Research Article

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One-pot Multicomponent Synthesis of Novel Polyfunctionalized Pyridines

Hayam H. Mohammed, Eman A. Ahmed, Bahgat R. M. Hussein* and Omran A. Omran

Chemistry Department, Faculty of Science, Sohag University, Sohag 82524, Egypt
**Email: bahgat.ramadan@yahoo.com & bahgat@science.sohag.edu.eg*

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Abstract: In this work, we synthesized a novel arylidene malononitrile **3** *via* the treatment of *o*-alkyl vanillin derivative **1** with malononitrile **2** in the presence of triethylamine (TEA) as a catalyst. The arylidene malononitrile **3** was subjected to react under one-pot multicomponent reaction (MCR) condition with respective methylarylketones **4a-f** and sodium ethoxide **5** in ethanol to afford a new series of 2-(4-(6-aryl-3-cyano-2-ethoxypyridin-4-yl)-2-methoxyphenoxy)-*N*-phenylacetamides **6a-f**. The structure of the new products was assured *via* spectral and elemental analysis. The reaction mechanism was suggested.
Keywords: *o*-alkyl vanillin, pyridine derivatives, arylidene, *N*-phenylacetamide, multicomponent reaction.

1. Introduction

Vanillin is considered one of the most important safe natural products for many uses. Not only that we can't do without it in our daily lives as a flavoring for taste and aroma [1], but also it has many biological properties as antitumor [2], antioxidant [3], antimicrobial [4], antibacterial [5], anti-inflammatory [6], antimutagenic [7], antialzheimer's [8], antiproliferative activities [9], antidiabetic [10] and antidepressant [11]. Furthermore, vanillin is low toxicity, easy decomposition possesses general bio-safety, environmental friendliness, and specificity to target species [12]. In addition, it is easily extracted from orchids (*Vanillaplanifolia*, *V. pompona*, or *V. tahitiensis*) [13].

Moreover, vanillin is used as a prodrug in the manufacture of *Aldomet* which is used for the treatment of hypertensive, *L-dopa* for the treatment of Parkinson's disease, and *trimethoprim* to treat some venereal diseases forms and upper respiratory tract infections **(Fig. 1) [14]**.

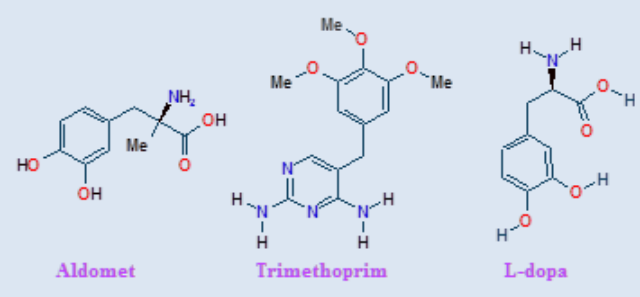


Fig. 1: Some of the drugs that were prepared from vanillin as starting material.

On the other side, Pyridines naturally occur in important vitamins such as vitamin B3, vitamin B6, and some alkaloids [15]. They have diverse pharmacological and biological applications such as: antidiabetic [16], anti-HIV [17], antitubercular [18], anti-bacterial [19], anticonvulsant [20], anticancer effects [21], COX inhibitor [22], antihypertensive [23], anti-oxidant [24], blood platelet aggregation inhibitors [25], and antifungal activities [26].

Furthermore, many marketing drugs contain pyridine moiety because it has effective biological activity such as amlodipine (anti-hypertensive) and isoniazide (anti-tuberculosis) [27, 28] (**Fig. 2**).

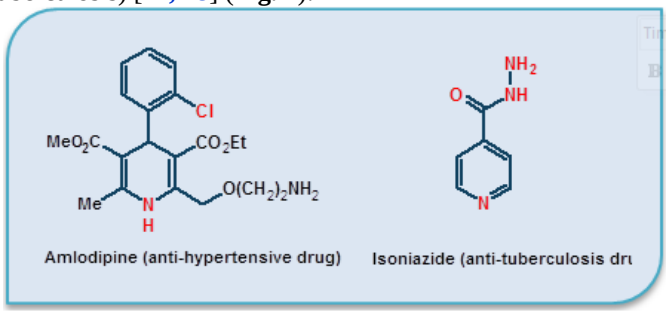


Fig. 2: Drugs consist of the pyridine moiety.

As a result, the vanillin and pyridine rings are ideal structures, and they have piqued the curiosity of organic synthesis researchers. Therefore, the synthesis of poly-functionalized aza-heterocyclic compounds especially pyridines from available simple natural starting materials *via* effectively one-pot multicomponent reactions (MCRs) technique, which has many advantages such as saving in cost, time of the reaction, and energy used, it achieves the most important principles of green chemistry, which is the atomic economy, in addition to their products can be easily separated and purified. [29].

On the basis of the abovementioned and for the continuation of our works [30-33], we have combined the properties of vanillin and pyridine to synthesize a novel series of 2-(4-(6-aryl-3-cyano-2-ethoxypyridin-4-yl)-2-methoxyphenoxy)-*N*-phenylacetamide **6a-f** through an effective one-pot multicomponent reaction.

2. Results and Discussion:

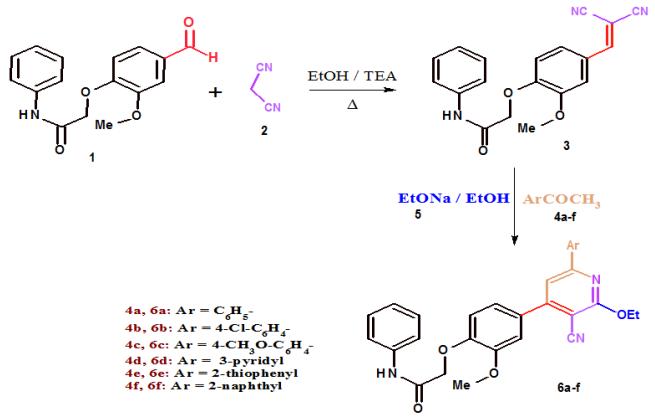
Herein, we synthesized the arylidene **3** *via* Knoevenagel condensation reaction of *O*-alkyl vanillin **1** [34] with malononitrile **2** using TEA as a basic catalyst in ethanol (**Scheme1**). The chemical structure of arylidene **3** was confirmed using IR, ^{1}H NMR, and elemental analysis data. The IR spectrum showed the absorption bands for amidic carbonyl at 1683 cm^{-1}, CN groups at 2216 cm^{-1}, CH aliphatic groups at 2924 and 2837 cm^{-1}, and CH of aromatic at 3040 cm^{-1}. Whereas the ^{1}H NMR spectrum showed two singlet signals for NH and $CH_{olefinic}$ at 10.24 ppm and 8.40 ppm, respectively beside one singlet, one multiplet, two triplet (coupling constant 7.8 Hz), and doublet signals (coupling constant 8 Hz) at range 7.70-7.08 ppm due to eight aromatic protons, in addition to, two singlet signals corresponding to methylene and methoxy groups at 4.92 and 3.86 ppm, respectively.

A novel series of 2-(4-(6-aryl-3-cyano-2-ethoxypyridin-4-yl)-2-methoxy-phenoxy)-*N*-phenylacetamides **6a-f** were synthesized *via* one-pot multicomponent reaction (MCR) of arylidene malononitrile **3**, with sodium ethoxide **5** and respective methylarylketones namely: acetophenone **4a**, 4-chloroacetophenone **4b**, 4-methoxyacetophenone **4c**, 3-acetylpyridine **4d**, 2-acetylthiophene **4e** and/or 2-acetylnaphthalene **4f** in ethanol (**Scheme1**).

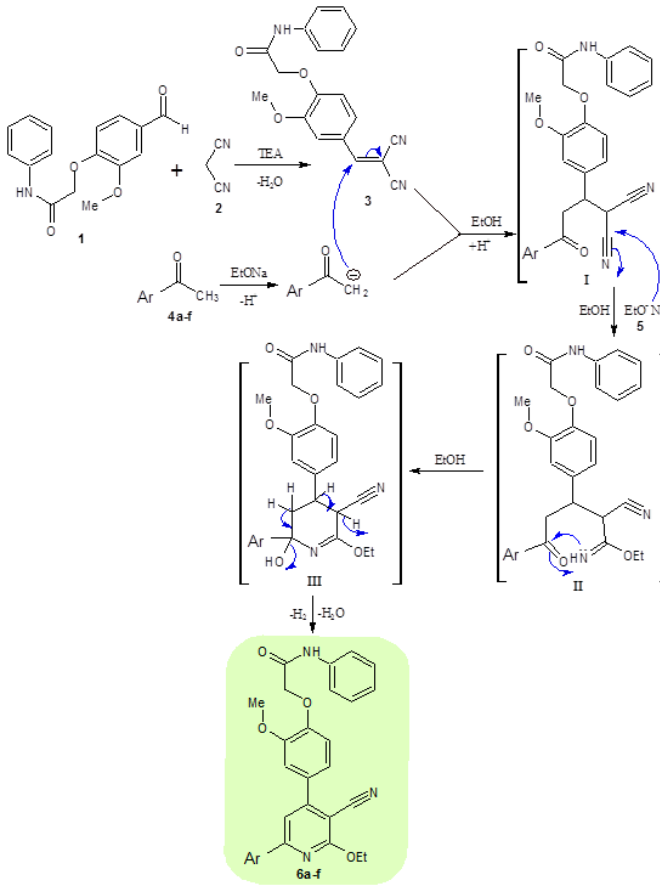
The chemical structure of pyridines **6a-f** was confirmed *via* different spectroscopic methods (IR, ^{1}H, ^{13}C, Dept-135 NMR) and elemental analysis (see **Experimental part**). The IR spectrum of pyridine derivative **6b** (as an example) showed the absorption bands corresponding to NH, $CH_{arom.}$ $CH_{aliph.}$, CN, and $C{=}O_{amidic}$ groups at 3421, 3055, 2975-2829, 2211 and 1633 cm^{-1}, respectively. The ^{1}H NMR spectrum of pyridine **6b** revealed thirteen aromatic protons that appeared as two singlet, two doublet, one multiplet, and one triplet signals at 7.82, 7.67, 8.29-8.27, 7.62-7.60, 7.32-7.22, 6.97-6.94 ppm, respectively, whereas three singlet signals due to NH, OCH_3, and CH_2 at 7.44, 3.97 and 3.36 ppm, respectively, quartet and triplet signals for methylene and methyl groups of OCH_2CH_3 at 4.67-4.62 and 1.47-1.44 ppm, respectively.

Whereas the ^{13}C NMR spectrum showed seven signals due to carbonyl, nitrile, $CH_{2\ ethoxy}$, $CH_{3\ methoxy}$, CH_2 and $CH_{3\ ethoxy}$ at 164.71, 116.42, 63.56, 61.90, 56.31, and 14.77 ppm, respectively in addition to, nineteen signals at 156.81, 156.13, 155.96, 148.60, 148.51, 142.35, 136.15, 135.85, 135.77, 129.61, 129.36, 126.26, 122.17, 121.85, 119.68, 113.91, 113.48, 111.89, 90.86 ppm assign to sp^2 aromatic carbons.
Also, the Dept-135 spectrum of pyridine derivative **6b** confirms its structure because it showed two signals in a negative direction for two methylene groups at 63.55 ppm and 61.90 ppm respectively, while the methoxy and methyl carbons appeared in a positive direction at 56.30 ppm and 14.77 ppm, respectively. Whereas C-H aromatic carbon appeared at 129.60, 129.56, 129.35, 122.17, 121.84, 119.68, 113.91, 113.48, 111.89 ppm.

The plausible reaction mechanism for the synthesis of pyridines **6a-f** can be postulated through the arylidene **3** experiences the reaction of nucleophilic addition by attacking an enolate ion of the activated methylarylketone **4a-f** in the presence of NaOEt to yield the intermediate **I**, which is followed by nucleophilic addition of Eto$^-$ anion on C≡N group to yield the intermediate **II**. The imino group of intermediate **II** experiences the reaction of intramolecular cyclization (Michael addition reaction) by attacking of C≡N group to give intermediate **III**, which is easily aromatized *via* the elimination of H_2O and H_2 molecules to give the target products (**Scheme 2**).



Scheme1: Synthesis of a novel arylidene **3** and pyridine derivatives **6a-f**.



Scheme 2: The possible reaction mechanism for the production of pyridine derivatives **6a-f**.

3. Conclusion

A novel series of 2-(4-(6-aryl-3-cyano-2-ethoxypyridin-4-yl)-2-methoxyphenoxy)-*N*-phenylacetamides **6a-f** was obtained through two steps: (i) preparation of the arylidene **3** from a simple and available natural product (vanillin)

derivative **1**. (ii) multicomponent reaction of the arylidene **3** with methylarylketones **4a-f** and sodium ethoxide **5** in ethanol to afford the target products.

4. Experimental

All melting points were measured and uncorrected by using the Kofeler melting point equipment. IR spectra (KBr pellets) were obtained using an FT-IR spectrophotometer. The ^{13}C NMR (DMSO- d_6) and Dept-135 (DMSO- d_6) spectra were recorded at 100 MHz on Bruker Bio Spin AG at Sohag University, while the ^{1}H NMR (DMSO- d_6) spectra were obtained at 400 M Hz. Perkin-Elmer CHN analyzer model provided elemental analysis. TLC plates (silica gel/UV light (254 nm/365 nm) for visualization) were used to monitor all reactions.

4.1. Synthesis of 2-[4-(2,2-dicyanovinyl)-2-methoxyphenoxy] -*N*-phenylacetamide (3):

A mixture of compound **1** (0.5 g, 2 mmol) and malononitrile (0.12 g, 2 mmol) in the presence of a few drops of TEA in 20 mL of ethanol was refluxed for 1 h. The formed precipitate was filtered off (on hot), washed with cold ethanol several times, and crystallized from acetonitrile.

Yellow powder, yield: 0.54 g (92%), mp. 234-236 °C; IR (ATR) ν max: 3377 (NH), 3040 ($CH_{arom.}$), 2924, 2837 ($CH_{aliph.}$), 2216 (CN), 1683 ($C=O_{amidic}$) cm^{-1}; ^{1}H NMR δ: 10.24 (s, 1H, NH), 8.40 (s, 1H, $CH_{olefinic}$), 7.70 (s, 1H, H-Ar), 7.63-7.59 (m, 3H, H-Ar), 7.36-7.32 (t, 2H, *J* = 7.8 Hz, H-Ar), 7.19, 7.17 (d, 1H, *J* = 8 Hz, H-Ar), 7.11-7.08 (t, 1H, *J* = 7.8 Hz, H-Ar), 4.92 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3). *Anal*. Calcd. for $C_{19}H_{15}N_3O_3$ (333.34): C, 68.46; H, 4.54; N, 12.61%. Found: C, 68.55; H, 4.34; N, 12.75%.

4.2. General procedure for synthesis of pyridines 6a-f

To a solution of arylidene **3** (0.5 g, 1 mmol) in 30 mL of ethanol was mixed with sodium ethoxide **5** (0.14 g, 2 mmol)), and 1 mmol of respective methylarylketones **4a-f** namely; acetophenone (0.12 g, 1 mmol), 4-chloroacetophenone (0.15 g, 1 mmol), 4-methoxyacetophenone (0.15 g, 1 mmol), 3-acetylpyidine (0.12 g, 1 mmol), 2-acetylthiophene (0.13 g, 1 mmol) and/or 2-acetylnaphthalene (0.17 g, 1 mmol) was added. The reaction mixture was refluxed and monitored using TLC for around 5 hours then allowed to cool to room temperature and poured into 30 mL of ice-cold water. The precipitate was filtered, washed multiple times with water, dried, and crystallised from ethanol.

2-(4-(3-Cyano-2-ethoxy-6-phenylpyridin-4-yl)-2-methoxy-phenoxy)-*N*-phenylacetamide (6a)

Pale yellow powder, yield: 0.58g (80%), mp. 203-205 °C; IR (ATR) ν max: 3423 (NH), 3051 ($CH_{arom.}$), 2977, 2918, 2847 ($CH_{aliph.}$), 2212 (CN), 1692 ($C=O_{amide}$) cm^{-1}; ^{1}H NMR: δ 8.24, 8.23 (d, 2H, *J* = 4 Hz, H-Ar), 7.78 (s, 1H, H-Ar), 7.62-7.54 (m, 4H, H-Ar), 7.43 (s, 1H, NH), 7.31-7.24 (m, 6H, H-Ar), 6.96 (s, 1H, H-Ar), 4.67-4.64 (q, 2H, *J* = 7 Hz, O**CH₂**CH_3), 3.97 (s, 3H, OCH_3), 3.38 (s, 2H, O**CH₂**CO), 1.47-1.45 (t, 3H, *J*= 7 Hz, OCH_2**CH₃**). *Anal*.Calcd. for $C_{29}H_{25}N_3O_4$ (479.5): C, 72.64; H, 5.25; N, 8.76%. Found: C, 72.52; H, 5.44; N, 8.66%.

2-(4-(6-(4-Chlorophenyl)-3-cyano-2-ethoxypyridin-4-yl)-2-methoxyphenoxy)-*N*-phenylacetamide (6b)

Pale yellow powder, yield: 0.59g (77%), mp. 198-200 °C; IR (ATR) ν max: 3421 (NH), 3055 ($CH_{arom.}$), 2975, 2920, 2829 ($CH_{aliph.}$), 2211 (CN), 1633 ($C=O_{amide}$) cm^{-1}; ^{1}H NMR: δ 8.29-8.27 (d, 2H, H-Ar), 7.82 (s, 1H, H-Ar), 7.67 (s, 1H, H-Ar), 7.62, 7.60 (d, 2H, *J* = 8 Hz, H-Ar), 7.44 (s, 1H, NH), 7.32-7.29 (m, 4H, H-Ar), 7.24-7.22 (m, 2H, *J* = 8 Hz, H-Ar), 6.97-6.94 (t, 1H, *J*= 7 Hz, H-Ar), 4.67-4.62 (q, 2H, *J* = 7 Hz, O**CH₂**CH_3), 3.97 (s, 3H, OCH_3) 3.36 (s, 2H, O**CH₂**CO), 1.47-1.44 (t, 3H, *J*= 7 Hz, OCH_2**CH₃**). ^{13}C NMR: δ 164.71, 156.81, 156.13, 155.96, 148.60, 148.51, 142.35, 136.15, 135.85, 135.77, 129.61, 129.36, 126.26, 122.17, 121.85, 119.68, 116.42 (CN), 113.91, 113.48, 111.89, 90.86, 63.56, 61.90, 56.31, 14.77, Dept-135 NMR: δ 129.60, 129.56, 129.35, 122.17, 121.84, 119.68, 113.91, 113.48, 111.89, 63.55 (O**CH₂**CH_3), 61.90 (O**CH₂**CO), 56.30 (OCH_3), 14.77 (OCH_2**CH₃**). *Anal*. Calcd. for $C_{29}H_{24}ClN_3O_4$ (513.97): C, 67.77; H, 4.71; N, 8.18%. Found: C, 67.60; H, 4.81; N, 8.08%.

2-(4-(3-Cyano-2-ethoxy-6-(4-methoxyphenyl)pyridin-4-yl)-2-methoxyphenoxy)-*N*-phenylacetamide (6c)

Pale yellow powder, yield: 0.6g (79%), mp. 198-200 °C; IR (ATR) ν max: 3403 (NH), 3051 ($CH_{arom.}$), 2962, 2936, 2835 ($CH_{aliph.}$), 2209 (CN), 1691 ($C=O_{amide}$) cm^{-1}; ^{1}H NMR: δ 8.23, 8.21 (d, 2H, *J* = 8 Hz, H-Ar), 7.71, 7.69 (d, 2H, *J*= 6 Hz, H-Ar), 7.41 (s, 1H, NH), 7.32-7.30 (m, 4H, H-Ar), 7.23-7.22 (m, 2H, H-Ar), 7.10, 7.08 (d, 2H, *J* = 8 Hz, H-Ar), 6.96-6.92 (t, 1H, *J* = 7 Hz, H-Ar), 4.65-4.60 (q, 2H, *J* = 7 Hz, O**CH₂**CH_3), 3.96 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.34 (s, 2H, O**CH₂**CO), 1.46-1.43 (t, 3H, *J* = 7 Hz, OCH_2**CH₃**). ^{13}C NMR: δ 164.68, 161.81, 157.23, 156.59, 156.50, 148.64, 142.60, 135.54, 129.83, 129.54, 127.07, 122.06, 121.60, 119.51, 116.61 (CN), 114.76, 114.20, 112.56, 112.07, 90.84, 63.27 (O**CH₂**CH_3), 61.61 (O**CH₂**CO), 56.33 (OCH_3), 55.86 (OCH_3), 14.86 (OCH_2**CH₃**). *Anal*. Calcd. for $C_{30}H_{27}N_3O_5$ (509.55): C, 70.71; H, 5.34; N, 8.25%. Found: C, 70.60; H, 5.51; N, 8.37%.

2-(4-(5-Cyano-6-ethoxy-2,3'-bipyridin-4-yl)-2-methoxy-phenoxy)-*N*-phenylacetamide (6d)

Pale yellow powder, yield: 0.49g (68%), mp. 176-178 °C; IR (ATR) ν max: 3405 (NH), 3054 ($CH_{arom.}$), 2987, 2933, 2832 ($CH_{aliph.}$), 2216 (CN), 1657 ($C=O_{amide}$) cm^{-1}; ^{1}H NMR: δ 9.42 (s, 1H, H-Ar), 8.71 (s, 1H, H-Ar), 8.59-8.57 (d, 1H, *J* = 7 Hz, H-Ar), 7.90 (s, 1H, H-Ar), 7.73 (s, 1H, H-Ar), 7.57 (s, 1H, H-Ar), 7.44 (s, 1H, NH), 7.31-7.23 (m, 6H, H-Ar), 6.97-6.94 (t, 1H, *J* = 6 Hz, H-Ar), 4.67-4.61 (q, 2H, *J* = 7 Hz, O**CH₂**CH_3), 3.98 (s, 3H, OCH_3), 3.36 (s, 2H, O**CH₂**CO), 1.47-1.44 (t, 3H, *J* = 6 Hz, OCH_2**CH₃**). ^{13}C NMR: δ 164.80, 156.83, 155.09, 151.47, 149.01, 148.52, 142.41, 135.77, 135.24, 132.96, 129.57, 126.40, 124.32, 122.27, 121.71, 119.65, 116.35 (CN), 113.95, 113.82, 112.02, 92.46, 63.64 (O**CH₂**CH_3), 61.96 (O**CH₂**CO), 56.29 (OCH_3), 14.81 (OCH_2**CH₃**). *Anal*. Calcd. for $C_{28}H_{24}N_4O_4$ (480.51): C, 69.99; H, 5.03; N, 11.66%. Found: C, 69.72; H, 5.22; N, 11.45%.

2-(4-(3-Cyano-2-ethoxy-6-(thiophen-2-yl)pyridin-4-yl)-2-methoxyphenoxy)-*N*-phenylacetamide (6e)

Pale yellow powder, yield: 0.54g (72%), mp. 158-160 °C;

IR (ATR) νmax: 3421 (NH), 3076 ($CH_{arom.}$), 2924, 2835 ($CH_{aliph.}$), 2211 (CN), 1691 ($C=O_{amide}$) cm^{-1}; ^1H NMR: δ 8.06, 8.05 (d, 1H, J = 2 Hz, H-Ar), 7.79, 7.78 (d, 1H, J = 4 Hz, H-Ar), 7.72, 7.71 (d, 2H, J = 3 Hz, H-Ar), 7.39 (s, 1H, NH), 7.32-7.22 (m, 7H, H-Ar), 6.96-6.93 (t, 1H, J= 7 Hz, H-Ar), 4.67-4.61 (q, 2H, J = 7 Hz, O**CH**$_2$CH$_3$), 3.98 (s, 3H, OCH_3), 3.27 (s, 2H, O**CH**$_2$CO), 1.45-1.42 (t, 3H, J= 7 Hz, OCH_2**CH**$_3$). ^{13}C NMR: δ 164.60, 156.47, 152.88, 148.53, 143.33, 142.51, 135.61, 131.32, 129.55, 129.35, 128.71, 126.59, 122.07, 121.61, 119.53, 116.48 (CN), 114.03, 111.94, 111.76, 90.98, 63.55 (O**CH**$_2$CH$_3$), 61.89 (O**CH**$_2$CO), 56.27 (OCH_3), 14.76 (OCH_2**CH**$_3$). *Anal*. Calcd. for $C_{27}H_{23}N_3O_4S$ (485.55): C, 66.79; H, 4.77; N, 8.65%. Found: C, 66.52; H, 4.88; N, 8.45%.

2-(4-(3-Cyano-2-ethoxy-6-(naphthalen-2-yl)pyridin-4-yl)-2-methoxyphenoxy)-N-phenylacetamide (6f)

Pale yellow powder, yield: 0.65g (82%), mp. 178-180 °C; IR (ATR) νmax: 3425 (NH), 3054 ($CH_{arom.}$), 2919, 2842 ($CH_{aliph.}$), 2207 (CN), 1695 ($C=O_{amide}$) cm^{-1}; ^1H NMR: δ 8.82 (s, 1H, H-Ar), 8.35, 8.33 (d, 1H, J = 8 Hz, H-Ar), 8.06-8.03 (m, 2H, H-Ar), 7.98, 7.96 (d, 1H, J = 8 Hz, H-Ar), 7.93 (s, 1H, H-Ar), 7.72 (s, 1H, H-Ar), 7.60, 7.58 (d, 2H, J = 8 Hz, H-Ar), 7.46 (s,1H, NH), 7.32-7.24 (m, 6H, H-Ar), 6.97-6.94 (t, 1H, J = 7 Hz, H-Ar), 4.69-4.65 (q, 2H, J = 6 Hz, O**CH**$_2$CH$_3$), 3.98 (s, 3H, OCH_3), 3.29 (s, 2H, O**CH**$_2$CO), 1.49-1.46 (t, 3H, J = 7 Hz, OCH_2**CH**$_3$). ^{13}C NMR: δ 164.75, 157.26, 156.64, 148.64, 142.59, 135.67, 134.80, 134.32, 133.34, 129.54, 129.36, 128.82, 128.06, 127.86, 127.11, 126.91, 124.84, 122.19, 121.63, 119.57, 116.49 (CN), 116.19, 114.19, 113.87, 112.12, 91.88, 63.55 (O**CH**$_2$CH$_3$), 61.80 (O**CH**$_2$CO), 56.37 (OCH_3), 14.87 (OCH_2**CH**$_3$). *Anal*. Calcd. for $C_{33}H_{27}N_3O_4$ (529.59): C, 74.84; H, 5.14; N, 7.93%. Found: C, 74.62; H, 5.34; N, 7.74%.

CRediT authorship contribution statement:

Conceptualization, B.R., O.A., E.A. and H.H.; methodology, O.A. E.A., B.R., and H.H.; software, O.A., E.A., B.R., and H.H.; validation, O.A., E.A., and B.R.; formal analysis, O.A., E.A., B.R., and H.H.; investigation, O.A., E.A., B.R. and H.H.; resources, O.A., E.A., B.R., and H.H.; data curation, H.H.; writing—original draft preparation, H.H.; writing—review and editing, O.A. E.A. and B.R.; supervision, O.A., E.A. and B.R.; project administration, B.R.; funding acquisition, H.H. All authors have read and agreed to the published version of the manuscript.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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