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Synthesis of novel fluorophenylpyrazole-picolinamide derivatives and determination of their anticancer activity

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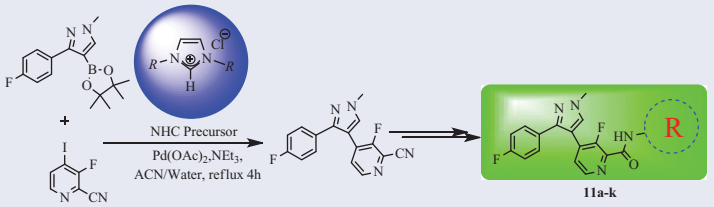
ABSTRACT

A series of fluorophenylpyrazole-picolinamide derivatives were synthesized in high yields using a cross-coupling reaction catalyzed by *in situ* formed palladium-N-heterocyclic carbenes (Pd-NHCs). The synthesized novel derivatives were evaluated for *in vitro* anticancer activity against a panel of four human tumor cell lines, HeLa (cervical), A-549 (lung), MCF-7 (breast), and IMR-32 (neuroblastoma). Four compounds, **11c**, **11e**, **11j**, and **11k**, showed growth inhibition (low μM) comparable with the standard drug cisplatin, providing a preliminary structure–activity relationship for the series. The present procedure is operationally simple and works with a wide range of substrates and may thus be useful in further compound optimization.

GRAPHICAL ABSTRACT



11 examples including aliphatic and aromatic amines with good to excellent yields.

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KEYWORDS
Fluorophenylpyrazole-picolinamide; cross-coupling; palladium-N-heterocyclic carbenes; anticancer activity

Introduction

Cancer is among the leading causes of human deaths worldwide, with ~9.5 million deaths in 2018. This very serious and potentially life-threatening illness is a heavy burden for the individual patients but also for the health care system and society as a whole. Thus, a constant search for new drugs and improved treatment modalities are needed. Cancer is a highly complex set of diseases; some forms are today efficiently

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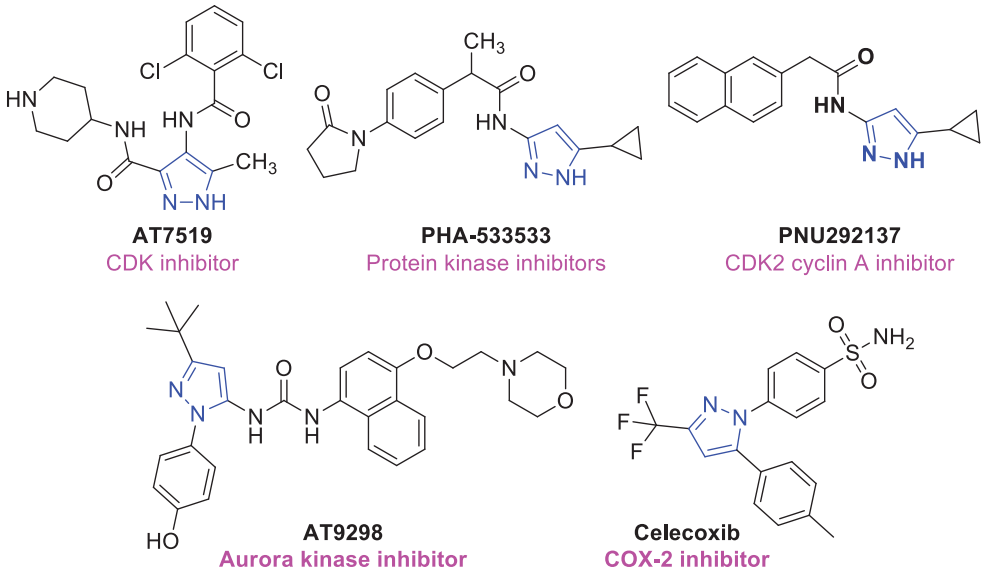


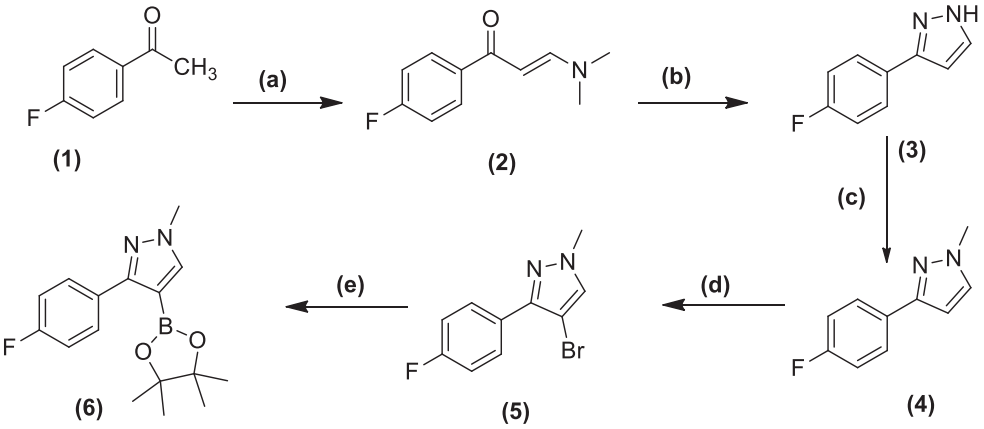
Figure 1. Some representative examples of active pharmaceutical ingredients containing a pyrazole group.

treated, such as testicular cancer, while others only have very limited treatment options, in particular in their advanced stages. There are several common hallmarks of cancer including sustained proliferative signaling, unlimited replicative potential, and activation of invasion and metastasis some of which may serve as therapeutic targets.[1]

In this article, we describe the synthesis and assessment of anticancer activity of a novel series of fluorophenylpyrazole-picolinamide derivatives. N, O, and S-heterocycles are structural units present in many drugs covering most therapeutic areas.[2] Among them the pyrazole group have been extensively used as scaffold for drug compounds (Figure 1).[3] For example, pyrazole containing derivatives have been found to posess potent anticancer activity by the inhibition of the cyclin-dependent kinases (CDKs).[4] Thus, an efficient synthesis of these is most desired. Previously we have reported the synthesis of isoxazole-indole,[5] and isoxazole-mercaptobenzimidazole,[6] derivatives, providing compounds with a combined anti-inflammatory and analgesic activity.

The combination of pyridine amides and pyrazole unit in one structure have been shown to provide synergistic effect in drug action and tunable structure–activity relationship (SAR). Recenlty researchers from Pfizer Inc, USA reported that pyrazole-pyridine derivatives provide potent inhibitors of Casein kinase 1 (CK1).[7] Inspired by this and in continuation of our research work in the fields of (i) N-heterocyclic carbene complexes (NHCs),[5,8] (ii) natural product based hybrid compounds,[9–11] and (iii) anticancer hybrid compounds[12–14] herein we report, a facile synthesis of new series of pyrazole-picolinamide derivatives, which to our knowledge have not previously been synthesized.

Compounds were designed and prepared through the combination of primary amines (aliphatic and aromatic), and fluorophenylpyrazole-picolinic acid. The straight forward



Scheme 1. Synthesis of Pyrazole-boran ester **6**. Reagents and conditions: (a) DMFDMA, DMF, 100 °C, 22 h, yield (87%); (b) Hydrazine, aq. EtOH, 12 h, RT, yield (64%); (c) CH_3I, Cs_2CO_3, DMF, 4 h, RT, yield (82%); (d) NBS, DCM, 4 h, RT, yield (85%); (e) Isopropoxyboronic acid pinacol ester, n-BuLi, THF, −78 °C, 1 h, yield (60%).

synthesis was accomplished by Suziki cross-coupling of readily obtained starting materials using *in situ* formed palladium-*N*-heterocyclic carbenes (Pd-NHCs). The prepared compounds were assessed *in vitro* for anticancer activity.

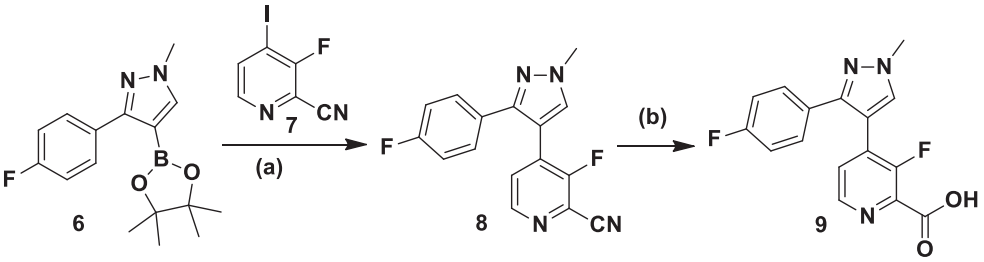
Results and discussion

The fluorophenylpyrazole-boran ester **6** and 3-fluoro-4-iodopicolinonitrile (**7**) are key intermediates for the preparation of fluorophenylpyrazole-picolinic acid **9**. The synthesis of target intermediate pyrazole-boran ester **6** was prepared in five-steps in good yields (Scheme 1).[15,16] Synthesis started with the condensation of 4-fluoroacetopheneone (**1**) with N,N-dimethylformamide dimethyl acetal (DMF-DMA) to afford corresponding enaminone **2**. Further, enaminone **2** was treated with hydrazine to yield 4-fluorophenylpyrazole (**3**). Then, the pyrazole compound **3** was N-alkylated using methyl iodide in the presence of cesium carbonate to furnish compound **4** followed by aromatic bromination using NBS in DCM to afford the brominated compound **5**. In the last step the Pyrazole-boran ester **6** was formed from **5** using isopropoxyboronic acid pinacol ester in the presence of butyllithium.

4-Fluorophenylpyrazole-picolinic acid (**9**) was coupled to primary amines (**10a–k**) to obtain fluorophenylpyrazole-picolinamide compounds (**11a–k**). The carboxylic acid fluorophenylpyrazole-picolinic acid (**9**) was obtained in a two-step synthesis (Scheme 2).

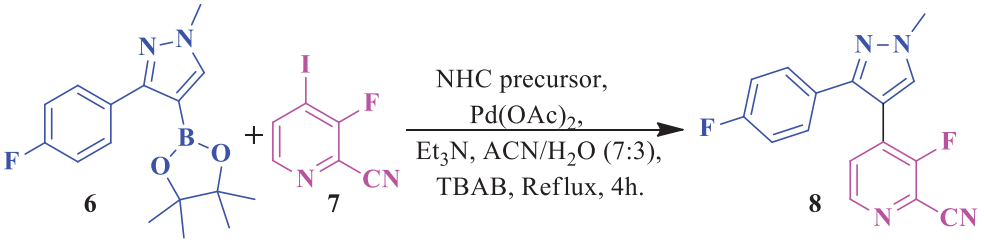
In the first step, the fluorophenylpyrazole-cyanopyridine (**8**) was obtained by Suziki cross-coupling of fluorophenylpyazole-boran ester (**6**) with 3-fluoro-4-iodo-cyanopyridine (**7**) using a catalytic system consisting of 1:2 $Pd(OAc)_2$ + Im-Cl, and slightly excess of base (Et_3N).

Initially the homogeneous Pd(II)-catalyzed Suziki-coupling between fluorophenylpyazole-boran ester (**6**) and 3-fluoro-4-iodo-cyanopyridine (**7**) was investigated as a model reaction using four different sets of catalytic conditions (Table 1, entries 1–4). These experiments were set to assess the influence of *N*-heterocyclic carbene (NHC) ligand



Scheme 2. Synthesis of fluorophenylpyrazole-picolinic acid **9**. Reagents and conditions: (a) 1,3-Bis(2,4,6-trimesitylphenyl)imidazolium chloride, $Pd(OAc)_2$, Triethylamine, ACN/H_2O (7:3), TBAB, Reflux, 4 h yield (96%); (b) aq.KOH, Reflux, 16 h yield (85%).

Table 1. Optimization of reaction condition for the Pd-NHC-catalyzed suziki cross coupling[a].



Entry	Catalyst	Base	Reaction time (h)	Yield (%)[b]
1	$Pd(OAc)_2$	Et_3N	14	43
2	$PdCl_2$	Et_3N	16	52
3	$Pd(OAc)_2$/Im-Cl	Et_3N	6	82
4	$PdCl_2$/Im-Cl	Et_3N	6	79
5	$Pd(OAc)_2$/Im-Cl/TBAB	Et_3N	4	96
6	$PdCl_2$/Im-Cl/TBAB	Et_3N	4	88
7	$PdCl_2$/TBAB	Et_3N	12	40
8	$Pd(OAc)_2$/Im-Cl/TBAB	Cs_2CO_3	5	90
9	$Pd(OAc)_2$/Im-Cl/TBAB	NaOAc	4	92
10	$Pd(OAc)_2$/Im-Cl/TBAB	K_2CO_3	4	88

[a]All products were characterized $^1H/^{13}C$ NMR and mass spectral analysis.
[b]GC yields.

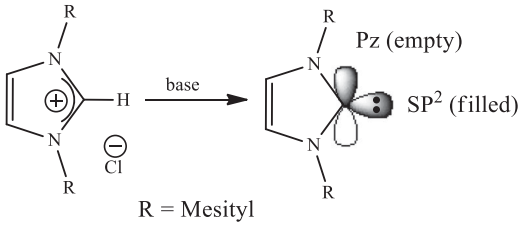
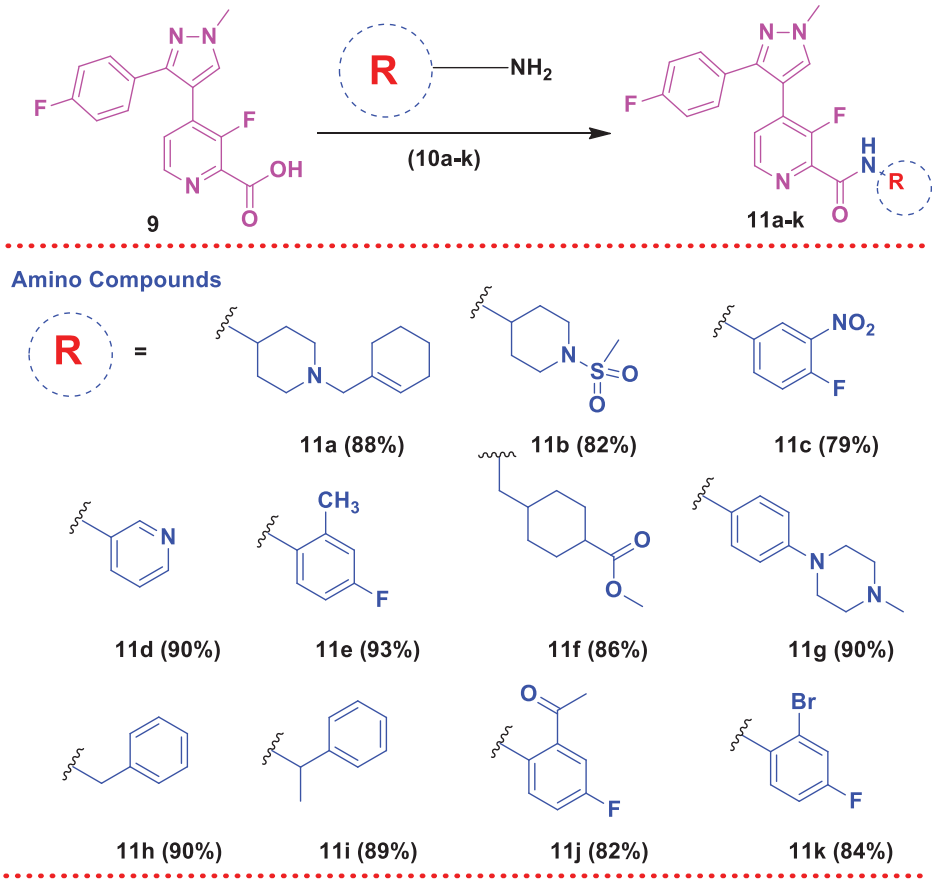


Figure 2. NHC precursor investigated in this work.

(Figure 2), phase transfer catalyst (PTC (TBAB = Tetra-n-butylammonium bromide)) and the influence of the base in accelerating the Suziki coupling reaction. For preparation of compound **8** (Table 1).

As a further improvement, addition of a TBAB produced a maximum 96% yield in short reaction time of ~4 h with the combination of $Pd(OAc)_2$ + NHC ligand precursor



Scheme 3. Synthesis of pyrazole-picolinamides **11a–k**. Reagents and conditions: (a) EDCl, HOBt, DIPEA, DMF, 6 h, RT.

(1,3-Bis(2,4,6-trimesitylphenyl)imidazolium chloride) + Et_3N (Table 1, entry 5). Replacement of $Pd(OAc)_2$ by $PdCl_2$, did not improve the yield of **8** (Table 1, entry 6). In this transformation, no Pd-black was observed. The role of a PTC to form and stabilize the metal nanoparticles including PdNPs is previously described.[17,18]

Overall the Pd(II)/NHC/PTC/Et_3N catalytic system provided better yields (Table 1, entry 5) than those without NHC ligand. The effect of PTC was by self, not significant (Table 1, entry 7). Furthermore, an exchange of base to Cs_2CO_3, NaOAc, or K_2CO_3 from Et_3N did not improve the yield of **8** (Table 1, entries 8–10). This system proved to be more efficient for the Suziki coupling of **6** with **7** than ligand-free Pd(II).

Compound **8** was then converted into the fluorophenylpyrazole-picolinic acid (**9**) intermediate by alkali hydrolysis (aq. KOH) (Scheme 2). Thereafter, compound **9** was subjected to amide coupling with primary amines **10a–k** in the presence of ehtyl(dimethylaminopropyl)carbodiimide (EDCl), hydroxybenzatriazole (HOBt) and diisopropylethylamine (DIPEA) as coupling reagents to afford pure pyrazole-picolinamide **11a-k** in high yields (Scheme 3).

The synthesized fluorophenylpyrazole-picolinamide (**11a–k**) compounds were characterized by $^1H/^{13}C$ NMR, mass spectroscopy and elemental analysis.

Table 2. *In vitro* cytotoxic activity of Pyrazole-picolinamide hybrids (**11a–k**) on human cancer cell lines[a] (IC_{50} μM/mL)[b].

Entry	Compound	HeLa	A549	MCF-7	IMR-32
1	11a	10.43 ± 0.21	11.22 ± 0.04	1.72 ± 0.04	20.56 ± 0.01
2	11b	8.62 ± 0.021	10.04 ± 0.02	1.35 ± 0.002	18.58 ± 0.19
3	**11c**	**4.25 ± 0.55**	**3.44 ± 0.01**	**2.63 ± 0.016**	**8.99 ± 0.38**
4	11d	10.74 ± 0.41	10.21 ± 0.07	1.88 ± 0.004	20.68 ± 0.26
5	**11e**	**4.88 ± 0.01**	**4.01 ± 0.26**	**2.89 ± 0.002**	**13.22 ± 0.21**
6	11f	22.42 ± 0.12	24.31 ± 0.06	4.10 ± 0.018	56.24 ± 0.65
7	11g	8.92 ± 0.01	12.38 ± 0.22	1.55 ± 0.003	20.74 ± 0.71
8	11h	22.58 ± 0.24	24.82 ± 0.22	3.82 ± 0.022	52.17 ± 0.12
9	11i	18.59 ± 0.11	26.01 ± 0.14	5.42 ± 0.001	54.01 ± 0.22
10	**11j**	**5.60 ± 0.07**	**3.89 ± 0.24**	**3.43 ± 0.07**	**11.87 ± 0.10**
11	**11k**	**4.62 ± 0.18**	**3.62 ± 0.12**	**2.06 ± 0.04**	**9.26 ± 0.05**
12	9	25.15 ± 0.22	28.04 ± 0.001	15.26 ± 0.12	66.41 ± 0.11
13	Cisplatin	4.98 ± 0.21	3.55 ± 0.007	1.56 ± 0.005	9.23 ± 1.21

[a]Data represent mean values ± SEM. Cytotoxicity as IC50 for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cell with respect to untreated cells using the MTT assay.
[b]Data represent as mean ± SEM values of these independent determinations.

Biological studies: antiproliferative activity

Many pyrazole containing molecules have shown biological activity toward several drug targets in the past (Figure 1). However, pyrazole-picolinamides have not been synthesized and studied. The new compounds **11a–k** were investigated for their anticancer activity in human cancer cell lines in comparison with the standard drug cisplatin. The cell lines used were (i) HeLa (cervical), (ii) A-549 (Lung), (iii) MCF-7 (Breast) and (iv) IMR-32 (neuroblastoma). The cytotoxic activity (IC_{50}) were determined *in vitro* using a MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay as previously reported.[19]

The IC_{50} values presented in Table 2 indicate that all the 11 fluorophenylpyrazole-picolinamide hybrids (**11a–k**) possess growth inhibitory activity against all the four human cancer cell lines tested with activities comparable to cisplatin. In particular, some of the compounds (**11c, 11e, 11j**, and **11k**) were slightly more potent than cisplatin against the HeLa (cervical), A-549 (Lung) and IMR-32 (neuroblastoma) cell lines. In respect to the structure–activity relationship, for this set of compounds only limited conclusions can be made. In comparison with starting compound **9** all new derivatives showed a increased antiproliferative activity. This suggests an improved drug–target interaction. Since the drug target is not known, further conclusions regarding stereochemical or electronic properties needed to obtain improved activity will only be speculative.

However, the synthetic options for modification of the most potent compounds are vast, which could lead to further amplification of the cytotoxic activity. As discussed above, compounds **11c, 11e, 11j, and 11k** with F-aryl substituent on amide linker showed the highest antiproliferative activity (Table 2, entries 3, 5, 10, and 11) particularly against the four cancer cell lines (HeLa, A-549, MCF-7, and IMR-32). However, in the case of breast cancer cell line MCF-7 the cytotoxic activity of **11c** was less than cisplatin (Entry 3). Compound **11k**, with a $-$2-Br-4-F-C_6H_4 substituent (Entry 11), was also more active than cisplatin in all the cell lines except the MCF-7.

Compounds **11f**, **11h**, and **11i** (entries 6, 8, and 9) with a simple cyclohexyl/phenyl substituent (i.e. without heteroatom substituent) on amide linkers showed moderate

inhibitory activity against all the cell lines. These findings may guide further modifications with respect to cancer cell selectivety and potency.

Experimental

General

All chemicals or reagents were purchased from standard commercial suppliers and treated with standard methods before use. Solvents were dried and deoxygenated by heating at reflux and storing over sodium. The reactions were monitored by thin layer chromatography (TLC) on pre-coated silica GF254 plates. Melting points were determined on a XT4MP apparatus (Taike Corp., Beijing, China), and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker MHz spectra were recorded on a Brucker 400 NMR (for ^{1}H), 100 NMR (for ^{13}C) spectrometer with DMSO-d_6 and $CDCl_3$ as the solvent.

General procedure for the synthesis of compound (9)

4-Fluorophenylpyazole-boran ester (**6**) (1 mmol), 3-fluoro-4-iodopicolinonitrile (**7**) (1 mmol), $Pd(OAc)_2$ (0.25 mmol%), NHC-precursor (0.5 mmol%), Triethylamine (2 mmol) and TBAB were suspended in acetonitrile and water (7:3). The mixture was stirred at 80 °C for 4 h under inert atmosphere. After the reaction, aqueous-ACN was removed in a rotavapor and the residue was extracted with cold ether (5 × 15 ml). The combined ether layers were washed with brine, dried (anhydrous Na_2SO_4) and evaporated under reduced pressure to afford a crude product which was subjected to column chromatography (silica gel, 60–120 mesh, eluent; n-hexane/EtOAc, 8:2 gradient) to afford pure nitrile compound (**8**). Further subjected to hydrolysis by using 10% KOH solution and then refluxed for 16 h, at which point it cleared and TLC analysis indicated complete consumption of the compound **8**. The reaction mixture was neutralized with acetic acid and cooled in ice, and the precipitate was collected by filtration. After being washed with cold water (2 × 25 mL), the precipitate was dried under vacuum to afford a pure product (**9**).

General procedure for the synthesis of title compounds (11a–k)

4-fluorophenylpyrazole-picolinic acid (**9**), amine (10a–k) (1 eq), EDCl (1.1 eq), HOBt (1.1 eq) and DIPEA (2.5 eq) were suspended in DMF. The reaction mixture was stirred at room temperature for 6 h. After completion of the reaction added water and extracted with ethylacetate. The combined organic layers were washed with brine, dried (anhydrous Na_2SO_4) and evaporated under reduced pressure to afford a crude product which was subjected to column chromatography (silica gel, 60–120 mesh, eluent; *n*-hexane/EtOAc, 8:2 gradient) to afford pure title compounds (**11a–k**).

Spectral data of the compounds 8, 9, and 11a

3-Fluoro-4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)picolinonitrile (8)

Tan yellow solid: mp 124–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.03 (s, 3H), 7.06–7.10 (t, 2H), 7.26–7.29 (t, 1H), 7.38–7.42 (m, 2H), 7.85–7.86 (d, 1H), 8.27–8.28 (d, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 39.31, 108.64, 113.13, 115.91, 123.24, 127.38, 128.40, 130.10, 130.67, 132.73, 146.49, 149.49, 156.77, 159.44, 161.60, 164.07 ppm. MS (ESI), $m/z = 297.094$ $[M + H]^+$. EA calcd (%) for $C_{16}H_{10}F_2N_4$ (296.087): calcd. C 64.86, H 3.40, N 18.91; found. C 64.82, H 3.36, N 18.87.

3-Fluoro-4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)picolinic acid (9)

Yellow solid: mp 130–131 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.95 (s, 3H), 7.18–7.25 (t, 2H), 7.39–7.49 (m, 3H), 8.18–8.19 (d, 1H), 8.36–8.38 (d, 1H), 13.53 (bs, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): 109.41, 115.64, 127.69, 129.55, 130.73, 133.49, 138.91, 144.98, 147.84, 153.42, 156.06, 160.66, 163.10, 164.47 ppm. MS (ESI), $m/z = 316.089$ $[M + H]^+$. EA calcd (%) for $C_{16}H_{11}F_2N_3O_2$ (315.082): calcd. C 60.95, H 3.52, N 13.33; found. C 60.91, H 3.48, N 13.29.

N-(1-(cyclohex-1-en-1-ylmethyl)piperidin-4-yl)-3-fluoro-4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)picolinamide (11a)

Yellow solid: mp 182–184 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.53–1.58 (m, 5H), 1.91–2.19 (m, 9H), 2.89–3.35 (m, 3H), 4.18–4.22 (s, 3H), 5.84 (s, 1H), 7.18–7.22 (m, 2H), 7.29–7.51 (m, 4H), 8.19 (s, 1H), 8.32–8.33 (d, 1H), 8.72 (s, 1H), 9.70–10.9 (br s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): 21.90, 22.48, 25.26, 27.55, 109.94, 115.89, 116.11, 127.45, 129.90, 130.01, 130.08, 131.07, 131.20, 133.98, 141.59, 144.69, 148.29, 153.19, 155.83, 161.14, 162.97, 163.57 ppm. MS (ESI), $m/z = 492.256$ $[M + H]^+$. EA calcd (%) for $C_{28}H_{31}F_2N_5O$ (491.250): calcd. C 68.41, H 6.36, N 14.25; found. C 68.38, H 6.32, N 14.21.

Conclusions

In conclusion, a facile and simple catalytic method for the synthesis of fluorophenylpyrazole-picolinamide derivatives in high yields was developed using a cross-coupling reaction catalyzed by palladium-N-heterocyclic carbenes (Pd-NHCs). The proposed method represents a cost-effective, eco-friendly, and practical/scalable process for synthesis of fluorophenylpyrazole-picolinamide. The conditions applied and the results obtained in our work for the synthesis of pyrazole-picolinamides which is believed to be an improvement to other reported procedures. Pyrazole-picolinamide derivatives were evaluated for *in vitro* anticancer activity against a panel of four human tumor cell lines, i.e. HeLa (cervical), A-549 (Lung), MCF-7 (Breast) and IMR-32 (neuroblastoma), and features important for the structure-activity relationship (SAR) demonstrated. The derivatives with an electron-withdrawing group, i.e. F- & NO_2-aryl substituent displayed higher activity than the compounds containing electron-donating groups, i.e. CH_3- and aliphatic/aromatic N-heterocycle and without heteroatom substituents. The compounds **11c, 11e, 11j, and 11k** with F-aryl substituent on amide linker showed the highest antiproliferative activity which compared well with the standard drug cisplatin.

The broad spectrum of anticancer activity displayed by these pyrazole-picolinamides provide a valuable starting point for further optimization and biological studies *in vitro* and *in vivo*.

Experimental procedures, Spectral data of compounds 9 and 11a–k. Supplementary data associated with this article can be found, in the online version.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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