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L-Proline-catalyzed three-component domino reactions in the regioselective synthesis of novel densely functionalized pyrazolo[3,4-*b*]pyridines†

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The L-proline-catalyzed three-component synthesis of novel 3-methyl-1-aryl-1*H*-pyrazolo[3,4-*b*]pyridines in good yields from the reaction of 3-methyl-1-aryl-1*H*-pyrazol-5-amines, 1,3-dicarbonyl compounds and aromatic aldehydes in ethanol is described. This domino transformation presumably involves the formation of two C–C bonds and one C–N bond in a single synthetic operation.

Introduction

The chemistry of pyrazolopyridine derivatives has attracted much attention in view of their importance as bio-active drug targets[1] in the pharmaceutical industry and their prevalence as the core structure of numerous biologically active compounds.[2] Pyrazolopyridines act as potent cyclin dependent kinase 1 (CDK1) inhibitors,[3] HIV reverse transcriptase inhibitors,[4] CCR1 antagonists,[5] protein kinase inhibitors,[6] inhibitors of cGMP degradation, dopamine D3 receptor antagonists, besides possessing antiherpetic and antiallergic,[7] herbicidal and fungicidal activities.[8] In particular, pyrazolo[3,4-*b*]pyridines *viz.* cartazolate, etazolate and tracazolate (Fig. 1) are known as anxiolytic drugs.[9]

Previously reported methods for the synthesis of variously functionalized pyrazolo[3,4-*b*]pyridines include: (i) hetero Diels–Alder reactions of azadienes with alkynes and alkenes,[10] (ii) reactions of pyrazolamines with electron-deficient alkenes, isoflavones and coumarinaldehydes,[11] (iii) three-component reaction of pyrazolamines with (a) isatin and cyclic diketones in presence of CAN catalyst[12] and (b) salicylaldehyde and ethyl acetoacetate in the presence of piperidine and acetic acid,[13] (iv) reactions of pyrazolamines having a benzotriazolylmethyl group at the 4-position/amino nitrogen with unactivated and electron-rich alkenes in the presence of *p*-TSA followed by heterocyclization,[14] (v) four-component reactions of indolin-2-one, 3-oxo-3-phenylpropanenitrile, hydrazines and aldehydes in the presence of *p*-TSA catalyst[15] in ionic liquid, ([BMIm]Br) as solvent and (vii) transformations using appropriately substituted pyridines as synthons *via* linear synthesis involving two or more steps.[16] These methods suffer from one or more disadvantages such as environmentally unfriendly catalysts (metal, corrosive acid and toxic substances) low or inconsistent yields, lack of convergence and tedious work up.

Fluorinated organic compounds have gained significant importance due to their unique chemical and biological properties.[17] In particular, the reactions of fluorinated 1,3-dicarbonyl compounds as synthons are attractive[18] in the assembly of heterocycles[19,20] of medicinal and agricultural relevance.[21]

The biological importance of pyrazolopyridines and fluorinated heterocycles, in conjunction with our recently embarked research programme on the construction of novel heterocycles of varying complexity and diversity employing novel green transformations[22] and domino processes[23] led us to report in this manuscript the synthesis of 1-aryl-3-methyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridines (Table 2) as promising candidates for biological evaluation in good yields from the three-component reactions of 1,3-dicarbonyl compounds, *viz.* 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione/1-phenylbutane-1,3-dione/methyl acetoacetate **1**, aromatic aldehydes **2** and 3-methyl-1-aryl-1*H*-pyrazol-5-amines **3** in ethanol employing organocatalyst, L-proline (Table 2).

It is pertinent to note that L-proline is an abundant, inexpensive and eco-friendly amino acid capable of catalyzing diverse organic reactions[24] and domino transformations.[25]

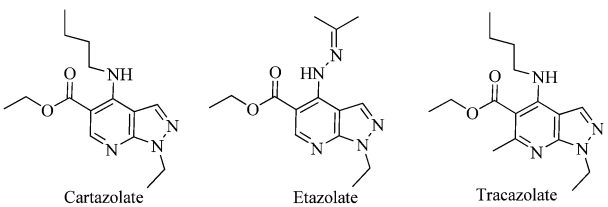

Fig. 1 Some pyrazolopyridine drugs.

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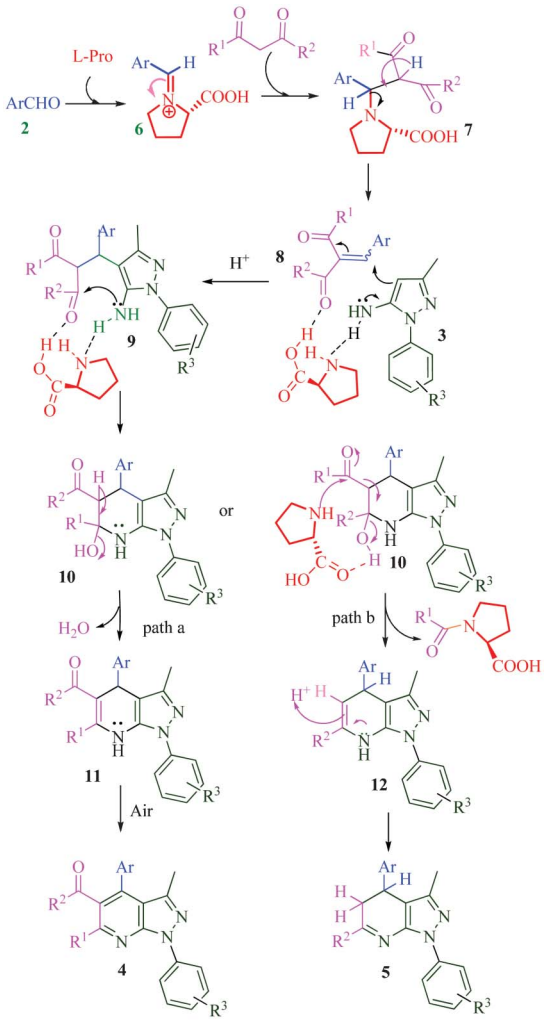
† Electronic supplementary information (ESI) available. CCDC reference number 909204. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra00136a



Scheme 1 Plausible mechanistic pathway for L-proline-catalyzed formation of pyrazolopyridines **4** and dihydropyrazolopyridines **5**.

The unique catalytic efficacy of L-proline in a variety of organic transformations is ascribable to its multiple catalytic functions as an acid or a base or both simultaneously, as a nucleophile and its ability to form enamine/iminium intermediates upon reaction with carbonyl/α,β-unsaturated carbonyl compounds respectively.[26]

Results and discussion

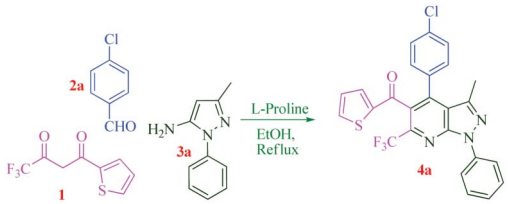
We started our study by examining the model reaction of 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione **1** (1 mmol), 4-chlorobenzaldehyde **2** (1 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **3** (1 mmol) in presence of L-proline (1 mmol), which afforded compound **4a** (Table 1). Initially, the reaction was investigated using different catalysts, solvents and under solvent- as well as catalyst-free conditions (Table 1) with a view to finding optimal conditions to maximize the yield of the product. The reaction in the absence of catalyst in either water or ethanol failed to afford the product (entry 1). The reaction in the presence of pyrrolidine, Et_3N and ammonium acetate afforded a low/no yield of the product **4a** (Table 1, entries 10–14 and 20–29), whilst with HCOOH, acetic acid, *p*-TSA, pyrrolidine–acetic acid mixture (1 : 1) and pyrrolidine–HCOOH mixture (1 : 1) in ethanol (Table 1, entries 16–20) the reaction failed to occur. This reaction afforded a maximum yield (78%) of **4a** with 20 mol% of L-proline in ethanol at 80 °C (entry 6). The data in Table 1 also disclose that the yield of **4a** remains almost the same, when the amount of L-proline was increased to 100 mol%, *albeit* different reaction times were required (Table 1, entries 4–6). From these observations, the L-proline–ethanol pair emerges as the most suitable catalyst–solvent combination, among those examined.

Consequently, for all subsequent reactions, 20 mol% of L-proline was employed in ethanol at 80 °C. With these results in hand, the scope of the reaction was investigated under the optimal conditions established above using diketones/keto ester, pyrazolamines and aromatic aldehydes bearing different substituents in the aryl rings (Table 2). Typically, the reaction of a mixture of 1,3-dicarbonyl compound **1** (1 mmol), aromatic aldehyde **2** (1 mmol) and 3-methyl-1-aryl-1*H*-pyrazol-5-amine **3** (1 mmol) in presence of L-proline (0.20 mmol) in ethanol (15 ml) at 80 °C for 10–19 h afforded a library of novel 3-methyl-1-aryl-1*H*-pyrazolo[3,4-*b*]pyridines **4** in 70–85% yields. In the case of 3-methyl-1-aryl-1*H*-pyrazol-5-amines having *p*-F, *p*-Cl and *p*-OMe phenyl rings on the nitrogen, the above reaction resulted in the formation of either pyrazolopyridines **4** or dihydropyrazolopyridines **5** lacking a trifluoroacetyl group (Table 2, entries 18–22) or both **4** and **5** disclosing that the product-selectivity of the reaction is subtly influenced by the nature of the substituent present in the aryl ring of the pyrazolamine as well as the aromatic aldehyde (Table 2, entries 19–21). The reaction of a representative β-ketoester, *viz.* methyl acetoacetate with 4-chlorobenzaldehyde and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine in the presence of L-proline at 80 °C also furnished the corresponding methyl pyrazolopyridine carboxylate ester, *viz.* methyl 4-(4-chlorophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (**4w**) in 71% yield. The reaction of 1-phenylbutane-1,3-dione, an unsymmetrical 1,3-diketone, with a methyl group in place of a trifluoromethyl group, with *p*-anisaldehyde and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine in the presence of L-proline at 80 °C also afforded a good yield of the product **4x** in 85% yield. However, the reaction of acetylacetone in the above reaction led to a complex mixture of products, presumably due to self-condensation of the 1,3-diketone having only alkyl groups linked to carbonyl.

The structure and regiochemistry of all the products **4** and **5** were unambiguously determined from combustion data and one- and two-dimensional NMR spectroscopic data (see supporting information†). A single crystal X-ray crystallographic study of **4o** confirmed the structure deduced from NMR spectroscopic data (Fig. 2).

It is pertinent to note that all the products **4** generated from 1,3-diketones had the same regiochemistry with the trifluor-

Table 1 Optimization of catalyst,[a] solvent and reaction conditions for the synthesis of **4a**



Entry	Catalyst	Solvent	Time (h)	Yield of **4a**[b] (%)
1	—	Water/ethanol	20	—[c]
2	L-Proline	Water	14	35
3	L-Proline	Acetonitrile	7	55
4	L-Proline	Ethanol (100)[d]	6	78
5	L-Proline	Ethanol (50)[d]	6	75
6	L-Proline	Ethanol (20)[d]	12	78
7	L-Proline	Ethanol (15)[d]	14	55
8	L-Proline	Ethanol (10)[d]	15	45
9	L-Proline	Chloroform	20	—[c]
10	Pyrrolidine	Solvent-free	20	—[c]
11	Pyrrolidine	Acetonitrile	20	15
12	Pyrrolidine	Ethanol	20	33
13	Pyrrolidine	Chloroform	20	—[c]
14	Pyrrolidine	Water	15	—[c]
15	Pyrrolidine–HOAc mixture (1 : 1)	Ethanol	16	—[c]
16	Pyrrolidine-HCOOH mixture (1 : 1)	Ethanol	21	—[c]
17	HCOOH	Ethanol	21	—[c]
18	HOAc	Ethanol	16	—[c]
19	*p*-TSA	Ethanol	20	—[c]
20	Et_3N	Acetonitrile	7	10
21	Et_3N	Ethanol	8	31
22	Et_3N	Chloroform	20	25
23	Et_3N	Solvent-free	20	10
24	Et_3N	Water	18	—[c]
25	NH_4OAc	Acetonitrile	11	12
26	NH_4OAc	Ethanol	14	15
27	NH_4OAc	Chloroform	20	—[c]
28	NH_4OAc	Solvent-free	15	—[c]
29	NH_4OAc	Water	15	—[c]

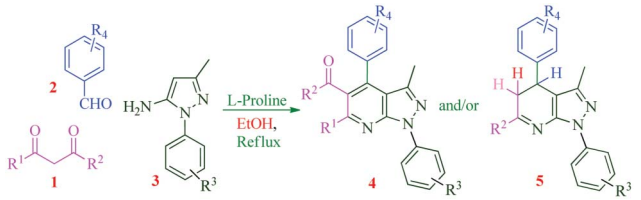
[a] 100 mol% of catalyst was employed in these reactions unless mentioned. [b] Yield of isolated product. [c] Reaction failed to occur. [d] Values in parentheses indicate mol% of L-Proline.

omethyl/methyl group at the 6-position and the carbonyl linked to the aryl/thienyl group at the 5-position of the pyrazolopyridine ring system. This regiochemistry is explicable on the basis of the greater electrophilicity of the carbonyl of $COCF_3$ and $COCH_3$ groups than the carbonyl of ArCO (Ar = 2-thienyl/substituted phenyl) groups. In the case of the reaction of the ketoester, CH_3COCH_2COOMe, in place of diketone, with *p*-chlorobenzaldehyde and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, the regiochemistry of the product, methyl 4-(4-chlorophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (**4w**) is controlled by the higher electrophilicity of the CH_3CO group than COOMe function.

A plausible mechanism for the formation of the 3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridines **4** depicted in Scheme 1, envisages the intervention of a Knoevenagel intermediate **8** (Scheme 1), which subsequently undergoes Michael addition with pyrazolamine and concomitant condensation to afford a dihydropyrazolopyridine intermediate **11** *via* **10**. Subsequently, the intermediate **11** undergoes air oxidation to afford the final product **4**. Our efforts to obtain evidence for the formation of (i) either the Knoevenagel intermediate **8** from the reaction of 4,4,4-trifluoro-1-phenylbutane-1,3-dione **1** (1 mmol), *p*-chlorobenzaldehyde (1 mmol) and L-proline (1 mmol) and (ii) dihydropyrazolopyridine intermediate **11** (Scheme 1) from the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol), 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (1 mmol), *p*-chlorobenzaldehyde (1 mmol) and L-proline (0.2 mmol) under nitrogen atmosphere did not succeed leading to an inseparable mixture of products.

The probable mechanism for the formation of dihydropyrazolopyridines **5** lacking a trifluoroacetyl group (Table 2 entries 18–20) from the reaction of 3-methyl-1-aryl-1*H*-pyrazol-5-amines with *p*-MeO and *p*-Cl phenyl rings is also depicted in Scheme 1. Presumably, the extended conjugation

Table 2 Synthesis of pyrazolo[3,4-*b*]pyridines **4** and **5**[a]



Entry	Comp	R^1	R^2	R^3	R^4	Time (h)	Yield (%)[b] **4** (**5**)
1	**4a**	CF_3	2-Th[c]	H	4-Cl	12	78
2	**4b**	CF_3	2-Th	H	4-O_2N	14	82
3	**4c**	CF_3	2-Th	H	4-F	11	85
4	**4d**	CF_3	2-Th	H	4-Br	16	81
5	**4e**	CF_3	2-Th	H	4-MeO	18	82
6	**4f**	CF_3	2-Th	H	3-Br	16	79
7	**4g**	CF_3	2-Th	H	3-F	11	75
8	**4h**	CF_3	2-Th	H	2-Br	16	79
9	**4i**	CF_3	2-Th	H	2-MeO	18	82
10	**4j**	CF_3	2-Th	H	2-Me	13	82
11	**4k**	CF_3	2-Th	H	2,3-Cl_2	19	70
12	**4l**	CF_3	2-Th	H	H	15	80
13	**4m**	CF_3	Ph	H	4-O_2N	10	78
14	**4n**	CF_3	Ph	H	4-Cl	12	75
15	**4o**	CF_3	Ph	H	4-Me	13	79
16	**4p**	CF_3	Ph	H	4-MeO	14	82
17	**4q**	CF_3	Ph	H	3-Br	13	84
18	**4r**	CF_3	Ph	4-OMe	4-O_2N	8	(85)
19	**4s**	CF_3	Ph	4-Cl	4-MeO	6	(83)
20	**4t**	CF_3	Ph	4-Cl	4-O_2N	7	39 (61)
21	**4u**	CF_3	2-Th	4-Cl	4-Cl	8	82
22	**4v**	CF_3	Ph	4-F	4-Cl	8	78
23	**4w**	CH_3	OMe	H	4-Cl	12	71
24	**4x**	CH_3	Ph	H	4-MeO	6	85

[a] Reaction conditions: dicarbonyl compound (1 mmol), aldehyde (1 mmol), pyrazol-5-amine (1 mmol) and L-proline (0.20 mmol) in ethanol (15 ml) stirred at 80 °C. [b] Yield of isolated product. [c] 2-Th = 2-Thienyl.

confers greater stability for **5** than **12**, which provides the impetus for the tautomeric equilibrium to lie in favour of **5**.[27] Further, the lack of a trifluoroacetyl group at position 6 in compound **5** is likely to diminish the acidity of the hydrogen in the same position which, in turn, renders aromatization difficult.

It is pertinent to note that L-proline catalyses the above transformation efficiently, whilst either pyrrolidine or formic/acetic acid or an equimolar mixture of the base and these acids failed to catalyse this reaction (Table 1). This suggests that the presence of both secondary amino and carboxyl functions in the same catalyst molecule is crucial for the success of this transformation. This, in turn, discloses that both the carboxyl as well as secondary amino functions are involved in catalysing the reactions in concert as shown in the Michael addition and condensation steps (Scheme 1). Presumably, catalysis by L-proline and the lack of it by an equimolar mixture of pyrrolidine and formic/acetic acid is ascribable to a favourable entropy factor on going to the transition state in the case of L-proline, as both the amino and carboxyl functions are present in the same molecule leading to less loss of entropy than that involved in the catalysis by pyrrolidine and formic/acetic acid.

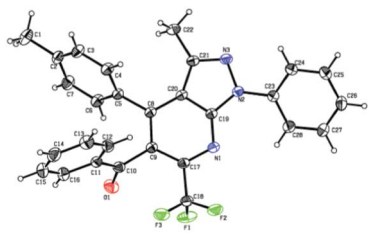


Fig. 2 Ortep diagram for compound **4o**.

This protocol furnishing a series of novel 3-methyl-1-aryl-1*H*-pyrazolo[3,4-*b*]pyridines proceeds *via* a one pot three-component reaction. It is pertinent to note that multi-component reactions (MCRs),[28] endowed with powerful bond forming and atom efficacies can afford libraries of new chemical entities of structural complexity and diversity facilitating new lead identification and optimization in drug discovery programmes.[29] As isolation and characterization of the intermediates of these MCRs are obviated in this protocol, considerable savings in solvent, adsorbent, energy, time and cost are achieved enabling them to conform to the tenets of green chemistry.

Conclusions

In conclusion, we have developed an expedient three-component domino protocol for the synthesis of novel 3-methyl-1-aryl-1*H*-pyrazolo[3,4-*b*]pyridines in good yields from the reaction of 3-methyl-1-aryl-1*H*-pyrazol-5-amines, 1,3-diketones/β-ketoester and aromatic aldehydes in the presence of a catalytic amount of green catalyst, L-proline. This one-pot transformation *via* a domino sequence of reactions involves the formation of two C–C bonds and one C–N bond in a single synthetic operation.

Experimental section

Melting points were measured in open capillary tubes and are uncorrected. The ^{1}H-NMR, ^{13}C-NMR, DEPT, H,H-COSY and C,H-COSY were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. ^{19}F NMR spectra were measured at 235 MHz in Bruker AC-250 NMR instrument. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. Mass spectra were recorded in a LCQ Fleet mass spectrometer, Thermo Fisher Instruments Limited, US. Electrospray ionisation mass spec-

trometry (ESI-MS) analysis was performed in the positive ion mode on a liquid chromatography ion trap.

General procedure for the synthesis of 3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridines 4

A mixture of 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione **1** (1 mmol), aromatic aldehyde **2** (1 mmol), 3-methyl-1-aryl-1*H*-pyrazol-5-amine **3** (1 mmol) and L-proline (0.20 mmol) in ethanol (15 ml) was stirred at 60 °C for the time given in Table 2. After completion of the reaction (TLC), the reaction mixture was extracted with ethyl acetate (2 × 40 ml) and the residue after removal of the solvent was chromatographed over silica gel (230–400 mesh) using a petroleum ether–ethyl acetate mixture (4 : 1 v/v), which afforded pure product **4**. The spectroscopic data for compounds **4** are given below.

(4-(4-Chlorophenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(thiophen-2-yl)methanone (4a). White solid; yield 78%; mp 223 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.12 (s, 3H, CH_3), 7.01 (t, 1H, J = 3.9 Hz, Ar-H), 7.05–7.08 (m, 1H, Ar–H), 7.20–7.23 (m, 2H, Ar–H), 7.33–7.42 (m, 3H, Ar–H), 7.56 (t, 2H, J = 8.3 Hz, Ar–H), 7.65 (d, 1H, J = 3.9 Hz, Ar–H), 8.34 (d, 2H, J = 8.3 Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.6, 116.3, 120.8, 121.3 ($^1J_{C,F}$ = 275.6 Hz, CF_3), 126.5, 126.9, 128.0, 128.8, 129.2, 129.3, 130.4, 131.3, 131.6, 134.9, 135.6, 138.8, 143.3, 144.7, 145.1, 148.7, 185.4. ESI-MS m/z calcd for $C_{25}H_{15}ClF_3N_3OS$ $[M + H]^+$ 498.05, found 498.17. Anal. Calcd for $C_{25}H_{15}ClF_3N_3OS$: C, 60.30; H, 3.04; N, 8.44%. Found C, 60.42; H, 3.18; N, 8.31%.

(3-Methyl-4-(4-nitrophenyl)-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(thiophen-2-yl)methanone (4b). Yellow solid; yield 82%; mp 185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.10 (s, 3H, CH_3), 7.02 (td, 1H, J = 4.5 Hz, 0.9 Hz, Ar–H), 7.23 (dd, 1H, J = 4.5 Hz, 0.9 Hz, Ar–H), 7.32–7.41 (m, 2H, Ar–H), 7.55–7.63 (m, 3H, Ar–H), 7.67 (dd, 1H, J = 5.4 Hz, 0.9 Hz, Ar–H), 8.14 (dd, 1H, J = 8.4 Hz, 2.1 Hz, Ar–H), 8.29–8.34 (m, 3H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.6, 115.7, 121.0, 122.8, 123.6, 126.5, 126.7, 128.2, 129.4, 130.1, 131.3, 135.2, 136.3, 138.6, 139.7, 142.8, 143.2, 144.8, 148.2, 148.5, 185.0. ESI-MS m/z calcd for $C_{25}H_{15}F_3N_4O_3S$ $[M + H]^+$ 509.47, found 509.39. Anal. Calcd for $C_{25}H_{15}F_3N_4O_3S$: C, 59.05; H, 2.97; N, 11.02%. Found C, 59.22; H, 3.07; N, 11.16%.

(4-(4-Fluorophenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(thiophen-2-yl)methanone (4c). Yellow solid; yield 85%; mp 164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.10 (s, 3H, CH_3), 6.93–7.01 (m, 2H, Ar–H), 7.10–7.15 (m, 2H, Ar–H), 7.20 (dd, 1H, J = 3.9 Hz, 0.9 Hz, Ar–H), 7.33–7.40 (m, 2H, Ar–H), 7.56 (t, 2H, J = 8.1 Hz, Ar–H), 7.26 (dd, 1H, J = 5.4 Hz, 1.2 Hz, Ar–H), 8.34 (dd, 2H, J = 5.4 Hz, 1.2 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.5, 114.9 ($^2J_{C,F}$ = 21.7 Hz, Ar–F), 116.1 ($^2J_{C,F}$ = 21.7 Hz, Ar–F), 116.5, 120.7, 121.3 ($^1J_{C,F}$ = 274.7 Hz, CF_3), 126.3, 126.9, 128.0, 128.1, 129.1, 130.9 ($^3J_{C,F}$ = 8.3 Hz, Ar–F), 131.7 ($^3J_{C,F}$ = 8.3 Hz, Ar–F), 135.0, 135.6, 138.7, 143.0, 143.3, 143.4, 145.0, 148.5, 163.0 ($^1J_{C,F}$ = 248.7 Hz, Ar–F), 185.7. ^{19}F NMR (235 MHz, $CDCl_3$) δ_F −62.4 (s, CF_3), δ_F 111.6–111.7 (m, Ar–CF). ESI-MS m/z calcd for $C_{25}H_{15}F_4N_3OS$ $[M + H]^+$ 482.46, found 482.58. Anal. Calcd for $C_{25}H_{15}F_4N_3OS$: C, 62.37; H, 3.14; N, 8.73%. Found C, 62.51; H, 3.31; N, 8.85%.

(4-(4-Bromophenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(thiophen-2-yl)methanone (4d). Yellow solid; yield 81%; mp 230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.11 (s, 3H, CH_3), 6.98-7.01 (m, 2H, Ar–H), 7.20–7.21 (m, 1H, Ar–H), 7.26–7.29 (m, 1H, Ar–H), 7.33–7.41 (m, 2H, Ar–H), 7.53–7.59 (m, 3H, Ar–H), 7.66 (dd, 1H, J = 7.8 Hz, 1.2 Hz, Ar–H), 8.33 (dd, 2H, J = 7.8 Hz, 1.2 Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.6, 116.2, 120.8, 121.6 ($^1J_{C,F}$ = 274.8 Hz, CF_3), 123.8, 126.4, 126.6, 128.0, 129.2, 130.5, 130.9, 131.5, 131.7, 131.9, 135.0, 135.6, 138.7, 143.2 ($^2J_{C,F}$ = 34.7 Hz, CF_3), 143.3, 144.6, 144.9, 148.5, 185.5. ESI-MS m/z calcd for $C_{25}H_{15}BrF_3N_3OS$ $[M + 2H]^+$ 544.37, found 544.63. Anal. Calcd for $C_{25}H_{15}BrF_3N_3OS$: C, 55.36; H, 2.79; N, 7.75%. Found C, 55.288; H, 2.93; N, 7.88%.

(4-(4-Methoxyphenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(thiophen-2-yl)methanone (4e). White solid; yield 82%; mp 185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.14 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.76–6.80 (m, 1H, Ar–H), 6.90–7.01 (m, 2H, Ar–H), 7.05 (d, 1H, J = 8.1 Hz, Ar–H), 7.18 (d, 1H, J = 3.9 Hz, Ar–H), 7.29–7.37 (m, 2H, Ar–H), 7.53–7.61 (m, 3H, Ar–H), 8.34 (d, 2H, J = 8.4 Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.6, 55.2, 113.4, 113.7, 116.8, 120.8, 125.2, 126.2, 127.1, 127.8, 129.1, 130.5, 131.3, 134.6, 135.0, 138.9, 143.6, 145.2, 146.0, 148.7, 160.2, 185.9. ^{19}F NMR (235 MHz, $CDCl_3$) δ_F −62.3 (s, CF_3). ESI-MS m/z calcd for $C_{26}H_{18}F_3N_3O_2S$ $[M + H]^+$ 494.50, found 494.35. Anal. Calcd for $C_{26}H_{18}F_3N_3O_2S$: C, 63.28; H, 3.68; N, 8.51%. Found C, 63.41; H, 3.80; N, 8.74%.

(4-(3-Bromophenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(thiophen-2-yl)methanone (4f). Yellow solid; yield 79%; mp 200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.12 (s, 3H, CH_3), 7.02–7.13 (m, 2H, Ar–H), 7.22–7.39 (m, 4H, Ar–H), 7.54 (d, 1H, J = 6.9 Hz, Ar–H), 7.54–7.60 (m, 2H, Ar–H), 7.67 (s, 1H, Ar–H), 8.33 (d, 2H, J = 8.4 Hz, Ar–H), ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.6, 116.1, 120.8, 121.3 ($^1J_{C,F}$ = 274.9 Hz, CF_3), 121.7, 122.5, 126.4, 126.7, 127.4, 128.0, 128.5, 129.1, 129.2, 130.1, 132.1, 132.2, 132.7, 138.7, 143.2, 143.3 ($^2J_{C,F}$ = 34.9 Hz, CF_3), 144.0, 148.5, 185.6. ESI-MS m/z calcd for $C_{25}H_{15}BrF_3N_3OS$ $[M + 2H]^+$ 544.37, found 544.23. Anal. Calcd for $C_{25}H_{15}BrF_3N_3OS$: C, 55.36; H, 2.79; N, 7.75%. Found C, 55.22; H, 2.63; N, 7.64%.

(4-(3-Fluorophenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(thiophen-2-yl)methanone (4g). White solid; yield 75%; mp 145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.12 (s, 3H, CH_3), 6.83–6.92 (m, 1H, Ar–H), 6.97–7.26 (m, 4H, Ar–H), 7.36 (t, 2H, J = 7.5 Hz, Ar–H), 7.57 (t, 2H, J = 8.2 Hz, Ar–H), 7.67 (s (br), 1H, Ar–H), 8.33 (dd, 2H, J = 8.7 Hz, 0.9 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.4, 115.8, 116.2 ($^2J_{C,F}$ = 20.8 Hz, Ar–F), 117.3 ($^2J_{C,F}$ = 23.2 Hz, Ar–F), 120.7, 121.3 ($^1J_{C,F}$ = 274.9 Hz, CF_3), 124.9, 125.8, 126.4, 126.6, 128.0, 129.2, 130.2 ($^3J_{C,F}$ = 8.3 Hz, Ar–F), 134.9, 135.2, 138.6, 143.2 ($^2J_{C,F}$ = 34.7 Hz, CF_3), 143.3, 144.2, 144.9, 148.5, 162.1 ($^1J_{C,F}$ = 248.9 Hz, Ar–F), 185.7. ESI-MS m/z calcd for $C_{25}H_{15}F_4N_3OS$ $[M + H]^+$ 482.46, found 482.32. Anal. Calcd for $C_{25}H_{15}F_4N_3OS$: C, 62.37; H, 3.14; N, 8.73%. Found C, 62.49; H, 3.26; N, 8.80%.

(4-(2-Bromophenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(thiophen-2-yl)methanone (4h). White solid; yield 79%; mp 153 °C; ^{1}H NMR (300 MHz, $CDCl_3$)

δ_H: 2.14 (s, 3H, CH_3), 7.01–7.02 (m, 1H, Ar–H), 7.24–7.26 (m, 2H, Ar–H), 7.33–7.50 (m, 4H, Ar–H), 7.54–7.68 (m, 3H, Ar–H), 8.36 (d, 2H, J = 8.1 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 13.4, 116.6, 119.5, 120.7, 121.3, 122.8, 126.3, 126.6, 127.4, 127.8, 129.2, 130.8, 132.1, 132.5, 133.7, 135.7, 136.0, 143.6, 144.1, 148.5, 185.7. ^{19}F NMR (235 MHz, $CDCl_3$) δ_F −62.3 (s, CF_3). ESI-MS m/z calcd for $C_{25}H_{15}BrF_3N_3OS$ $[M + 2H]^+$ 544.37, found 544.73. Anal. Calcd for $C_{25}H_{15}BrF_3N_3OS$: C, 55.36; H, 2.79; N, 7.75%. Found C, 55.22; H, 2.88; N, 7.88%.

(4-(2-Methoxyphenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(thiophen-2-yl)methanone(4i). Yellow solid; yield 82%; mp 213 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.12 (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 6.71 (d, 1H, J = 8.2 Hz, Ar–H), 6.90–6.92 (m, 1H, Ar–H), 7.01 (t, 1H, J = 7.5 Hz, Ar–H), 7.19 (d, 1H, J = 7.5 Hz, Ar–H), 7.25–7.36 (m, 3H, Ar–H), 7.52–7.58 (m, 3H, Ar–H), 8.35 (d, 2H, J = 9.0 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 13.1, 54.7, 109.9, 117.5, 120.6, 121.4 ($^1J_{C,F}$ = 274.7 Hz, CF_3), 121.9, 126.0, 127.1, 127.2, 127.8, 129.1, 131.1, 132.2, 134.8, 135.2, 139.0, 143.1, 143.5, 144.0, 144.5, 148.3, 155.7, 186.2. ESI-MS m/z calcd for $C_{26}H_{18}F_3N_3O_2S$ $[M + H]^+$ 494.50, found 494.30. Anal. Calcd for $C_{26}H_{18}F_3N_3O_2S$: C, 63.28; H, 3.68; N, 8.51%. Found C, 63.17; H, 3.59; N, 8.44%.

(3-Methyl-1-phenyl-4-(2-tolyl)-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(thiophen-2-yl)methanone (4j). Yellow solid; yield 82%; mp 173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.10 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 7.01–7.06 (m, 3H, Ar–H), 7.19–7.20 (m, 2H, Ar–H), 7.25–7.26 (m, 1H, Ar–H), 7.35 (t, 1H, J = 7.5 Hz, Ar–H), 7.53–7.61 (m, 3H, Ar–H), 8.34 (dd, 2H, J = 9.0 Hz, 1.2 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.5, 21.2, 115.9, 116.7, 120.8, 121.1 ($^1J_{C,F}$ = 274.8 Hz, CF_3), 126.2, 126.9, 127.8, 128.3, 129.0, 129.2, 129.8, 130,1, 134.8, 135.1, 138.9, 139.1, 143.2 ($^2J_{C,F}$ = 34.6 Hz, CF_3), 143.7, 144.0, 145.2, 146.4, 148.7, 185.8. ^{19}F NMR (235 MHz, $CDCl_3$) δ_F −62.3 (s, CF_3). ESI-MS m/z calcd for $C_{26}H_{18}F_3N_3OS$ $[M + H]^+$ 478.11, found 478.36. Anal. Calcd for $C_{26}H_{18}F_3N_3OS$: C, 65.40; H, 3.80; N, 8.80%. Found C, 65.28; H, 3.69; N, 8.72%.

(4-(2,3-Dichlorophenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(thiophen-2-yl)methanone (4k). Yellow solid; yield 70%; mp 188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.10 (s, 3H, CH_3), 7.01–7.03 (m, 1H, Ar–H), 7.25–7.39 (m, 4H, Ar–H), 7.49 (t, 1H, J = 4.8 Hz, Ar–H), 7.57 (td, 2H, J = 7.5 Hz, 1.8 Hz, Ar–H), 7.65 (d, 1H, J = 4.2 Hz, Ar–H), 8.34 (dd, 2H, J = 8.7 Hz, 1.2 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 13.1, 115.8, 116.3, 120.8, 121.3 ($^1J_{C,F}$ = 274.7 Hz, CF_3), 126.4, 127.4, 127.9, 129.2, 130.3, 131.5, 133.5, 134.1, 135.5, 135.8, 138.8, 141.7, 143.2, 143.6, 144.0, 148.5, 185.3. Anal. Calcd for $C_{25}H_{14}Cl_2F_3N_3OS$: C, 56.40; H, 2.65; N, 7.89%. Found 56.57; H, 2.78; N, 7.78%.

(3-Methyl-1,4-diphenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(thiophen-2-yl)methanone (4l). White solid; yield 80%; mp 178 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.10 (s, 3H, CH_3), 6.95–6.98 (m, 1H, Ar–H), 7.10–7.13 (m, 1H, Ar–H), 7.19–7.26 (m, 2H, Ar–H), 7.32–7.39 (m, 4H, Ar–H), 7.53–7.61 (m, 3H, Ar–H), 8.35 (d, 2H, J = 8.1 Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.4, 116.5, 120.8, 121.5 ($^1J_{C,F}$ = 274.9 Hz, CF_3) 126.3, 126.9, 127.6, 127.9, 128.4, 129.1, 129.2, 129.9, 133.1, 134.8, 135.2, 138.9, 143.7, 145.2, 146.1, 148.7, 185.7. ^{19}F NMR (235 MHz, $CDCl_3$) δ_F −62.3 (s, CF_3). ESI-MS m/z calcd for $C_{25}H_{16}F_3N_3OS$ $[M + H]^+$ 464.47, found 464.38. Anal. Calcd $C_{25}H_{16}F_3N_3OS$: C, 64.79; H, 3.48; N, 9.07%. Found C, 64.68; H, 3.39; N, 9.01%.

(3-Methyl-4-(4-nitrophenyl)-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(phenyl)methanone (4m). White solid; yield 78%; mp 205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.08 (s, 3H, CH_3), 7.26–7.41 (m, 5H, Ar–H), 7.49–7.61 (m, 5H, Ar–H), 8.15 (s (br), 2H, Ar–H), 8.33 (dd, 2H, J = 8.7 Hz, 1.2 Hz, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.4, 115.6, 120.8, 121.1, 126.6, 126.8, 128.5, 129.2, 130.5, 134.1, 137.2, 138.5, 139.7, 142.6, 142.8, 143.5 ($^2J_{C,F}$ = 34.8 Hz, CF_3), 148.0, 148.5, 193.3. ^{19}F NMR (235 MHz, $CDCl_3$) δ_F −62.3 (s, CF_3). ESI-MS m/z calcd for $C_{27}H_{17}F_3N_4O_3$ $[M + H]^+$ 503.44, found 503.41. Anal. Calcd for $C_{27}H_{17}F_3N_4O_3$: C, 64.54; H, 3.41; N, 11.15%. Found C, 64.66; H, 3.28; N, 11.29%.

(4-(4-Chlorophenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(phenyl)methanone (4n). White solid; yield 75%; mp 204 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.13 (s, 3H, CH_3), 7.26–7.38 (m, 6H, Ar–H), 7.50–7.60 (m, 6H, Ar–H), 8.40 (d, 2H, J = 8.4 Hz, Ar–H); ^{13}C NMR (75 MHz, CDCl3) δ_C: 14.5, 116.3, 120.8, 121.4 ($^1J_{C,F}$ = 274.5 Hz, CF_3), 126.4, 127.1, 128.4, 129.2, 129.3, 130.7, 131.6, 133.7, 135.5, 137.6, 138.8, 143.5 ($^2J_{C,F}$ = 34.7 Hz, CF_3), 144.4, 148.7, 193.9. ^{19}F NMR (235 MHz, $CDCl_3$) δ_F −62.3 (s, CF_3). ESI-MS m/z calcd for $C_{27}H_{17}ClF_3N_3O$ $[M + H]^+$ 492.10, found 492.22. Anal. Calcd for $C_{27}H_{17}ClF_3N_3O$: C, 65.93; H, 3.48; N, 8.54%. Found C, 65.80; H, 3.36; N, 8.48%.

(3-Methyl-1-phenyl-4-*p*-tolyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(phenyl)methanone (4o). White solid; yield 79%; mp 155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.10 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 6.95–7.15 (m (br), 4H, Ar–H), 7.26–7.37 (m, 3H, Ar–H), 7.47 (tt, 2H, J = 5.2 Hz, 1.2 Hz, Ar–H), 7.53–7.57 (m, 4H, Ar–H), 8.35 (dd, 2H, J = 8.7 Hz, 1.2 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.5, 21.1, 116.6, 120.6, 121.4 126.1, 127.1, 128.2, 128.7(br), 128.9(br), 129.1, 129.3, 130.0, 133.4, 137.6, 138.8, 139.0, 143.3 ($^2J_{C,F}$ = 34.5 Hz, CF_3), 143.6, 146.1, 148.6, 194.3. ESI-MS m/z calcd for $C_{28}H_{20}F_3N_3O$ $[M + H]^+$ 472.15, found 472.38. Anal. Calcd for $C_{28}H_{20}F_3N_3O$: C, 71.33; H, 4.28; N, 8.91%. Found C, 71.39; H, 4.38; N, 8.99%.

(4-(4-Methoxyphenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(phenyl)methanone (4p). White solid; yield 82%; mp 152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.13 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 6.73–7.03 (m (br), 4H, Ar–H), 7.26–7.37 (m, 2H, Ar–H), 7.46 (td, 2H, J = 6.6 Hz, 1.2 Hz, Ar–H), 7.54–7.59 (m, 4H, Ar–H), 8.35 (dd, 2H, J = 8.7 Hz, 1.2 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.6, 53.2, 113.5, 116.9, 120.8, 125.3, 126.2, 127.4, 128.3, 129.2, 129.3, 130.9, 133.4, 137.8, 139.0, 143.3, 145.9, 148.8, 160.2, 194.3. ESI-MS m/z calcd for $C_{28}H_{20}F_3N_3O_2$ $[M + H]^+$ 488.47, found 488.58. Anal. Calcd for $C_{28}H_{20}F_3N_3O_2$: C, 68.99; H, 4.14; N, 8.62%. Found C, 68.87; H, 4.24; N, 8.76%.

(4-(3-Bromophenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(phenyl)methanone (4q). White solid; yield 84%; mp 159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.12 (s, 3H, CH_3), 7.16–7.20 (m (br), 2H, Ar–H), 7.30–7.60 (m, 10H, Ar–H), 8.34 (dd, 2H, J = 8.4 Hz, 0.9 Hz, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.6, 116.1, 120.8, 121.3 ($^1J_{C,F}$ = 275.0 Hz, CF_3), 122.0, 123.1, 126.4, 126.9, 128.4, 129.2, 129.3, 132.1,

133.7, 135.0, 137.5, 138.7, 143.2, 143.3, 143.7, 148.6, 193.9. ^{19}F NMR (235 MHz, $CDCl_3$) δ_F −62.3 (s, CF_3). ESI-MS *m*/*z* calcd for $C_{27}H_{17}BrF_3N_3O$ $[M]^+$ 536.34, found 536.29, $[M + 2H]^+$ 538.27. Anal. Calcd for $C_{27}H_{17}BrF_3N_3O$: C, 60.46; H, 3.19; N, 7.83%. Found C, 60.32; H, 3.08; N, 7.71%.

1-(4-Methoxyphenyl)-3-methyl-4-(4-nitrophenyl)-6-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine (5r). White solid; yield 85%; mp 187 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.99 (s, 3H, CH_3), 3.15 (qd, *J* = 17.2, 8.0 Hz, 2H), 3.83 (s, 3H, OCH_3), 4.19 (t, *J* = 7.9 Hz, 1H), 6.99 (dd, *J* = 7.0, 2.1 Hz, 2H, Ar–H), 7.12 (d, *J* = 8.4 Hz, 2H, Ar–H), 7.23 (d, *J* = 8.4 Hz, 2H, Ar–H), 7.39 (d, *J* = 7.0 Hz, 3H, Ar–H), 7.99–7.82 (m, 4H, Ar–H).^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 12.5, 34.6, 55.4, 105.0, 113.9, 123.7, 127.1, 128.5, 128.5, 128.8, 130.9, 132.7, 132.8, 137.9, 141.9, 144.7, 146.1, 157.8, 165.1.Anal. Calcd for $C_{26}H_{22}N_4O_3$: C, 71.22; H, 5.04; N, 12.78%. Found C, 71.29; H, 5.12; N, 12.70%.

1-(4-Chlorophenyl)-4-(4-methoxyphenyl)-3-methyl-6-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine (5s). White solid; yield 83%; mp 145 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.06 (s, 3H, CH_3), 3. 12–3. 37 (m, 2H), 3.78 (s, 3H, OCH_3), 4.20 (t, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H, Ar–H), 7.13 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.26 (s, 1H, Ar–H), 7.42–7.54 (m, 5H, Ar–H), 7.90–8.01 (m, 3H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C:12.6, 34.4, 35.1, 55.2, 106.7, 113.3, 114.2, 121.6, 123.2, 127.2, 128.2, 128.6, 128.8, 129.3, 131.1, 131.2, 133.4, 135.2, 138.0, 145.8, 146.6, 158.9, 166.0. Anal. Calcd for $C_{26}H_{22}ClN_3O$: C, 72.97; H, 5.18; N, 9.82%. Found C, 72.97; H, 5.18; N, 9.82%.

1-(4-Chlorophenyl)-3-methyl-4-(4-nitrophenyl)-6-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine (5t). White solid; yield 61%; mp 187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.02 (s, 3H, CH_3). 3.19–3.36 (m, 2H), 4.37 (t, *J* = 6.7 Hz, 1H), 7. 36–7. 46 (m, 7H, Ar–H), 7.91–8.02 (m, 4H, Ar–H), 8.15 (d, *J* = 6.2 Hz, 2H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C:12.6, 34.3, 34.9, 76.6, 77.0, 77.4, 97.3, 104.8, 123.3, 124.4, 127.2, 128.0, 128.7, 128.9, 131.5, 131.6, 137.6, 137.7, 144.3, 145.5, 146.6, 147.1, 150.6, 165.3. Anal. Calcd for $C_{25}H_{19}ClN_4O_2$: C, 67.80; H, 4.32; N, 12.65%. Found C, 67.75; H, 4.39; N, 12.68%.

(1-(4-Chlorophenyl)-3-methyl-4-(4-nitrophenyl)-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(phenyl)methanone (4t). White solid; yield 39%; mp 169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.10 (s, 3H, CH_3), 7.10–7.40 (m, 4H, Ar–H), 7.50–7.56 (m, 5H, Ar–H), 8.20 (s, 2H, Ar–H), 8.29–8.35 (m, 2H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.58, 115.91, 119.31, 121.78, 123.13, 127.00, 128.63, 129.31, 129.38, 131.96, 134.22, 137.16, 139.60, 143.05, 143.47, 143.94, 148.13, 148.53, 193.28. Anal. Calcd for $C_{27}H_{16}ClF_3N_4O_3$: C, 60.40; H, 3.00; N, 10.44%. Found C, 60.37; H, 3.08; N, 10.49%.

(1,4-Bis(4-chlorophenyl)-3-methyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(thiophen-2-yl)methanone (4u). White solid; yield 82%; mp 179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.11 (s, 3H, CH_3), 6.96–7.03 (m, 2H), 7.06 (d, *J* = 8.1 Hz, 1H, Ar–H), 7.23 (dd, *J* = 14.2, 5.6 Hz, 1H, Ar–H), 7.33 (d, *J* = 8.2 Hz, 1H, Ar–H), 7.41 (d, *J* = 7.9 Hz, 1H, Ar–H), 7.52 (d, *J* = 8.9 Hz, 2H, Ar–H), 7.65 (d, *J* = 4.8 Hz, 1H, Ar–H), 8.33 (d, *J* = 8.9 Hz, 2H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.63. 116.47, 119.35, 121.67, 122.98, 126.97128.04, 128.8, 129.29, 130.25, 131.22, 131.30, 131.69, 135.00, 135.63, 135.80, 137.30, 143.15, 143.66, 144.80, 148.54, 185.32. Anal. Calcd for $C_{25}H_{14}Cl_2F_3N_3OS_3$: C, 56.40; H, 2.65; N, 7.89%. Found C, 56.46; H, 2.60; N, 7.94%.

(4-(4-Chlorophenyl)-1-(4-fluorophenyl)-3-methyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(phenyl)methanone (4v). White solid; yield 78%; mp 195 °C; ^{1}H-NMR (300 MHz, CDCl3) δ_H 2.10 (s, 1H). 6.70–7.43 (m, 5H), 7.45–7.61 (m, 1H), 8. 21–8. 48 (m, 1H). ^{13}C-NMR (75 MHz, CDCl3) δ_C 14.5, 115.8, 116.1, 116.2, 122.5, 122.4, 127.1, 128.2, 128.4, 128.5, 129.2, 131.4, 133.7, 134.8, 134.9, 135.4, 137.4, 143.2, 144.5, 148.4, 159.6, 161.8, 193.87. Anal. Calcd for $C_{27}H_{16}ClF_4N_3O$: C, 63.60; H, 3.16; N, 8.24%. Found C, 63.66; H, 3.13; N, 8.29%.

Methyl 4-(4-chlorophenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4w). White solid; yield 71%; mp 159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.08 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 7.24–7.35 (m, 4H, Ar–H), 7.44–7.54 (m, 3H, Ar–H), 8.25–8.30 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.6, 23.8, 29.6, 52.0, 113.0, 121.0, 123.5, 125.7, 127.7, 128.3, 128.5, 128.9, 129.9, 133.9, 134.9, 139.3, 143.0, 155.9, 168.8. Anal. Calcd for $C_{22}H_{18}ClN_3O_2$: C, 67.43; H, 4.63; N, 10.72%. Found 67.49; H, 4.60; N, 10.79%.

(4-(4-Methoxyphenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)(phenyl)methanone (4x). White solid; yield 85%; mp 191 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.13 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 6.77 (d, *J* = 7.6 Hz, 2H, Ar–H), 7.14 (d, *J* = 8.2 Hz, 2H, Ar–H), 7.25–7.37 (m, 3H, Ar–H), 7.46 (d, *J* = 7.5 Hz, 1H, Ar–H), 7.49–7.57 (m, 2H, Ar–H), 7.61 (d, *J* = 7.4 Hz, 2H, Ar–H), 8.33 (d, *J* = 7.6 Hz, 2H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 14.8, 23.9, 55.1, 113.3, 114.4, 121.1, 125.6, 126.7, 128.5, 128.9, 129.17, 129.3, 130.7, 133.4, 137.7, 139.5, 143.3, 143.3, 150.4, 155.3, 159.7, 198.4. Anal. Calcd for $C_{28}H_{23}N_3O_2$: C, 77.58; H, 5.35; N, 9.69%. Found C, 77.64; H, 5.39; N, 9.64%.

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