), 4.15 (s, 3H), 2.22 (s, 3H). MS (ES+) $m/z$ 472 $(M-H)^{+1}$. HPLC Method A: room temperature, 4.43 min, 99.0%. HPLC Method B: room temperature, 4.04 min, 99.0%.

**6-Methyl-2-(6-oxo-1,6-dihydro-3-pyridazinyl)-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (6h).** From **3a** (1.53 g, 4 mmol) and 3-chloro-6-hydrazinopyridazine (0.87 g, 6 mmol). Yield: 0.956 g, 48% $^1$H NMR (THF-$d_8$) δ 9.8 (s, 1H), 8.15 (s, 1H), 7.79–7.55 (m, 4H), 7.38 (d, $J=0.026$ Hz, 1H), 7.07 (d, $J=0.026$ Hz, 1H), 3.93 (s, 3H), 3.82 (m, 2H), 0.83 (m, 3H). MS (ES+) $m/z$ 492.2 $(M+H)^{+1}$. To a solution of this intermediate (0.95 g, 1.9 mmol) in DMF (5 mL) was added NaH (0.16 g, 4.8 mmol). The solution was heated at 70 °C for 24 h, poured into ice water and the pH adjusted to 3. The mixture was filtered and the solid washed with cold EtOAc to give 0.8 g of a white powder. $^1$H NMR (THF-$d_8$) δ 8.59 (d, $J=0.032$ Hz, 1H), 8.44 (s, 1H), 8.35 (d, $J=0.022$ Hz, 1H), 8.06 (s, 1H), 7.80 (m, 1H), 7.72 (m, 1H), 7.29 (m, 1H), 4.48 (q, $J=0.024$ Hz, H), 4.02 (s, 3H), 1.41 (t, $J=0.047$ Hz, $J=0.024$, 3H). MS (ES+) $m/z$ 478.3 $(M+H)^{+1}$. To a solution of this material (0.1 g, 0.2 mmol) in HOAc (2 mL) and water (0.2 mL) was added KI (1 mg) The solution was heated at 100 °C for 5 days and poured into ice water. The mixture was filtered and the solid washed with cold EtOAc to give **6h** (0.51 g, 55%) as a white powder. $^1$H NMR (DMSO-$d_6$) δ 8.49 (d, $J=10.2$ Hz, 1H), 8.33 (s, 1H), 8.28–8.23 (m, 2H), 7.88 (d, $J=7.8$ Hz, 1H), 7.75 (m, 1H), 7.09 (d, $J=10.2$ Hz, 1H), 4.10 (s, 3H). MS (ES+) $m/z$ 428.1 $(M+H)^{+1}$.

HPLC Method A: room temperature, 4.51 min, 100%. HPLC Method B: room temperature, 3.91 min, 100%.

**2-(4-*tert*-Butylphenyl)-6-methyl-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (6i).** Prepared from 4-*tert*-butylphenylhydrazine and **3a** and obtained in 83% yield, mp 326 °C (dec.). $^1$H NMR (DMSO-$d_6$) δ 8.40 (s, 1H), 8.32 (d, $J$ = 8.25 Hz, 1H), 8.12 (s, 1H), 7.87 (d, $J$ = 8.1 Hz 1, 1H), 7.75 (m, 3H), 7.53 (d, $J$ = 8.71 Hz, 2H), 4.15 (s, 3H), 1.33 (s, 9H). MS (ES+) $m/z$ 466 $(M+H)^{+1}$. HPLC Method A: room temperature, 5.04 min, 100%. HPLC Method B: room temperature, 5.03 min, 100%.

**4-(6-Methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzenesulfonamide (6j).** This compound was obtained in 56% yield, mp 272–274 °C. $^1$H NMR (acetone-$d_6$) δ 8.53–8.45 (m, 3H), 8.01 (s, 1H), 7.88–7.83 (m, 3H), 7.76–7.73 (m, 2H), 4.16 (s, 3H). MS (ES+) $m/z$ 489 $(M+H)^{+1}$. HPLC Method A: room temperature, 3.40 min, 100%. HPLC Method B: room temperature, 4.49 min, 100%.

**2-(1,1′-Biphenyl-4-yl)-6-methyl-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo-[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (6k).** To a dry, single-necked, round-bottomed flask, was added biphenyl-4-yl-hydrazine HCl salt (574 mg, 2.6 mmol) and ethylene glycol (6.5 mL), followed by the addition of sodium-*tert*-butoxide (260 mg, 2.7 mmol). This heterogenous mixture was then heated to 70 °C and allowed to stir for 1 h. As the mixture cooled down to room temperature **3a** (500 mg, 1.3 mmol) was added. The reaction mixture was set to heat at 105 °C for 16 h. After heating, the reaction mixture was allowed to cool to room temperature and quenched with dilute HCl (0.6 N) and partitioned with EtOAc. The layers were separated and the organic layer was dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The crude residue obtained was purified by flash chromatography on silica gel using 7:2:1 toluene/EtOAc/hexanes to give the hydrazine derivative. A portion of this purified material was used directly in the next step: To a solution of this intermediate (80 mg, 0.15 mmol) in EtOH (1 mL), was added NaH (60% in oil; 13 mg, 0.32 mmol). After 1 h at room temperature, the reaction was quenched with dilute HCl (0.5 N) and partitioned with EtOAc. The organic layer was washed with saturated NaCl solution and dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The title compound was obtained in 0.037 g (51%) as a gold-orange solid, mp 321.3–324 °C. $^1$H NMR (acetone-$d_6$) δ 3.74 (br s, 3H), 6.95 (br m, 1H), 7.07 (m, 2H), 7.15–7.54 (br m, 6H), 7.54–7.93 (br m, 3H), 7.93–8.2 (m, 2H). MS $m/z$ 484 (M−H). HPLC Method A: room temperature, 4.40 min, 100%. HPLC Method B: room temperature, 3.09 min, 100%.

**2-[4-(Benzyloxy)phenyl]-6-methyl-4-[3-(trifluoromethyl)-phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]-pyridin-3(2*H*)-one (6l).** Prepared according to the procedure for **6l** in 45% yield after flash chromatography (1:1, hexanes/EtOAc), followed by trituration from hexanes, mp 221–223.4 °C. $^1$H NMR (acetone-$d_6$) δ 4.05 (s, 3H), 5.04 (s, 2H), 6.8 (m, 1H), 7.15–7.32 (m, 4H), 7.35–7.44 (br m, 3H), 7.55–7.66 (m, 2H), 7.72 (d, $J$ = 7.84 Hz, 1H), 8.06 (s, 1H), 8.31 (d, $J$ = 7.88 Hz, 1H), 8.37 (br s, 1H). MS $m/z$ 514 (M−H). HPLC Method A: room temperature, 4.46 min, 100%. HPLC Method Example B: room temperature, 4.59 min, 100%.

**2-[4-(Hydroxymethyl)phenyl]-6-methyl-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (6m).** To a solution of **36a** (2.0 g, 4.4 mmol) in THF (40 mL) at room temperature, was added a solution of $BH_3$ in THF (22 mL, 1 M) at a rate of 50 μL/min. A precipitate began to form, the reaction was stirred overnight at room temperature, at which time it became a homogeneous red solution. The reaction was quenched with MeOH/$H_2O$ (1:1, 30 mL) and the organic layer was removed under reduced pressure. The residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$, water and brine, dried and concentrated. Flash chromatography EtOAc/$CH_2Cl_2$; 9:1) gave 1.01 g (55%) of **6m** as a white crystalline solid, mp 97.2–100.1 °C. $^1$H NMR (DMSO-$d_6$) δ 8.51 (s, 1H), 8.42 (d, $J$ = 7.6 Hz, 1H), 8.07 (d, $J$ = 8.7 Hz, 2H), 7.93 (s, 1H), 7.69 (d, $J$ = 7.7 Hz, 1H), 7.60 (t, $J$ = 7.7 Hz, 1H), 7.34 (d, $J$ = 8.7 Hz, 2H), 4.56 (s, 2H), 4.05 (s, 3H). MS (ES+) $m/z$ 440 $(M+H)^{+1}$. HPLC Method A: room temperature, 3.37 min, 98.1%. HPLC Method B: room temperature, 4.49 min, 98.8%.

**6-Methyl-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (6n).** A solution of chloride (767 mg, 2.0 mmol) and hydrazine monohydrate (0.29 mL, 300 mg, 6.0 mmol) in 20 mL of ethanol was refluxed for 4 h. After cooling to room temperature, the precipitate was collected by filtration and then washed with water and ethyl acetate. The light-tan solid was dried in vacuum oven overnight and 474 mg (71%) of pure product was obtained, mp 281–283.2 °C. $^1$H NMR (DMSO) δ 12.81 (br s, 1H), 11.30 (br s, 1H), 8.29 (s, 1H), 8.27 (d, $J$ = 8.23 Hz, 1H), 8.12 (s, 1H), 7.88 (d, $J$ = 8.11 Hz, 1H), 7.76 (dd, $J$ = 8.22, 8.11 Hz, 1H), 4.14 (s, 3H); MS (ES+) $m/z$ 334 (100%, $M+H^+$). HPLC Method A: room temperature, 4.32 min, 99.0%. HPLC Method B: room temperature, 3.15 min, 99.0%.

**2-Benzyl-6-methyl-4-(3-trifluoromethyl-phenyl)-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (6o).** To a solution of 6-methyl-4-(3-trifluoromethyl-phenyl)-1,6-dihydro-2*H*-1,2,5,6,7-pentaaza-as-indacen-3-one (256 mg, 0.768 mmol) in a mixed solvent of dioxane and $H_2O$ (2:1, v/v, 6 mL) at 0 °C were added $Na_2CO_3$ (89 mg, 0.84 mmol) and $BOC_2O$ (184 mg, 0.843 mmol) and the reaction mixture was allowed to warm to room temperature. After 18 h, an aqueous workup provided 6-methyl-3-oxo-4-(3-trifluoromethyl-phenyl)-3,6-dihydro-2*H*-1,2,5,6,7-pentaaza-as-indacene-1-carboxylic acid *tert*-butyl ester in 95% yield (318 mg). To 6-methyl-3-oxo-4-(3-trifluoromethyl-phenyl)-3,6-dihydro-2*H*-1,2,5,6,7-pentaaza-as-indacene-1-carboxylic acid *tert*-butyl ester (0.10 mmol) in THF (1.5 mL) at 0 °C were added PS-triphenylphosphine (120 mg, 1.61 mmol/g, 0.19 mmol, Argonaut), benzyl alcohol (0.13 mmol), and DIAD (0.16 mmol). The reaction mixture was allowed

to warm to room temperature and stirred for 4 h before an aqueous workup. Silica gel chromatography yielded the desired 2-benzyl-6-methyl-3-oxo-4-(3-trifluoromethyl-phenyl)-3,6-dihydro-2*H*-1,2,5,6,7-pentaaza-as-indacene-1-carboxylic acid *tert*-butyl ester which was subjected to TFA treatment to give the title compound. $^1$H NMR ($CDCl_3$) δ 9.35 (s, 1H), 8.40 (s, 1H), 8.31 (d, $J$ = 7.5 Hz, 1H), 7.89 (s, 1H), 7.67 ( d, $J$ = 7.5 Hz, 1H), 7.54 (t, $J$ = 7.7 Hz, 1H), 7.35–7.20 (m, 5H), 4.98 (s, 2H), 4.15 (s, 3H). MS (ES+) $m/z$ 424 $(M+H)^{+1}$.

**3-[2-(3-Fluorophenyl)-6-methyl-3-oxo-1,2,3,6-tetrahydro-dipyrazolo[3,4-*b*:3,4-*d*]pyridin-4-yl]benzonitrile (6p).** Prepared according to the procedure described for **1**. $^1$H NMR ($CDCl_3$) δ 8.42 (s, 1H), 8.31 (d, $J$ = 7.8 Hz, 1H), 8.24 (s, 1H), 8.03 ($J$ = 7.6 Hz, 1H), 7.82 (m, 2H), 7.80 (m, 1H), 7.55 (m, 1H), 7.11 (m, 1H), 4.13 (s, 3H). MS (ES+) $m/z$ 385 $(M+H)^{+1}$.

**2-(3-Fluorophenyl)-6-methyl-4-(3-nitrophenyl)-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (6q).** Prepared according to the procedure of **1** to give **4c**. The crude material was used without further purification in the next step. Yield 63%. $^1$H NMR ($CDCl_3$) δ 8.42 (s, 1H), 8.28 (s, 1H), 7.88 (d, $J$ = 6.3 Hz, 2H), 7.62 (m, 1H), 7.24 (d, $J$ = 6.55 Hz, 2H), 6.97 (d, $J$ = 8.9 Hz, 2H), 4.08 (s, 3H), 3.46 (s, 3H). Cyclization in refluxing HOAc and recrystallization (EtOAc, EtOH) afforded 150 mg (85%) of **6q** as a off-white powder, mp 313 °C (dec.). $^1$H NMR ($D_2O$, 600 MHz) δ 8.73 (s, 1H), 8.42 (d, $J$ = 7.32 Hz, 1H), 8.25 (d, $J$ = 7.66 Hz, 1H), 8.20 (s, 1H), 7.79 (m, 1H), 7.64 (m, 2H), 7.58 (m, 1H), 7.11 (m, 1H), 4.12 (s, 3H). HPLC Method A: room temperature, 4.61 min, 100%. HPLC Method B: room temperature, 3.73 min, 100%.

**2-(3-Fluorophenyl)-6-methyl-4-[3-bromophenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (6r).** Prepared from 3-bromophenylhydrazine and **3a**. Recrystallization from EtOAc/EtOH provided 2.5 g (74%) of **6r** as a tan crystalline solid. $^1$H NMR (DMSO-$d_6$) δ 8.23 (s, 1H), 8.21 (d, $J$ = 1.6 Hz, 1H), 8.03 (d, $J$ = 7.8 Hz, 1H), 7.95 (d, $J$ = 7.8 Hz, 1H), 7.87 (d, $J$ = 11.5 Hz, 1H), 7.79 (dd, $J$ = 7.9, 0.85 Hz, 1H), 7.60 (d, $J$ = 7.4 Hz, 1H), 7.53 (d, $J$ = 7.4 Hz, 1H), 7.08 (ddd, $J$ = 8.3, 2.1 Hz, 1H), 4.21 (s, 3H); HPLC Method A: room temperature, 3.70 min, 98%; HPLC Method Example B: room temperature, 4.54 min, 98%.

**3-[2-(3-Fluorophenyl)-6-methyl-3-oxo-1,2,3,6-tetrahydro-dipyrazolo[3,4-*b*:3,4-*d*]pyridin-4-yl]benzoic acid (6s).** To a solution of **6p** (332 mg, 0.86 mmol) in ethylene glycol (50 mL) was added with aqueous NaOH (4.3 mL, 1 N, 4.32 mmol). The resulted yellow solution was heated to 130 °C for 20 h. The mixture was acidified with 1 N HCl solution and partitioned between $H_2O$ and EtOAc. Organic phase was neutralized by aqueous $NaHCO_3$ solution. The organic layer was removed and the aqueous phase was reacidified to pH 1. The resulting precipitate was collected by filtration to afford **6s** (331 mg, 95%) as a white solid, mp 352–354 °C. $^1$H NMR (DMSO-$d_6$) δ 8.49 (s, 1H), 8.28 (s, 1H), 8.17 (dd, $J$ = 7.82, 20.3 Hz, 1H), 8.06 (m, 1H), 7.85 (dd, $J$ = 11.5, 21.0 Hz, 2H), 7.65 (t, $J$ = 7.69 Hz, 1H), 7.51 (m, 1H), 7.07 (m, 1H), 4.11 (s, 3H). MS (ES+) $m/z$ 404 $(M+H)^{+1}$. HPLC Method A: 3.14 min, 100%. HPLC Method B: 4.28 min, 100%.

**3-[2-(3-Fluorophenyl)-6-methyl-3-oxo-1,2,3,6-tetrahydro-dipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-4-yl]benzamide (6t).** To a solution of **6p** (217 mg, 0.56 mmol) in DMSO (25 mL) and ethylene glycol (5 mL) was added 30% $H_2O_2$ (10 mL) followed by potassium carbonate (34 mg) in $H_2O$ (4 mL). After stirring for 4 h, the pH of the reaction mixture was adjusted to 5 and extracted with EtOAc (50 mL). The organic layer was dried and concentrated to afford **6t** (92 mg, 40%), mp 332–335 °C. $^1$H NMR ($D_2O$, 600 MHz) δ 8.40 (s, 1H), 8.23 (d, 10.3, 1H), 8.07 (m, 2H), 7.78 (m, 2H), 7.67 (dd, $J$ = 10.1, 7.8 Hz, 1H), 7.51 (m, 1H), 7.09 (m, 1H), 4.07 (s, 3H). MS (ES+) $m/z$ 403 $(M+H)^{+1}$. HPLC Method A: room temperature 4.04 min, 100%. HPLC Method B: room temperature 2.84 min, 100%.

**4-(5-Bromo-3-pyridinyl)-2-(3-fluorophenyl)-6-methyl-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2H)-one (6u).** To a solution of **3e** (1.3 g, 3.28 mmol) in ethanol (30 mL) was added 3-fluorophenylhydrazine (1.03 g, 8.2 mmol). The reaction was heated at reflux temperature for 6 h then concentrated. Chromatography on silica gel (hexane/EtOAc, 1:1) gave 1.1 g of **4e** (69%) as a white foam. $^1$H NMR ($CDCl_3$) δ 10.1 (s, 1H) 8.73 (s, 1H), 8.67 (s, 1H), 8.27 (s, 1H), 8.16 (d, $J$ = 0.035 Hz, 1H), 7.22 (m, 1H), 6.66 (m, 3H), 6.28 (s, 1H), 4.08 (s, 3H), 4.04 (s, 3H); MS (ES+) $m/z$ 471.3, 473.3 $(M+H)^{+1}$. To a solution of this foam (1.0 g) in DMF (20 mL) was added NaH (0.15 g). The solution was heated at 90 °C for 12 h, poured into ice water and the pH adjusted to 4. The mixture was filtered and the solid washed with cold EtOAc to give **6u** (0.8 g, 55% for two steps) as an off-white foam. $^1$H NMR (300 M, THF-$d_8$) δ 9.24 (br s, 1H), 8.78 (br s, 1H), 8.72 (s, 1H), 8.20 (s, 1H), 7.83 (d, 1H), 7.81 (d, 1H), 7.55 (m, 1H), 6.99 (m, 1H), 4.08 (s, 3H); MS (ES+) $m/z$ 441.2, 439.2 $(M+H)^{+1}$. HPLC Method A: room temperature 5.13 min, 100%. HPLC Method B: room temperature 3.59 min, 100%.

**2-(4-Fluorophenyl)-6-methyl-4-(3-nitrophenyl)-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (6v).** Prepared from 4-chlorophenylhydrazine and **3c** in 25% overall yield, mp 317–319.3 °C; $^1$H NMR (DMSO-$d_6$) 8.86 (s, 1H), 8.48 (d, 7.83, 1H), 8.39 (d, 7.97, 1H), 8.24 (s, 1H), 7.85 (m, 2H), 7.81 (m, 1H), 7.40 (m, 2H), 4.18 (s, 3H). HPLC Method A: room temperature 4.51 min, 99.1%. HPLC Method B: room temperature 3.61 min, 99.2%.

**4-(3-Aminophenyl)-2-(4-fluorophenyl)-6-methyl-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (6w).** To a solution of **6v** (102 mg, 0.25 mmol) in EtOAc (5 mL) and MeOH (10 mL) in a Parr bottle, Pd/C catalyst (27 mg) was added under nitrogen and the mixture was hydrogenated at 20 psi for 3 h. Filtration and silica gel chromatography (EtOAc) gave **6w** in 67% yield, mp 204–207 °C. $^1$H NMR (DMSO-$d_6$) 8.15 (s, 1H), 8.04 (m, 2H), 7.30 (m, 2H), 7.27 (dd, $J$ = 7.97, 8.65, 1H), 7.07 (m, 2H),

6.78 (d, $J=7.83$ Hz, 1H), 4.08 (s, 3H). HPLC Method A: room temperature 3.64 min, 96.9%. HPLC Method B: room temperature 2.46 min, 100%.

**4-(3-Fluorophenyl)-2-phenyl-6-methyl-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (6x).** Prepared according to the procedure for **1** from **2f**. $^1$H NMR (MeOH-$d_4$) δ 8.08 (s, 1H), 7.88 (m, 4H), 7.41 (m, 5H), 5.41 (s, 1H), 4.02 (s, 3H). MS (ES+) $m/z$ 376.4 $(M+H)^{+1}$. HPLC Method A: room temperature 4.72 min, 100%. HPLC Method B: room temperature 3.85 min, 100%.

**4-(3-Fluorophenyl)-2-(4-chlorophenyl)-6-methyl-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (6y).** Prepared according to the procedure for **1** from **2g**. $^1$H NMR (300 M, MeOH-$d_4$) δ 8.39 (s, 1H), 8.01 (d, $J=0.032$ Hz, 2H), 7.92 (m, 1H), 7.71 (m, 2H), 7.62 (d, $J=0.032$ Hz, 2H), 7.43 (m, 1H), 4.4 (s, 3H). MS (ES-) $m/z$ 394.3 $(M-H)^{-1}$. HPLC Method A: room temperature, 4.68 min, 100%. HPLC Method B: room temperature, 4.67 min, 100%.

**4-(3-Fluorophenyl)-6-methyl-4-(3-pyridinyl)-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (6z).** Prepared from 4-chlorophenylhydrazine and **3h** in 25% overall yield. $^1$H NMR ($CDCl_3$): 8.88 (s, 1H), 8.75 (d, $J=5.4$ Hz, 1H), 8.38 (d, $J=7.7$ Hz, 1H), 8.32 (s, 1H), 7.84 (m, 1H), 7.63 (m, 1H), 6.65 (d, $J=6.5$ Hz, 1H), 6.61 (m, 2H), 4.08 (s, 3H), 4.02 (q, $J=5.72$ Hz, 2H), 0.95 (t, $J=5.9$ Hz, 3H). MS (CI) $m/z=407$ (100%, $M+H)^{+1}$. HPLC Method A: room temperature 3.88 min, 100%. HPLC Method B: room temperature 2.52 min, 100%.

**Ethyl-4-hydroxy-1-methyl-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (8).** Sodium metal (12.7 g, 0.55 mol) was dissolved ethanol (200 mL) at room temperature. To this solution was added the ethyl aminopyrazole (25 g, 0.148 mmol) and the mixture was allowed to stir for 30 min. A solution of diethylmalonate (80 mL, 0.52 mol) in ethanol (75 mL) was added dropwise over a period of 30 min during which time the reaction was heated to reflux temperature for 56 h. After allowing the thick mixture to cool to room temperature water (500 mL) was added with stirring. The aqueous phase was washed with ethyl acetate (3 × 250 mL), then acidified with hydrochloric acid to pH 2. The resulting white solid was filtered, washed with water then ethanol then ethyl acetate and finally toluene. The cake was dried in a vacuum oven at 40 °C overnight to give 28.7 g (82%). $^1$H NMR (DMSO-$d_6$): 7.35 (s, 1H), 3.77 (q, 2H, $J=7.3$ Hz), 3.31 (s, 3H), 0.81 (t, 3H, $J=7.3$ Hz).

**Ethyl-4-chloro-1-methyl-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (9).** To a solution of **8** (10 g, 42.2 mmol) in acetonitrile (165 mL) was added benzyltriethylammonium chloride (40.4 g, 169 mmol), followed by phosphorus oxychloride (17.6 mL, 190 mmol). The mixture was heated at 40 °C for 30 min and at reflux temperature for 2.5 h. After the mixture cooled to room temperature, water was added (300 mL—CAUTION EXOTHERMIC!!). This mixture was allowed to stir overnight and then filtered. The resulting solid was washed with cyclohexane (3 × 200 mL) and dried in a vacuum oven for 24 h to give 7.87 g (73%). $^1$H NMR ($CDCl_3$): 8.15 (s, 1H), 4.59 (q, 2H, $J=7.3$ Hz), 4.07 (s, 3H), 1.51 (t, 3H, $J=7.3$ Hz).

**Ethyl-4-chloro-1-methyl-6-trifluoromethanesulfonyloxy-1*H*-pyrazolo[3,4-b]pyridine-5-carboxylate (13).** To a solution of the chloropyridone (2.56 g, 10 mmol) in methylene chloride (50 mL) and 2,6-di-*tert*-butyl-4-methylpyridine (3.07 g, 15 mmol) was cooled to −78 °C and trifluoromethanesulfonyl anhydride (3.30 mL, 18 mmol) in methylene chloride (20 mL) was added dropwise. After the addition the suspension was stirred at 0 °C for 4 h, diluted with ethyl acetate (40 mL), washed with saturated aqueous sodium bicarbonate (3 × 30 mL), water, 10% aqueous hydrochloric acid (3 × 30 mL), water and then brine. The organic layer was dried over sodium sulfate and concentrated to give 3.56 g (92%) of a tan oil that solidified in a freezer. $^1$H NMR ($CDCl_3$): 8.15 (s, 1H), 4.48 (q, 2H, $J=7.3$ Hz), 4.05 (s, 3H), 1.41 (t, 3H, $J=7.3$ Hz); MS (ES+) $m/z$: 456, 457 $(M+H)^{+1}$.

**4-(3,5-Dichlorophenyl)-2-(3-fluorophenyl)-6-methyl-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (15a).** To a solution of **13** (387 mg, 1 mmol) in THF (4 mL) was added tetrakistriphenylphosphine palladium (115 mg, 10 mol%). After stirring for 20 min at room temperature, 3,5-dichlorobenzeneboronic acid (285 mg, 1.5 mmol) was added, followed by 2 N $K_2CO_3$ (0.7 mL) and benzyltriethylammonium chloride (319 mg, 1.4 mmol). The mixture was heated at reflux temperature for 4 h, allowed to cool to room temperature and diluted with EtOAc (20 mL). The organic layer was washed with water and brine then dried over sodium sulfate and concentrated. The crude residue was chromatographed (hexane/EtOAc, 5:1) to give 127 mg (33%) of **14a** as a white solid. To this solid (120 mg, 0.31 mmol) in DMF (3 mL) was added 3-fluorophenylhydrazine (99 mg, 0.78 mmol). The reaction was heated at 100 °C for 10 h and then allowed to cool to room temperature. The reaction was diluted with EtOAc (10 mL) and water (5 mL) and the resulting precipitate collected by filtration to afford 80 mg of an off-white solid. To a suspension of this intermediate (65 mg, 0.13 mmol) in DMF (1 mL) was added NaH (14 mg, 0.41 mmol). The homogeneous solution was stirred at 100 °C for 3 h, allowed to cool to room temperature, diluted with EtOAc and collected by filtration to give 44 mg (22% for three steps) of **15a** as a pink solid. $^1$H NMR (DMSO) δ 8.29 (s, 1H), 7.88 (s, *3*H), 7.79 (m, 2H), 7.66 (m, 1H), 7.09 (s, 1H), 4.08 (s, 3H); MS (ES+) $m/z$: 430, 429 $(M+H)^{+1}$. HPLC Method A: room temperature, 4.47 min, 100%. HPLC Method B: room temperature, 3.47 min, 100%.

**2-(3-Fluorophenyl)-6-methyl-4-thien-3-yl-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2H)-one (15b).** Prepared according to the same reaction sequence as **15a** to give 35 mg (25% yield) of the title compound as an off-white solid. $^1$H NMR (acetone-$d_6$) δ 8.89 (s, 1H), 8.08 (s, 1H), 8.01 (m, 1H), 7.76 (m, 2H), 7.45 (m, 2H), 6.94 (m, 1H), 4.03 (s, 3H); MS (ES+) $m/z$: 434 $(M+H)^{+1}$.

**4-(1,3-Benzodioxol-5-yl)-2-(3-fluorophenyl)-6-methyl-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (15d).** Prepared according to the same reaction sequence as **15a** to give 41 mg (39% yield) of the title compound as an off-white solid. HPLC Method A: room temperature, 4.46 min, 100%. HPLC Method B: room temperature, 3.54 min, 100%.

**2-(3-Fluorophenyl)-4-(3-methoxyphenyl)-6-methyl-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (15c).** Prepared according to the same reaction sequence as **15a** to give 39 mg (34% yield) of the title compound as an off-white solid. $^1$H NMR (DMSO) δ 8.31 (s, 1H), 8.00 (m, 1H), 7.91 (m, 1H), 7.75–7.40 (m, 4H), 7.01 (m, 1H), 6.95 (m, 1H), 4.21 (s, 3H), 3.96 (s, 3H). HPLC Method A: room temperature, 4.23 min, 98.2%. HPLC Method B: room temperature, 3.51 min, 100%.

**2-(3-Fluorophenyl)-6-methyl-1,2,5,6-tetrahydrodipyrazolopyridin-3,4-dione (11).** To a suspension of the chloropyridone (524 mg, 2.05 mmol) in toluene (15 mL) was added the hydrazine (651 mg, 5.13 mmol) and a catalytic amount of 2,6-di-*tert*-butyl-4-methylpyridine. The mixture was heated at reflux temperature for 36 h slowly becoming homogeneous then becoming a thick slurry. The mixture was filtered and washed with cold toluene to give 624 mg (88%) of a white powder. To 550 mg of this product in 35 mL of THF was added NaH (187 mg, 60% in oil, 5.58 mmol). The mixture was heated for 24 h at reflux temperature, cooled and carefully quenched with 10% hydrochloric acid, diluted with ethyl acetate (30 mL), filtered, then washed with water and ethyl acetate to give 391 mg (83%, 73% for both steps) of a white powder. $^1$H NMR (DMSO) δ 7.91 (s, 1H), 7.69 (m, 3H), 7.01 (m, 1H), 3.98 (s, 3H).

**3-Chloro-4-chloro-2-(3-fluorophenyl)-6-methyl-2,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]-pyridine (12).** A mixture of **11** (1.5 g, 5.02 mmol) and phosphorous oxychloride (20 mL) was heated at reflux temperature for 5 h. The phosphorous oxychloride was removed in vacuo the crude residue was treated with ice water and the resulting precipitate was neutralized to pH 7 with aqueous $Na_2CO_3$. The slurry was extracted with EtOAc and the organic layer was dried over $Na_2SO_4$, filtered, and concentrated in vacuo to afford 1.2 g (75%) of the title compound as a light-yellow solid. $^1$H NMR (DMSO) δ 4.1 (s, 3H), 7.54 (br m, 1H), 7.63–7.82 (m, 3H), 8.32 (s, 1H). MS *m*/*z*: 336 (M + H).

**4-(2,6-Dimethyl-4-morpholinyl)-2-(3-fluorophenyl)-6-methyl-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (15e).** A mixture of 12 (100 mg, 0.315 mmol) and 2,6-di-methylmorpholine (0.097 mL, 0.787 mmol) in DMF (0.4 mL) was heated at 140 °C for 4 h. The reaction mixture was cooled to room temperature, quenched with water, and the pH was adjusted to ~3 with 3 N HCl. The aqueous mixture was extracted with EtOAc and the organic layer was dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel using 0.5% MeOH/$CHCl_3$ to afford 90 mg (69%) of 3-chloro-4-(2,6-dimethyl-4-morpholinyl)-2-(3-flurophenyl)-6-methyl-2,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]-pyridine as a yellow solid, mp 194.5–197 °C. $^1$H NMR ($CDCl_3$) δ 1.21 (d, $J$ = 6.27 Hz, 6H), [minor isomer 1.26 (d, $J$ = 6.47 Hz, 6H)], 2.74 (m, 2H), [minor isomer 3.07 (m, 2H)], [minor isomer 3.57 (d, $J$ = 12.73 Hz, 2H)], 3.74 (d, $J$ = 12.62 Hz, 2H), 3.9 (m, 2H), 4.00 (s, 3H), [minor isomer 4.26 (m, 2H)], 7.13–7.22 (m, 1H), 7.33–7.49 (m, 3H), 8.02 (s, 1H). MS *m*/*z*: 415 (M + H).

To a solution of 3-chloro-4-(2,6-dimethyl-4-morpholinyl)-2-(3-flurophenyl)-6-methyl-2,6-dihydrodipyrazolo-[3,4-*b*:3′,4′-*d*]-pyridine (48 mg, 0.116 mmol) and 3:1 MeOH/THF (1.6 mL), was added 4 N NaOH (0.4 mL). The reaction mixture was heated at reflux temperature for 16 h. Upon cooling to room temperature, the mixture was quenched with 3 N HCl and partitioned with EtOAc. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated in vacuo to obtain 40 mg (87%) of the title compound as a beige powder, mp 204.7–207 °C. $^1$H NMR (acetone-$d_6$) δ 1.06 (d, $J$ = 6.26 Hz, 6H), [minor isomer 1.14 (m, 6H)], 2.5 (dd, $J$ = 12.74 Hz, 10.38, 2H), [minor isomer 3.46 (m, 2H)], 3.7 (m, 2H), 3.81 (s, 3H), [minor isomer 4.05 (m, 2H)], 4.43 (d, $J$ = 12.53 Hz, 2H), 6.86 (m, 1H), 7.37 (m, 1H), 7.59 (m, 1H), 7.71 (m, 1H), 7.78 (s, 1H). MS *m*/*z*: 395 (M−H). HPLC Method A: room temperature 3.59 min, 100%. HPLC Method Example B: 4.68 min, 100%.

**2-(4-Chlorophenyl)-1,6-dimethyl-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (7a).** A solution of 46284 (49 mg, 0.12 mmol) in dry DMF ( 5 mL) was added with NaH (12 mg, 60%, 0.3 mmol) under argon at room temperature. The suspension was stirred for 30 min and then followed by the dropwise addition of methyl triflate. The mixture was stirred at room temperature for a further 30 min, and diluted with ethyl acetate. The organic layer was washed with $H_2O$ (3×), brine, and dried over $MgO_4$. The crude residue obtained was purified by flash chromatography on silica gel using 1:1 EtOAc/hexane as the eluant to give **7a** as a yellow solid (41 mg, 82%), mp 203.9–204.4 °C. $^1$H NMR ($CDCl_3$) δ 8.34 (s, 1H), 8.29 (d, $J$ = 8.65 Hz, 1H), 8.22 (s, 1H), 7.75 (d, $J$ = 8.43 Hz, 1H), 7.63 (dd, $J$ = 8.62, 8.43 Hz, 1H), 7.50 (m, 4H), 4.30 (s, 3H), 3.61 (s, 3H). MS (ES+) *m*/*z* 458 $(M+H)^{+1}$. HPLC Method A: room temperature, 4.44 min, 100%. HPLC Method B: room temperature, 4.82 min, 100%.

**7-Methyl-2-phenyl-5-[3-(trifluoromethyl)phenyl]-1,7-dihydro-4*H*-pyrazolo[4′,3′:5,6]pyrido[4,3-d]pyrimidin-4-one (19).** Benzamidine hydrochloride salt (5.0 g, 32 mmol) was dissolved in $CH_2Cl_2$ (100 mL) and $H_2O$ (100 mL) and neutralized by adding NaOH (12.8 mL, 2.5 M, 32 mmol). After stirring at room temperature for 2 h, organic layer was separated, washed with brine and dried with $MgO_4$. Benzamidine was obtained as white solid (3.01 g, 78%) and used for the following reaction. Starting material chloride (0.43 g, 1.12 mmol) was dissolved in 20 mL of ethanol and added with benzamidine (0.404 g, 3.36 mmol). The mixture was heat to reflux for 2 days and then cool to room temperature. After removing ethanol in vacuo, the residue was partitioned between EtOAc and $H_2O$. Regular workup and chro-

matography afford the desired product (0.208 g, 44%) as a white solid with starting material (0.129 g, 30%) recovered, mp 344.3–346.1 °C. $^1$H NMR (DMSO-$d_6$) δ 8.58 (s, 1H), 8.34 (d, $J$ = 7.01 Hz, 2H), 7.90 (m, 2H), 7.81 (d, $J$ = 6.83 Hz, 1H), 7.65 (m, 4H), 4.11 (s, 3H). MS (ES+) $m/z$ 421 $(M+H)^{+1}$. HPLC Method A: room temperature 4.14 min, 100%; HPLC Method B: 4.89 min, 100%.

**Ethyl 2-[3-(trifluoromethyl)phenyl]nicotinate (22).** In a flask flushed with nitrogen was placed ethyl 2-chloronicotinate (1.24 g, 6.67 mmol), DME (20 mL), and tetrakistriphenylphosphine palladium (385 mg, 0.33 mmol, 0.05 equiv). Potassium carbonate (1.84 g, 13.34 mmol, 2 equiv), in water (4 mL) and *m*-trifluoromethylphenylboronic acid (1.65 g, 8.67 mmol, 1.3 equiv) in 4 mL of DME were added sequentially, and the mixture was heated to reflux temperature for 20 h. Evaporation of the solvent left a residue, which was purified by chromatography on silica gel to give 1.67 g of desired coupling product **22** in 85% yield. $^1$H NMR ($CDCl_3$) δ 8.82 (d, $J$ = 6.9 Hz, 1H), 8.25 (d, $J$ = 8.5 Hz, 1H), 7.83 (s, 1H), 7.75 (m, 2H), 7.6 (dd, $J$ = 6.5 Hz, $J$ = 8.3 Hz, 1H), 7.4 (dd, $J$ = 6.6 Hz, $J$ = 6.5 Hz, 1H), 4.20 (q, $J$ = 6.3 Hz, 2H), 1.1 (t, $J$ = 6.2 Hz, 3H). MS (CI) $m/z$ = 296 $(M+H^+)$.

**4-Bromo-2-[3-(trifluoromethyl)phenyl]nicotinic acid (23).** To a solution of **22** (1.38 g, 4.71 mmol) dissolved in DMSO (15 mL) and methanol (15 mL) was added with a 2 N NaOH solution (14 mL, 28 mmol, 6 equiv). The mixture was stirred at room temperature for 3 h. The mixture was then diluted with ethyl acetate, neutralized with 2 N HCl, and washed with water (3×), brine, and dried. Concentration in vacuo gave 1.18 g of 2-[3-(trifluoromethyl)phenyl]nicotinic acid in 95% yield. $^1$H NMR ($CDCl_3$) δ 8.82 (d, $J$ = 4.2 Hz, 1H), 8.27 (d, $J$ = 6.3 Hz, 1H), 7.78 (s, 1H), 7.54 (m, 4H). MS (CI) $m/z$ = 266 $(M-H^+)$. This intermediate was dissolved in dry THF (20 mL) and TMEDA (0.31 mL, 2.1 equiv). The solution was cooled to −78 °C and added to a solution of 2.5 M *n*-BuLi (0.84 mL, 2.1 mmol, 2.1 equiv) dropwise via cannula. After the addition was complete, the resulting yellow solution was stirred for 1 h. A solution of trimethylphenylammonium tribromide (789 mg, 2.1 mmol, 2.1 equiv) in THF (8 mL) was added slowly and the mixture was kept at this temperature for 0.5 h then slowly warm to room temperature. Regular workup and column chromatography provided 155 mg of product **23** in 45% yield. $^1$H NMR (MeOH) δ 8.31 (d, $J$ = 4.1 Hz, 1H), 8.0 (s, 1H), 7.94 (m, 1H), 7.7 (m, 4H). MS (CI) $m/z$ = 345 $(M-H^+)$.

**2-(3-Fluorophenyl)-4-[3-(trifluoromethyl)phenyl]-1,2-dihydro-3*H*-pyrazolo[4,3-*c*]pyridin-3-one (24).** Treatment of **23** with TMS-diazomethane, addition of 3-fluorophenyl hydrazine and cyclization in refluxing ethanol gave compound **24** in 39% yield, mp 185–187 °C. $^1$H NMR ($CDCl_3$) δ 8.80 (d, $J$ = 6.10 Hz, 1H), 8.47 (s, 1H), 8.39 (d, $J$ = 7.75 Hz, 1H), 7.96 (d, $J$ = 7.85 Hz, 1H), 7.81 (dd, $J$ = 7.75, 7.76 Hz, 1H), 7.71 (dd, $J$ = 8.96, 7.28 Hz, 2H), 7.60 (m, 1H), 7.54 (m, 1H), 7.33 (m, 1H). HPLC Method A: room temperature, 3.40 min, 100%. HPLC method B: room temperature, 4.63 min, 100%.

**2-(3-Fluorophenyl)-6-phenyl-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (27).** Prepared according to the procedure of **1** from 3-fluorophenyl hydrazine and **26a** (0.03 g, 21% overall) as a white foam. $^1$H NMR (300 M, THF-$d_8$) δ 11.45 (s, 1H), 8.61 (s, 1H), 8.41 (m, 3H), 7.80 (m, 3H), 7.64 (m, 1H), 7.50 (m, 4H), 7.35 (m, 1H), 6.99 (m, 1H) MS (ES-) $m/z$ 488.2 $(M-H)^{-1}$. HPLC Method A: room temperature 5.15 min, 98.2%. HPLC method B: room temperature 4.71 min, 100%.

**6-Benzyl-2-(4-fluorophenyl)-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (32).** Prepared according to the procedure of **1** from 4-fluorophenyl hydrazine and **26b**. Cyclization and flash chromatography on silica gel (25:60:15 to 40:40:20 EtOAc/hexane/$CH_2Cl_2$) gave **32** as a brownish foam in 82% yield. $^1$H NMR ($CDCl_3$ + acetone-$d_6$) δ 8.36 (s, 3H), 8.33 (s, 3H), 8.14 (s, 1H), 7.84–7.80 (m, 2H), 7.70 (d, $J$ = 8.2 Hz, 1H), 7.62 (m, 1H), 7.36 (d, $J$ = 7.2 Hz, 2H), 7.29–7.21 (m, 3H), 7.13 (t, $J$ = 8.8 Hz, 2H). MS (ES+) $m/z$ 504.2 $(M+H)^{+1}$. HPLC Method A: room temperature 5.00 min, 97.2%. HPLC method B: room temperature 4.47 min, 100%.

**2-(4-Fluorophenyl)-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (29).** To a suspension of **32** (964 mg, 1.91 mmol) in methanol (96 mL) were added 4 M HCl (20 mL, in 1,4-dioxane) and Pd/C (10%, 650 mg). The reaction mixture was stirred at room temperature under 1 atm $H_2$ for 18 h before it was filtered through Celite and rinsed with methanol. The volatiles were evaporated and the residue was redistributed in EtOAc and water. After adjustment of the pH to 8, the layers were separated and the aqueous was further extracted with EtOAc. The combined organic layers were dried over $K_2CO_3$ and evaporated to yield the title compound in quantitative yield as an orange solid. MS (ES+) $m/z$ 414.2 $(M+H)^{+1}$. HPLC Method A: room temperature, 4.44 min, 100%. HPLC method B: room temperature, 3.33 min, 100%.

**1-Benzyl-2-(4-fluorophenyl)-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (28a).** To a solution of **29** (720 mg, 1.74 mmol) in DMF (20 mL) at 0 °C were added *i*$Pr_2$NEt (606 μL, 3.48 mmol) and BnBr (228 μL, 1.91 mmol). The reaction mixture was maintained at 4 °C for 16 h before partitioning into EtOAc/water. Extractive workup followed by column chromatography on silica gel (30–40% EtOAc in hexanes) gave the title compound in 78% yield.

**6-Ethyl-2-(4-fluorophenyl)-4-[3-(trifluoromethyl)phenyl)-1,2-dihydro-3H-pyrazolo[4,3-*c*]pyridin-3-one (30).** To **28a** in methanol (1 mL) was added NaH (0.70 mmol) at 0 °C and the reaction mixture was stirred at the same temperature for 20 min before iodoethane (0.89 mmol) was introduced. The reaction mixture was allowed to warm to room temperature and stirring was continued for 4.5 days before aqueous workup. Silica gel chroma-

tography gave **28b** in 38% yield along with 32% of its N-1 regioisomer. **28b** was subjected to hydrogenolysis using $Pd(OH)_2$ in methanol to give the title compound in 41% yield after silica gel chromatography (70% EtOAc in hexanes). MS (ES+) $m/z$ 442.3 $(M+H)^{+1}$.

**2-(4-Fluorophenyl)-6-propyl-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (31).** The title compound was prepared according to the procedure for **30** except that allyl bromide was used in the alkylation step to give **28c**. Hydogenolysis afforded **31** in 43% yield (for two steps). MS (ES+) $m/z$ 456.4 $(M+H)^{+1}$.

**2-(4-Fluorophenyl)-4-[3-(trifluoromethyl)phenyl]-1,2-dihydro-3H-pyrazolo[3,4-*d*]thieno[2,3-*b*]pyridin-3-one (7).** The title compound was prepared according to the procedure for **6a** except that 2-amino-thiophene-3-carboxylic acid methyl ester was used in the condensation with **2a**. $^1$H NMR ($CDCl_3$) δ 8.03 (d, $J=7.14$ Hz, 1H), 7.98–7.93 (m, 2H), 7.87 (s, 1H), 7.59 (d, $J=8.0$ Hz, 1H), 7.49 (d, $J=8.0$ Hz, 1H), 7.14 (d, $J=5.2$ Hz, 1H), 6.82 (app t, $J=9.1$ Hz, 2H).

**3-(6-Methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzoic acid (35a).** To a solution of 3-hydrazino-benzoic acid **34a** (7.14 g, 0.047 mol) and ethylene glycol (160 mL) was added sodium-*tert*-butoxide (4.5 g, 0.047 mol). The mixture was stirred at 75 °C for 1 h. Upon cooling to room temperature **3a** (6 g, 15.6 mmol) was added. Heating was resumed and increased to 100 °C where the reaction mixture was allowed to stir for an additional 16 h. After 16 h, additional sodium *tert*-butoxide (2.5 g, 0.026 mol) was added. The mixture was allowed to cool to room temperature and quenched with water (200 mL) followed by acidification using 3 N HCl to pH ~3. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to a hot trituration (65 °C for 1 h) in EtOAc/MeOH (1.5:1) with stirring at room temperature for 3 h. The slurry was filtered and washed with cold EtOAc to afford 5.8 g (82%) of the title compound as a tan powder, mp 289–291 °C. $^1$H NMR [acetone-$d_6$ (5% v/v DMSO-$d_6$)] δ 4.05 (s, 3H), 7.51 (t, $J=7.97$ Hz, 1H), 7.63 (dd, $J=7.83$ Hz, 7.55, 1H), 7.75 (m, 2H), 8.11 (s, 1H), 8.2 (d, $J=7.97$ Hz, 1H), 8.3 (d, $J=7.83$ Hz, 1H), 8.36 (s, 1H), 8.44 (s, 1H). MS (ES+) $m/z$: 454 $(M+H)^{+1}$. HPLC Method A: room temperature, 3.52 min, 100%. HPLC method B: room temperature, 3.94 min, 100%.

**2-Chloro-5-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyra-zolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzoic acid (35b).** To solution of 5-amino-2-chlorobenzoic acid **33b** (10.3 g, 60 mmol) in hydrochloric acid 40 mL at 0 °C was added $NaNO_2$ (4.8 g, 70 mmol) in water (20 mL) at a rate that maintained the temperature below 10 °C. After stirring for 30 min, a solution of tin chloride dihydrate (33.9 g, 150 mmol) in water (10 mL) and HCl (40 mL) was added at a rate that maintained the temperature below 10 °C. Stirring of this viscous mixture was maintained by periodically adding additional water and HCl as necessary. The mixture was stirred at 5 °C for an additional 1 h and filtered. The crude material was dissolved in hot water (250 mL), filtered twice and the crystals collected upon cooling to give 9.6 g, 71% of 2-chloro-5-hydrazinobenzoic acid hydrochloride (**34b**). $^1$H NMR (DMSO-$d_6$) δ 8.49 (s, 1H), 7.46 (d, $J=6.3$ Hz, 1H), 7.35 (s, 1H), 7.06 (d, $J=6.3$ Hz, 1H).

Starting from 4-amino-2-chlorobenzoic acid **33c**, 2-chloro-4-hydrazinobenzoic acid **34c** was prepared in the same manner. Yield: 7.62 g, 57%. A solution of 2-chloro-5-hydrazino-benzoic acid-HCl **34b** (2.32 g, 10.4 mmol) and ethylene glycol (15 mL) was treated with sodium-*tert*-butoxide (2.0 g, 20.8 mmol) in portions maintaining the temperature <35 °C. Following the addition this solution was inversely added to a hot (120 °C) solution of **3a** (2.0 g, 5.2 mmol) and ethylene glycol (12 mL). The reaction mixture was stirred at 125 °C for 15 h. After allowing the mixture to cool to room temperature, more sodium-*tert*-butoxide (0.76 mg, 7.9 mmol) was added and heating was resumed (125 °C) for an additional 2–3 h. The reaction mixture was allowed to cool to room temperature and quenched with dilute HCl (0.6 N) and partitioned with EtOAc. The layers were separated and the organic layer was dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The crude residue obtained was subjected to a hot trituration in EtOAc/MeOH (1.25:1) for 1 h at reflux. When cooled to room temperature, the slurry was filtered and washed with a 4:1 EtOAc/MeOH solution to afford 1.2 g (42%) of the title compound as a tan solid, mp 335.6–338 °C. $^1$H NMR [acetone-$d_6$ (5% v/v DMSO-$d_6$)] δ 3.74 (s, 3H), 7.21 (d, $J=8.82$ Hz, 1H), 7.34 (t, $J=7.81$ Hz, 1H), 7.44 (d, $J=7.78$ Hz, 1H), 7.82 (br s, 2H), 7.96 (d, $J=7.72$ Hz, 1H), 8.02 (br s, 2H). MS $m/z$: 488 (M+H). HPLC Method A: room temperature 4.69 min, 100%. HPLC method B: room temperature 3.64 min, 100%.

**2-Fluoro-5-[6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-2(1*H*)-yl]benzoic acid (35c).** Prepared in 92% yield according to the procedure above from **34d** and **3a**, mp >375 °C. $^1$H NMR (methanol-$d_4$) 8.25 (s, 1H), 8.15 (m, 3H), 7.82 (m, 3H), 7.19 (m, 1H), 4.13 (br s, 3H). MS (ES+) $m/z$ 472.1 $(M+H)^{+1}$. HPLC Method A: room temperature 4.56 min, 100%. HPLC method B: room temperature 3.50 min, 100%.

**Methyl 3-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzoate (35d).** To a dry, single-necked, round-bottomed flask was added **35a**, (300 mg, 0.662 mmol) followed by MeOH (2 mL) and HCl (4 M solution in dioxane, 0.7 mL). The resulting suspension was heated to reflux for 10 h. The reaction mixture was quenched with $H_2O$ and partitioned with EtOAc and saturated NaCl solution. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated. The crude residue obtained was triturated from diethyl ether followed by filtration to afford 205 mg (66%) of the title compound as a bright orange solid, mp 275–277 °C. $^1$H NMR (DMSO-$d_6$) δ 3.91 (s, 3H), 4.13 (s, 3H), 7.6–8.08 (m, 4H), 8.15–8.42 (m, 4H), 8.51 (s, 1H). MS (ES+) $m/z$: 468.2 $(M+H)^{+1}$

HPLC Method A: room temperature, 3.99 min, 100%. HPLC Method Example B: room temperature, 4.79 min, 100%.

**Methyl-2-chloro-5-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]-pyridin-2(1*H*)-yl)benzoate (35e).** Prepared by the method described for **35d** starting from **35b**. Yield: 65 mg (63%) of an orange-brown solid, mp 211–214 °C. $^1$H NMR (acetone-$d_6$): 3.75 (s, 3H), 3.89 (s, 3H), 7.29 (d, $J$ = 8.86 Hz, 1H), 7.45 (m, 1H), 7.55 (m, 1H), 7.77 (s, 1H), 8.39 (d, $J$ = 7.79 Hz, 1H), 8.44 (s, 1H), 8.46 (s, 1H), 8.70 (s, 1H). MS $m/z$ 502 (M + H). HPLC Method A: 4.13 min, 100%. HPLC Method Example B: 4.87 min, 97.29%.

**Methyl 2-chloro-4-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzoate (36e).** To a solution of methyl 2-chloro-4-nitrobenzoate (5 g, 23 mmol) in EtOAc (100 mL) was added a tin chloride dihydrate (17.6 g, 78 mmol). After stirring overnight at room temperature a solution of 1 N NaOH was added to bring the pH 9. The aqueous solution was extracted with EtOAc (5 × 100 mL), washed with water, brine and concentrated to give methyl 4-amino-2-chlorobenzoate as a white solid 2.74 g, 64%. This ester was then treated according to the procedure for the preparation of 2-chloro-5-hydrazinobenzoic acid hydrochloride (the internal temperature of these reactions were maintained at −5 °C to prevent possible ester hydrolysis) to give methyl 2-chloro-4-hydrazinobenzoate **34e** as a white crystalline solid (2.35 g, 50%). $^1$H NMR (DMSO-$d_6$) 8.01 (s, 1H), 7.68 (dd, $J$ = 8.7 Hz, 1H), 6.86 (d, $J$ = 1.9 Hz, 1H), 6.69 (dd, $J$ = 8.7 Hz, 1.9, 1H) 5.02 (br s, 2H) 3.74 (s, 3H).

Starting from methyl 2-chloro-5-nitrobenzoate **33f**, methyl 2-chloro-5-hydrazinobenzoate **34f** was prepared in the same manner. Yield: 7.4 g, 80% $^1$H NMR (DMSO-$d_6$) δ 8.43 (br s, 1H) 8.01 (s, 1H), 7.52 (dd, $J$ = 2.6 Hz, 1H), 7.26 (d, $J$ = 8.7 Hz, 1H), 7.22 (dd, $J$ = 8.7 Hz, 2.6, 1H), 3.86 (s, 3H). 2.92 (br s, 2H).

**Methyl-2-fluoro-5-[6-methyl-3-oxo-4-[3-(trifluoromethyl)-phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-2(1*H*)-yl]benzoate (35f).** Methyl 2-fluoro-4-hydrazinobenzoate **34g** was prepared from methyl 2-fluoro-4-nitrobenzoate **33g** as described in the procedure for **36e**. The title compound was prepared in 53% yield following the procedure above, mp 263–265.8 °C. $^1$H NMR (acetone-$d_6$) δ 8.42 (s, 1H), 8.35 (m, 4H), 7.55 (m, 2H), 7.48 (m, 2H), 3.82 (s, 3H), 1.95 (s, 3H). MS (ES+) $m/z$ 486.2 $(M+H)^{+1}$. HPLC Method A: room temperature, 3.95 min, 100%; HPLC Method B: room temperature, 4.73 min, 96.3%.

**4-(6-Methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzoic acid (36a).** Obtained in 69% yield according to the procedure for **35a** starting from 4-hydrazinobenzoic acid **34h**, mp 315–318.6 °C; $^1$H NMR (DMSO) δ 8.25 (m, 3H), 8.07 (br s, 4H), 7.94 (d, $J$ = 7.5 Hz, 1H), 7.78 (t, $J$ = 7.5 Hz, 1H), 4.15 (s, 3H); MS (ES+) $m/z$ 454.1 $(M+H)^{+1}$ HPLC Method A: room temperature 3.53 min, 97.2%; HPLC Method Example B: room temperature 4.92 min, 100%.

**2-Chloro-4-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzoic acid (36b).** To a solution of THF (4 mL), MeOH (1 mL), and 1 N LiOH (2.57 mL) was added **36e** (129 mg). The mixture was stirred overnight and acidified with aqueous HCl to pH 4. The aqueous layer was extracted with EtOAc, dried and concentrated to give a white foam that was recrystallized from hot EtOAc to give the title compound as a white solid (121 mg, 97%). $^1$H NMR (DMSO-$d_6$) δ 8.55 (d, $J$ = 1.6 Hz, 1H), 8.39–8.30 (m, 3H), 7.94 (s, 1H), 7.88 (d, $J$ = 8.7 Hz, 1H), 7.77 (d, $J$ = 7.7 Hz, 1H), 7.68 (m, 1H), 3.97 (s, 3H).

**Methyl 4-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzoate (36d).** Obtained in 57% yield according to the procedure for **35d** starting from **36a**: mp 292–294.2 °C. $^1$H NMR (DMSO-$d_6$) δ 8.31 (m, 4H), 8.01 (s, 1H), 7.94 (d, $J$ = 8.8 Hz, 2H), 7.63 (d, $J$ = 7.7 Hz, 1H), 7.55 (t, $J$ = 7.7 Hz, 1H), 3.94 (s, 3H), 3.68 (s, 3H); MS (ES+) $m/z$ 468.1 $(M+H)^{+1}$. HPLC Method A: room temperature, 4.07 min, 97.4%; HPLC Method Example B: room temperature, 4.85 min, 100%.

**Methyl-2-fluoro-4-[6-methyl-3-oxo-4-[3-(trifluoromethyl)-phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-2(1*H*)-yl]benzoate (36f).** Isolated in 95% yield according to the procedure for **36e**, mp 260–262.4 °C. $^1$H NMR ($CDCl_3$) 8.16 (s, 1H), 8.08 (d, $J$ = 7.40 Hz, 1H), 7.97 (s, 1H), 7.75 (dd, $J$ = 8.23 Hz, 8.32, 1H), 7.51 (m, 4H), 4.14 (s, 3H), 3.81 (s, 3H). MS (ES+) $m/z$ 486.2 $(M+H)^{+1}$. HPLC Method A: room temperature 4.04 min, 100%. HPLC Method B: 4.86 min, 100%.

**2-Fluoro-4-[6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-2(1*H*)-yl]benzoic acid (36c).** Obtained in 86% yield from **36f** according to the procedure for **36b**, mp 235 °C (dec.). $^1$H NMR (methanol-$d_4$) 8.27 (s, 1H), 8.21 (d, $J$ = 7.64 Hz, 1H), 8.14 (s, 1H), 7.97 (m, 2H), 7.85 (m, 2H), 7.68 (dd, $J$ = 7.73, 7.77 Hz, 1H), 4.12 (s, 3H). MS (ES+) $m/z$ 472.1 $(M+H)^{+1}$. HPLC Method A: room temperature 4.63 min, 100%. HPLC method B: room temperature 3.56 min, 100%.

### General procedure for the preparation of dihyrodipyrazolopyridine carboxamides

To a dry, single-necked, round-bottomed flask were added the appropriate dihydrodipyrazolo pyridine benzoic acid and DMF (0.2 M) followed by the subsequent addition of the desired amine (3 equiv), EDC HCl salt (2 equiv), and diisopropylethylamine (1.8 equiv). After the additions were complete, the solution was allowed to stir at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate and partitioned with dilute acid (0.5 N HCl). After the layers were separated, the organic layer was washed with saturated aqueous NaCl, dried over $Na_2SO_4$, filtered, and concentrated on

a rotary evaporator. The crude residue obtained was further purified by flash chromatography where needed.

**N-(3-Hydroxypropyl)-4-[6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-2(1*H*)-yl]benzamide (36g).** Obtained in 42% yield, mp 193 °C (dec.). $^1$H NMR (DMSO-$d_6$) δ 8.21 (s, 1H), 8.16 (d, $J$ = 7.69 Hz, 1H), 8.05 (m, 3H), 7.84 (d, $J$ = 8.79 Hz, 2H), 7.69 (d, $J$ = 8.35 Hz, 1H), 7.61 (dd, $J$ = 7.69, 8.73 Hz, 1H), 4.87 (s, 1H), 4.05 (s, 3H), 3.61 (t, $J$ = 6.32 Hz, 2H), 3.44 (t, $J$ = 6.80 Hz, 2H), 3.26 (br s, 1H), 1.79 (m, 2H). MS (ES+) $m/z$ 511 $(M+H)^{+1}$. HPLC Method A: room temperature 3.31 min, 100%. HPLC Method B: room temperature 4.88 min, 98.9%.

***N*-(3-Methoxypropyl)-4-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzamide (36h).** Isolated in 85% yield as yellow solid. mp: 160 °C (dec). $^1$H NMR ($CDCl_3$) 8.24 (d, $J$ = 9.2 Hz, 1H), 8.2 (s, 1H), 7.61 (d, $J$ = 7.96 Hz, 2H), 7.49 (m, 1H), 7.38 (d, $J$ = 7.82 Hz, 2H), 7.35 (m, 1H), 4.19 (s, 3H), 3.44 (m, 4H), 3.28 (s, 3H), 1.77 (m, 2H). MS (ES+) $m/z$ 525 $(M+H)^{+1}$. HPLC Method A: room temperature 3.48 min, 96%. HPLC Method B: room temperature 4.33 min, 99%.

***N*-(3-Methoxypropyl)-3-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzamide (35g).** Yield: 0.025 g (14%) of an orange-brown solid after flash chromatography (95:5%, $CH_2Cl_2$/MeOH), mp 180.9–183.7 °C. $^1$H NMR ($CDCl_3$): 3.36 (s, 3H), 3.4–3.57 (br m, 4H), 4.24 (s, 3H), 7.15 (br s, 2H), 7.32 (br s, 1H), 7.57 (m, 1H), 7.61–7.75 (br m, 2H), 7.84 (s, 1H), 8.16–8.27 (m, 2H), 8.33 (s, 1H). MS $m/z$: 523 (M−H). HPLC Method A: room temperature 3.53 min, 100%. HPLC Method B: room temperature 4.84 min, 100%.

**6-Methyl-2-{4-[(4-methyl-1-piperazinyl)carbonyl]phenyl}-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (36i).** Obtained in 70% yield, mp 191–193.5 °C. $^1$H NMR ($CDCl_3$) 8.32 (s, 1H), 8.29 (s, 1H), 8.25 (d, $J$ = 7.97 Hz, 1H), 8.04 (d, $J$ = 8.51 Hz, 2H), 7.89 (d, $J$ = 7.83 Hz, 1H), 7.75 (dd, $J$ = 7.97 Hz, 8.41, 1H), 7.60 (d, $J$ = 8.51 Hz, 2H), 4.10 (s, 3H), 3.4 (m, 4H), 3.18 (m, 2H), 2.77 (br s, 3H), 2.43 (m, 2H). MS (ES+) $m/z$ 536 $(M+H)^{+1}$. HPLC Method A: room temperature 2.69 min, 100%. HPLC Method B: room temperature 3.80 min, 100%.

**6-Methyl-2-[4-(4-morpholinylcarbonyl)phenyl]-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (36j).** Obtained in 35% yield, mp 286.8–290.1 °C. $^1$H NMR (DMSO-$d_6$) 8.49–8.32 (m, 4H), 7.94 (s, 1H), 7.80 (d, $J$ = 7.9 Hz, 1H), 7.62 (t, $J$ = 7.9 Hz, 1H), 7.41 (d, $J$ = 8.8 Hz, 2H), 3.96 (s, 3H), 3.62–3.35 (m, 8H). MS (ES+) $m/z$ 523 $(M+H)^{+1}$. HPLC Method A: room temperature 3.41 min, 100%. HPLC Method B: room temperature 4.52 min, 100%.

**2-[3-Fluoro-4-(morpholin-4-ylcarbonyl)phenyl]-6-methyl-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(2*H*)-one (36k).** Obtained in 26% yield, mp 219 °C (dec.). $^1$H NMR ($CDCl_3$) 8.18 (s, 1H), 8.07 (d, $J$ = 6.38 Hz, 2H), 7.55 (br s, 1H), 7.42 (m, 3H), 6.89 (m, 1H), 4.14 (s, 3H), 3.65 (m, 4H), 3.45 (m, 2H), 3.14 (m, 2H). MS (ES+) $m/z$ 541 $(M+H)^{+1}$. HPLC Method A: room temperature 4.59 min, 100%. HPLC Method B: room temperature 4.57 min, 100%.

**6-Methyl-2-[3-(4-morpholinylcarbonyl)phenyl]-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo-[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (35h).** Obtained in 66% yield (0.113 g) of a yellow solid after flash chromatography (80:20%, EtOAc/EtOH), mp 234.8 °C (dec.). $^1$H NMR ($CD_3OD$): 3.33–3.77 (br m, 8H), 4.08 (s, 3H), 7.24 (d, $J$ = 7.28 Hz, 1H), 7.52 (dd, $J$ = 7.69 Hz, 7.42, 1H), 7.64 (dd, $J$ = 7.89 Hz, 8.1, 1H), 7.76 (d, $J$ = 7.69 Hz, 1H), 7.94, (br s, 2H), 8.12 (s, 1H), 8.22 (d, $J$ = 7.55 Hz, 1H), 8.28 (s, 1H). MS $m/z$: 525 (M + H). HPLC Method A: room temperature 4.41 min, 100%. HPLC method B: room temperature 3.44 min, 100%.

**6-Methyl-2-[3-(1-pyrrolidinylcarbonyl)phenyl]-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (35k).** Yield: 0.06 g (36%) of a light yellow solid after flash chromatography (95:5%, $CH_2Cl_2$/MeOH), mp 255–258 °C. $^1$H NMR ($CDCl_3$): 1.9 (m, 2H), 2.0 (m, 2H), 3.36 (m, 2H), 3.7 (m, 2H), 4.26 (s, 3H), 6.76 (d, $J$ = 7.28 Hz, 1H), 7.12 (dd, $J$ = 7.89 Hz, 7.83, 1H), 7.33 (d, $J$ = 8.38 Hz, 1H), 7.6 (dd, $J$ = 7.76, 7.69 Hz, 1H), 7.72 (d, $J$ = 7.83 Hz, 1H), 7.8 (s, 1H), 8.24 (d, $J$ = 7.55 Hz, 1H), 8.3 (s, 1H), 8.41 (s, 1H). MS $m/z$: 507 (M + H). HPLC Method A: room temperature 4.03 min, 100%. HPLC method B: room temperature 3.65 min, 100%.

**6-Methyl-2-[4-(1-pyrrolidinylcarbonyl)phenyl]-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (36n).** Isolated in 78% yield as yellow solid. $^1$H NMR (DMSO-$d_6$) 8.30 (s, 1H), 8.19 (d, 8.3 Hz, 1H), 8.01 (d, 7.9 Hz, 2H), 7.89 (s, 1H), 7.66 (d, 7.88 Hz, 1H), 7.60 (m, 1H), 7.36 (d, 8.21 Hz, 2H), 3.94 (s, 3H), 3.60 (m, 4H), 2.58 (m, 4H); MS (CI) $m/z$ = 507 (95%, $M+H^+$). HPLC Method A: room temperature 2.77 min, 97%; HPLC Method B: room temperature 3.87 min, 98%.

**Methyl-(2*R*)-1-[3-(6-methyl-3-oxo-4-[3-(trifluoromethyl)-phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyri-din-2(1*H*)-yl)benzoyl]-2-pyrrolidinecarboxylate (35m).** Yield: 0.114 g (61%) of a gold-orange solid from flash chromatography (95:5%, $CH_2Cl_2$/MeOH), mp 180 °C (dec.). $^1$H NMR ($CDCl_3$): 1.86–2.16 (m, 3H), 2.39 (m, 1H), 3.56–3.72 (m, 2H), 3.9 (s, 3H), 4.26 (s, 3H), 4.7 (dd, $J$ = 8.17 Hz, 4.81, 1H), 6.92 (d, $J$ = 7.42 Hz, 1H), 7.16 (dd, $J$ = 7.97 Hz, 8.1, 1H), 7.3 (br s, 1H), 7.59 (dd, $J$ = 7.69, 7.83 Hz, 1H), 7.72 (d, $J$ = 7.97 Hz, 1H), 7.86 (s, 1H), 8.24 (d, $J$ = 7.83 Hz, 1H), 8.32 (s, 2H). MS $m/z$: 565 (M + H). HPLC Method A: room temperature 3.71 min, 100%. HPLC Method B: room temperature 4.63 min, 100%.

**(2*R*)-1-[3-(6-Methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzoyl]-2-pyrrolidinecarboxylic acid (35n).** Yield: 0.06 g

(>99%) of a gold-orange solid, mp 199–202 °C. $^1$H NMR (DMSO-$d_6$): 1.95–2.24 (br m, 3H), 2.5 (br s, 1H), 3.62–3.84 (br m, 2H), 4.29 (s, 3H), 4.63 (br s, 1H), 7.6 (d, $J$ = 7.69 Hz, 1H), 7.8 (m, 1H), 7.96 (m, 1H), 8.1 (d, $J$ = 7.69 Hz, 1H), 8.16 (d, $J$ = 8.52 Hz, 1H), 8.25 (s, 1H), 8.39–8.49 (m, 3H). MS $m/z$: 551 (M + H). HPLC Method A: room temperature 4.53 min, 100%. HPLC method B: room temperature 3.38 min, 100%.

**1-{2-Chloro-5-[6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-2(1*H*)-yl]-benzoyl}-D-proline (35o).** Yield: 0.07 g (92%) of a gold-orange solid, mp 214–218 °C. $^1$H NMR (acetone-$d_6$): 1.84–2.08 (m, 3H), 2.26 (m, 1H), 3.28 (m, 2H), 4.05 (s, 3H), 4.51 (m, 1H), 7.44 (d, $J$ = 8.88 Hz, 1H), 7.61 (m, 1H), 7.72 (br d, $J$ = 7.38 Hz, 2H), 7.96 (br s, 1H), 8.08 (s, 1H), 8.27 (br d, $J$ = 7.40 Hz, 1H), 8.33 (br s, 1H). MS $m/z$: 583 (M − H).

**1-{3-[6-Methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-2(1*H*)-yl]benzoyl}-L-proline (35p).** Yield: 0.136 g (50%) of a gold-orange solid, mp 168–171 °C. $^1$H NMR (DMSO-$d_6$): 1.92 (br m, 3H), 2.25 (br s, 1H), 3.52 (br m, 2H), 4.05 (s, 3H), 4.50 (br m, 1H), 7.32 (br m, 1H), 7.44 (br m, 1H), 7.61 (br d, $J$ = 7.57 Hz, 1H), 7.71 (br d, $J$ = 6.39 Hz, 1H), 7.94 (br s, 2H), 8.09 (s, 1H), 8.30 (d, $J$ = 6.98 Hz, 1H), 8.37 (s, 1H). MS $m/z$: 551 (M + H). HPLC Method A: room temperature 3.39 min, 100%. HPLC Method B: room temperature 4.56 min, 100%.

***N*-Benzyl-3-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]-pyridin-2(1*H*)-yl)benzamide (35q).** This compound was prepared by the general procedure for amides described above from the appropriate starting materials. Yield: 0.049 g (27%) of a yellow solid after flash chromatography (95:5%, EtOAc/EtOH). MS $m/z$: 543 (M + H). HPLC Method A: room temperature 4.85 min, 100%. HPLC method B: room temperature 3.94 min, 100%.

***N*-Benzyl-4-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzamide (36p).** Obtained in 45% yield, mp 440 °C (dec.). $^1$H NMR (DMSO-$d_6$) 9.05 (m, 1H), 8.35–8.29 (m, 2H), 8.25 (s, 1H), 8.09–8.01 (m, 3H), 7.89 (d, $J$ = 7.9 Hz, 1H), 7.80 (t, $J$ = 7.9 Hz, 1H), 7.34–7.24 (m, 5H), 4.50 (d, $J$ = 5.8 Hz, 2H), 4.11 (s, 3H). MS (ES+) $m/z$ 543 $(M + H)^{+1}$. HPLC Method A: room temperature 3.92 min, 97.9%. HPLC Method B: room temperature 4.79 min, 98.0%.

***N*-Benzyl-N-methyl-3-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]-pyridin-2(1*H*)-yl)benzamide (35r).** Yield: 0.076 g (41%) of a beige solid after flash chromatography (95:5%, $CH_2Cl_2$/MeOH), mp 163.7–165.6 °C. $^1$H NMR (*cis*/*trans* rotamer mixture) ($CDCl_3$): 2.87/3.1 (*cis*/*trans* 0.85:1), s, 3H), 4.24 (s, 3H), 4.44/4.81 (*cis*/*trans* 1.12:1, s, 2H), 6.78 (m, 1H), 7.02–7.21 (m, 2H), 7.26–7.44 (m, 5H), 7.58 (m, 1H), 7.72 (d, $J$ = 7.55 Hz, 1H), 7.8/7.89 (*cis*/*trans* 1:1, s, 1H), 8.22 (d, $J$ = 7.97 Hz, 1H), 8.29 (s, 1H), 8.34 (s, 1H). MS $m/z$: 557 (M + H). HPLC Method A: room temperature 4.07 min, 100%. HPLC Method B: room temperature 4.87 min, 100%.

**2-[3-(3,4-Dihydro-2(1*H*)-isoquinolinylcarbonyl)phenyl]-6-methyl-4-[3-(trifluoromethyl)phenyl]-1,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-3(2*H*)-one (35s).** Yield: 0.154 g (82%) of a yellow solid after flash chromatography (80:20%, EtOAc/EtOH), mp 234 °C (dec.). $^1$H NMR (*cis*/*trans* rotamer mixture) (DMSO-$d_6$): 2.9 (br s, 2H), 3.62/3.88 (*cis*/*trans* 0.6:1, br s, 2H), 4.06 (s, 3H), 4.61/4.8 (*cis*/*trans* 1.7:1, br s, 2H), 6.99–7.34 (m, 5H), (dd, $J$ = 7.97, 7.69 Hz, 1H), 7.72 (dd, $J$ = 7.89, 7.97 Hz, 1H), 7.84 (d, $J$ = 7.55 Hz, 1H), 8.08 (s, 1H), 8.12–8.3 (m, 2H), 8.35 (d, $J$ = 8.1 Hz, 1H), 8.42 (br s, 1H). MS $m/z$: 569 (M + H). HPLC Method A: room temperature 4.16 min, 100%. HPLC Method B: room temperature 4.17 min, 100%.

***N*-(3,4-Dihydroxybenzyl)-4-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzamide (36q).** Isolated in 64% yield as light yellow solid, mp: 206–209 °C. $^1$H NMR (DMSO-$d_6$) 8.35 (s, 1H), 8.29 (d, $J$ = 8.4 Hz, 1H), 8.20 (s, 1H), 8.02 (m, 4H), 7.78 (m, 1H), 7.75 (dd, $J$ = 6.8, 7.5 Hz, 1H), 6.72 (s, 1H), 6.63 (d, $J$ = 7.8 Hz, 2H), 4.63 (s, 2H), 4.21 (s, 3H). MS (ES+) $m/z$ 575 $(M + H)^{+1}$. HPLC Method A: room temperature 3.38 min, 100%. HPLC Method B: room temperature 4.55 min, 99%.

***N*-(3,4-Dihydroxybenzyl)-3-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzamide (35t).** Yield: 0.045 g (24%) of a gold-orange solid after flash chromatography (90:10%, $CH_2Cl_2$/MeOH), mp 177.7–179.8 °C. $^1$H NMR (acetone-$d_6$): 4.11 (s, 3H), 4.44 (d, $J$ = 5.49 Hz, 2H), 6.7 (m, 2H), 6.88 (s, 1H), 7.46 (m, 1H), 7.6–7.8 (m, 3H), 8.09 (s, 1H), 8.27 (d, $J$ = 7.69 Hz, 1H), 8.38–8.52 (m, 3H). MS $m/z$: 575 (M + H). HPLC Method A: room temperature 4.49 min, 100%. HPLC method B: room temperature 3.39 min, 100%.

**2-Chloro-*N*-(3,4-dihydroxybenzyl)-5-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzamide (35u).** Yield: 0.030 g (8%) of a gold-orange solid after flash chromatography (90:10%, $CH_2Cl_2$/MeOH), mp 212–215 °C. $^1$H NMR (acetone-$d_6$) δ 3.97 (s, 3H), 4.31 (d, $J$ = 5.78 Hz, 2H), 6.61 (br s, 2H), 6.86 (s, 1H), 7.27 (d, $J$ = 8.41 Hz, 1H), 7.55 (m, 1H), 7.66 (d, $J$ = 8.71 Hz, 1H), 7.83 (br m, 1H), 8.05 (d, $J$ = 5.31 Hz, 3H), 8.28 (d, $J$ = 7.44 Hz, 1H), 8.35 (s, 1H). MS $m/z$ 607 (M − H). HPLC Method A: room temperature, 4.48 min, 100%. HPLC method B: room temperature, 3.45 min, 100%.

***N*-(4-Hydroxy-3-methoxybenzyl)-3-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzamide (35v).** Yield: 0.087 g (45%) of a gold-orange solid after flash chromatography (96:4%, $CH_2Cl_2$/MeOH), mp 172–176 °C. $^1$H NMR (acetone-$d_6$) δ 3.8 (s, 3H), 4.17 (s, 3H), 4.52 (d, $J$ = 6.04 Hz, 2H), 6.76 (d, $J$ = 7.97 Hz, 1H), 6.83 (d, $J$ = 7.97 Hz, 1H), 7.02 (s, 1H), 7.54 (m, 1H), 7.69–7.88

(m, 3H), 8.18 (s, 1H), 8.28 (m, 1H), 8.36–8.5 (m, 3H). MS *m*/*z* 589 (M + H). HPLC Method A: room temperature, 4.59 min, 100%. HPLC method B: room temperature, 3.57 min, 100%.

***N*-[4-(2-Hydroxyethyl)phenyl]-4-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzamide (36r).** Obtained in 100% yield, mp 270–274 °C. $^1$H NMR (DMSO-$d_6$) δ 10.17 (s, 1H), 8.34–8.25 (m, 3H), 8.10 (br s, 3H), 7.92 (d, $J$ = 7.6 Hz, 1H), 7.78 (t, $J$ = 7.6 Hz, 1H), 7.67 (d, $J$ = 8.4 Hz, 2H), 7.20 (d, $J$ = 8.4 Hz, 2H), 4.12 (s, 3H), 3.60 (t, $J$ = 7.1 Hz, 2H), 2.71 (t, $J$ = 7.1 Hz, 2H). MS (ES+) *m*/*z* 573 $(M+H)^{+1}$. HPLC Method A: room temperature, 3.58 min, 100%. HPLC Method B: room temperature, 4.66 min, 100%.

**2-Fluoro-*N*-[4-(2-hydroxyethyl)phenyl]-4-[6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-2(1*H*)-yl]benzamide (36s).** Obtained in 44.4% yield, mp 198–201.2 °C. $^1$H NMR (DMSO-$d_6$) δ 10.25 (s, 1H), 8.29 (s, 1H), 8.24 (d, $J$ = 7.82 Hz, 1H), 8.19 (s, 1H), 8.02 (d, $J$ = 8.32 Hz, 1H), 7.95 (d, $J$ = 7.77 Hz, 1H), 7.84 (d, $J$ = 8.20 Hz, 1H), 7.82 (m, 2H), 7.79 (d, $J$ = 8.31 Hz, 2H), 7.63 (d, $J$ = 8.28 Hz, 2H), 4.10 (s, 3H), 3.61 (t, $J$ = 6.25 Hz, 2H), 2.73 (t, $J$ = 6.35 Hz, 2H). MS (ES+) *m*/*z* 591 $(M+H)^{+1}$. HPLC Method A: room temperature, 3.69 min, 100%. HPLC Method B: room temperature, 4.70 min, 100%.

***N*-[3-(Hydroxymethyl)phenyl]-4-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzamide (36t).** Obtained in 22% yield, mp 440 °C (dec.). $^1$H NMR (DMSO-$d_6$) δ 8.16–8.11 (m, 4H), 8.01 (s, 1H), 7.92 (d, $J$ = 8.8 Hz, 2H), 7.67–7.51 (m, 4H), 7.24 (t, $J$ = 7.8 Hz, 1H), 7.07 (d, $J$ = 7.5 Hz, 1H), 4.53 (s, 2H), 4.00 (s, 3H). MS (ES+) *m*/*z* 559 $(M+H)^{+1}$. HPLC Method A: room temperature, 3.63 min, 100%. HPLC Method B: room temperature, 4.66 min, 100%.

***N*-[3-(Hydroxymethyl)phenyl]-3-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyra-zolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzamide (35w).** This compound was prepared by the general procedure for amides described above from the appropriate starting materials. Yield: 0.154 g (82%) of yellow solid after flash chromatography (80:20%, EtOAc/EtOH). MS *m*/*z* 569 (M + H). HPLC Method A: room temperature, 4.67 min, 97.5%. HPLC method B: room temperature, 3.58 min, 97.1%.

***N*-[3-(Methoxymethyl)phenyl]-4-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzamide (36u).** Obtained in 57% yield, mp 210 °C (dec.). $^1$H NMR (DMSO-$d_6$) δ 8.33 (m, 2H), 8.24 (s, 1H), 8.09 (m, 4H), 7.92 (m, 1H), 7.73 (m, 2H), 7.71 (d, $J$ = 7.32 Hz, 1H), 7.31 (dd, $J$ = 6.85, 7.42 Hz, 1H), 7.02 (d, $J$ = 6.83 Hz, 1H), 4.40 (s, 2H), 4.10 (s, 3H), 3.29 (s, 3H). MS (ES+) *m*/*z* 573 $(M+H)^{+1}$. HPLC Method A: room temperature, 3.99 min, 96%. HPLC Method B: room temperature, 4.84 min, 100%.

**Methyl-3-{[4-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzoyl]amino}benzoate (36v).** Obtained in 27% yield, mp 220.1–222.4 °C. $^1$H NMR (DMSO-$d_6$) δ 10.34 (s, 1H), 8.42 (s, 1H), 8.32 (d, $J$ = 8.2 Hz, 2H), 8.28–8.23 (m, 2H), 8.08 (m, 3H), 7.78 (d, $J$ = 8.2 Hz, 2H), 7.65 (t, $J$ = 7.4 Hz, 1H), 7.43 (t, $J$ = 8.2 Hz, 1H), 4.09 (s, 3H), 3.8 (s, 3H). MS (ES+) *m*/*z* 587 $(M+H)^{+1}$. HPLC Method A: room temperature, 4.05 min, 100%. HPLC Method B: room temperature, 4.87 min, 100%.

***N*-(3-Acetylphenyl)-4-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzamide (36w).** Obtained in 15% yield, mp 300 °C (dec.). $^1$H NMR (DMSO-$d_6$: MeOH/$d_4$, 1: 1) δ 8.37–8.00 (m, 7H), 7.90 (d, $J$ = 7.7 Hz, 2H), 7.82 (br s, 1H), 7.67 (d, $J$ = 7.7 Hz, 2H), 7.44 (t, $J$ = 8.2 Hz, 1H), 4.08 (br s, 3H), 2.54 (s, 3H). MS (ES+) *m*/*z* 571 $(M+H)^{+1}$. HPLC Method A: room temperature, 3.91 min, 100%. HPLC Method B: room temperature, 4.80 min, 100%

***N*-[3-(1-Hydroxyethyl)phenyl]-4-(6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3,4-*d*]pyridin-2(1*H*)-yl)benzamide (36x).** Obtained in 68% yield, mp 251–254 °C. $^1$H NMR ($CDCl_3$) δ 10.21 (s, 1H), 8.32 (m, 3H), 8.20 (s, 1H), 8.17 (m, 4H), 7.86 (m, 1H), 7.68 (m, 2H), 7.27 (t, $J$ = 7.83 Hz, 1H), 7.08 (d, $J$ = 7.52 Hz, 1H), 4.75 (m, 1H), 4.11 (s, 3H), 1.39 (d, 6.2, 3H). MS (ES+) *m*/*z* 573 $(M+H)^{+1}$. HPLC Method A: room temperature, 3.66 min, 100%. HPLC Method B: room temperature, 4.71 min, 100%.

**2-Chloro-*N*-[3-(1-hydroxyethyl)phenyl]-4-[6-methyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,6-dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-2(1*H*)-yl]benzamide (36y).** Obtained in 50% yield, mp 326 °C (dec.). $^1$H NMR (MeOH-$d_4$) δ 8.30 (s, 1H), 8.22 (d, $J$ = 7.6 Hz, 1H), 8.07 (s, 2H), 7.97–7.89 (m, 1H), 7.79–7.75 (m, 5H), 7.33 (t, $J$ = 7.8 Hz, 1H), 7.18 (d, $J$ = 7.6 Hz, 1H), 4.09 (s, 3H), 1.46 (d, $J$ = 6.4 Hz, 3H). MS (ES+) *m*/*z* 608 $(M+H)^{+1}$. HPLC Method A: room temperature, 4.00 min, 100%. HPLC Method B: room temperature, 4.81 min, 100%.

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