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FULL PAPER

Synthesis and characterization of some new pyrazolines and their inhibitory potencies against carbonic anhydrases

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Abstract

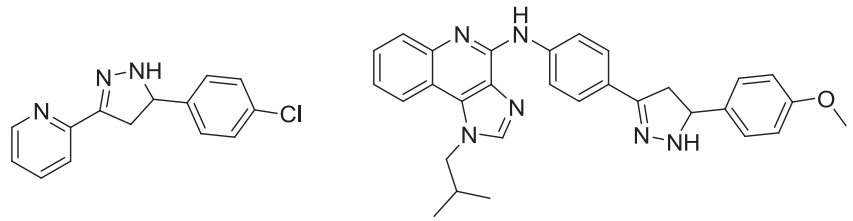
The inhibition of the two human cytosolic carbonic anhydrase (hCA; EC 4.2.1.1) isozymes I and II with some new pyrazoline derivatives was investigated for the first time. The structures of the newly synthesized pyrazoline derivatives were characterized by Fourier transform-infrared spectroscopy, ^{1}H-/^{13}C-nuclear magnetic resonance, and mass spectrometry, and elemental analysis. Compounds **1–6** showed K_i values in the range of 16.4–205.9 nM for hCA I and of 6.08–93.21 nM against hCA II. These hydroxyl and amino group-containing compounds generally were competitive inhibitors. The compounds investigated here showed effective hCA I and II inhibitory effects, in the same range as the clinically used acetazolamide, and might be used as leads for generating enzyme inhibitors, possibly targeting other CA isoforms that have not yet been assayed for their interactions with such agents.

KEYWORDS
carbonic anhydrase, chalcone, inhibitor, pyrazoline

1 | INTRODUCTION

Pyrazolines, which are one of the most studied groups of the azole family, consist of a five-membered aromatic system.[1] The wide variety of bioactivities of pyrazolines lead many researchers to synthesize new pyrazoline derivatives. Pyrazoline substituents are important target molecules for chemists because of their many potential applications, such as pharmaceuticals and the like.[1,2] Some pyrazoline derivatives have been shown to exhibit pharmacological effects such as antidepressant,[3] antibacterial,[4] antitumor,[5] and anti-inflammatory[6] activities. Furthermore, substituted pyrazolines have been reported to display multifarious pharmacological activities, including carbonic anhydrase (CA; EC 4.2.1.1) inhibitory activity.[7,8] In addition, some 1,3,5-trisubstituted-pyrazolines derivatives and polymethoxylated pyrazoline benzenesulfonamide derivatives have been used as CA inhibitors in some studies previously conducted by different research groups.[9,10] There is a considerable interest in the synthesis and characterization of pyrazoline compounds 2-[-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]pyridine (**I**) and 1-isobutyl-*N*-(4-(5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)phenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (**II**) were synthesized from chalcones (Figure 1). Compound **I** shows high antimicrobial and antioxidant activity. Moreover, compound **II** displays cytotoxicity toward HeLa cancer cell line.[11,12] The aim of this study is to synthesize and characterize some substituted pyrazoline molecules and to investigate the effects of synthesized pyrazolines on human CA I and II isoenzymes.

CAs (EC 4.2.1.1), which are essential metalloenzymes, are common to all organisms. These enzymes catalyze the reversible hydration of carbon dioxide to form bicarbonates with generation of protons.[13] The inhibitors of the two major cytosolic CA forms (hCA I and II) exhibit 60% sequence homology, several particular activities and several immunologic specificities.[14] Whereas CA I, which is the most abundant isozymes, has low enzyme activity, CA II (present in lower amounts) has high activity.[15] Both isoforms are used as drugs for the treatment of glaucoma and epilepsy for decades.[16] CA isozymes are involved in the pH homeostasis, ion transport, water and electrolyte balance, bone resorption, calcification, and tumorigenesis.[17] Over the last few years, pyrazoline and its derivatives have gained much interest because of their wide range of applications, especially in medicinal chemistry. Current research focuses on the synthesis of pyrazoline analogues. Thus, we have performed a facile synthesis of well-defined novel pyrazoline derivatives (**1–6**). We also investigated their inhibition potential toward hCA I and II isoenzymes.



I II

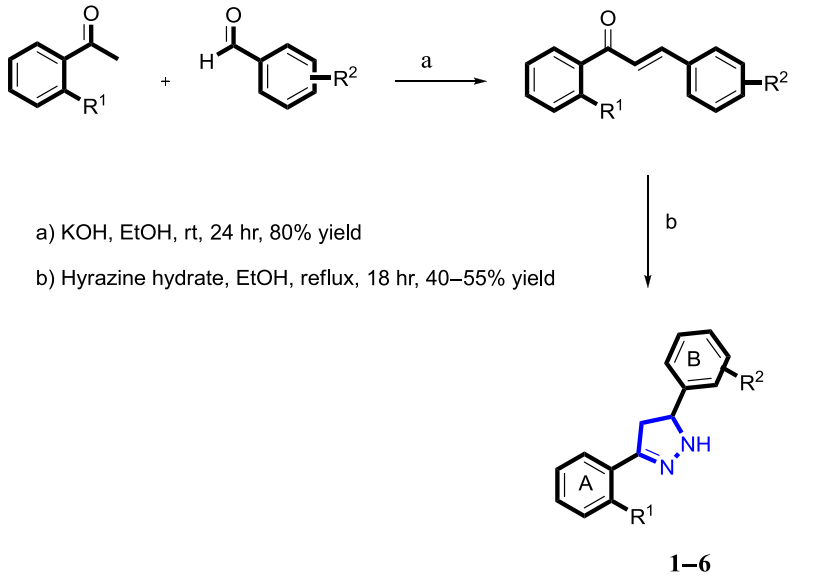
FIGURE 1 Examples of pyrazoline compounds with biological activity

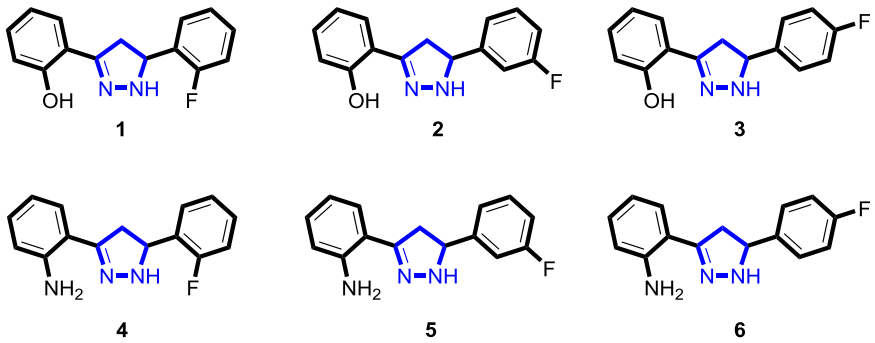
2 | RESULTS AND DISCUSSION

2.1 | Synthesis and characterization

The synthesis of 4,5-dihydro pyrazoline derivatives (**1–6**) followed the general pathway outlined in Scheme 1. They are prepared in two steps. First, the chalcones were obtained by direct Claisen–Schmidt condensation between aromatic aldehydes and the substituted acetophenone, using 20% potassium hydroxide/ethanol for 24 hr as stated in previous works.[18,19] The chalcones are considered to be useful intermediates in several cyclization reactions to produce different types of heterocyclic compounds of diverse biological importance. Second, for compounds **1**–**6**, cyclization of different chalcones with hydrazine hydrate under basic condition in refluxing ethanol leads to the formation of pyrazoline derivatives. At the end of the synthesis, the crude product was purified by recrystallization two times from EtOH/H_2O. Compounds **1** and **3** were reported in a previous study.[20] The synthesis of the compounds **2**, **4–6** is being reported for the first time in this study. The structures of synthesized compounds were confirmed by spectral methods (^{1}H-NMR [nuclear magnetic resonance],^{13}C-NMR, Fourier transform-infrared spectroscopy, mass spectroscopy, and elemental analysis). Both analytical and spectral data of all the synthesized compounds were in full agreement with the proposed structures. The detailed synthetic strategy is outlined in Scheme 1.

The formation of chalcones is observed in ^{1}H-NMR by the disappearance of the aldehydic proton signal and the appearance of AB spin systems due to the vinylic protons H-α and H-β. This





SCHEME 1 Synthetic route for the preparation of the pyrazoline derivatives **1–6**

anticipated spectral result was confirmed when compared to the known structures referenced in Sci Finder.[16–19] The IR spectra of the pyrazolines **1–6** revealed absorption bands in the regions 1,602–1,615 cm^{-1} corresponding to the C═N stretching bands because of ring closure. In addition, the absorption bands at 1,446–1,495 cm^{-1} were attributed to the (N–N) stretch vibrations, which also confirm the formation of the desired pyrazoline ring in all the compounds. The ^{1}H-NMR spectrum of pyrazolines **1–6** did not show the signals appearing as doublet for each of the alkenyl protons of chalcones, confirming the (3 + 2) annulations between chalcones and hydrazine hydrate to form the target compounds. The synthesized pyrazolines possessed characteristic peaks in the ^{1}H-NMR spectrum at 2.95–3.17 and 3.30–3.70 ppm, recorded as doublet of doublet (dd). These were assigned to the protons at the 4-position. Protons at the 5-position of pyrazoline rings are most likely to interact with 4-H protons, which was represented by a doublet of doublet signal peak at 4.74–5.38 ppm. The aromatic ring protons were observed at the expected chemical shifts and integral values. In the ^{13}C-NMR spectrum, the carbons of newly formed pyrazolines ring showed corresponding signals at δ 35.1, 77.2, and 147.3 ppm. The presence of carbon signals in this region confirms the formation of the pyrazoline ring. Aromatic carbons showed the signals in the region δ 112.2–164.2 ppm. All pyrazolines of the synthesized series **1–6** showed similar and consistent pattern signals in their respective spectra and showed satisfactory elemental analyses compared with theoretical values, which strongly favors the formation of the designed products. Additional support for the formation of the pyrazolines (**1–6**) was obtained by the appearance of molecular ion peak at corresponding *m/z* values, confirming their molecular masses.

2.2 | Biological evaluation of the synthesized and reference compounds for CA inhibitory activity

In this study, we obtained the effects of novel pyrazoline compound (**1–6**) derivatives against hCA I and hCA II, which were purified from human erythrocytes.[21] The inhibitory activity of the CA isoforms has pharmacologic applications in several fields, such as antiglaucoma, diuretics, antiobesity, anticonvulsant, and anticancer agents/diagnostic tools. Also, it can be used for designing anti-infective, that is, antibacterial, antifungal, and antiprotozoan agents with a new process of action.[22,23] For a long time, it has been considered that the pharmacologic effects of CA activation or inhibition are mostly due to effects on pH regulation in tissues or cells where the enzymes are present. We report the inhibition effects of these derivatives on the activity of hCA I, hCA II under in vitro conditions. The following results are presented in Table 1.

Abnormal levels of CA I enzyme in the blood are used as a marker for hemolytic anemia.[24] The slow cytosolic isoform hCA I was inhibited by the investigated novel pyrazoline compound (**1–6**) derivatives, with K_i values ranging between 16.4 and 205.9 nM. Furthermore, compounds **1–3** demonstrated the most powerful hCA I isoenzyme inhibition properties with K_i values of 16.4 and 26.5 nM. In addition, the molecules that had affinity against CA isoenzymes were known. The standard and clinically used drug acetazolamide (AZA) demonstrated a K_i value of 36,200 nM, respectively (Table 1). Thus, the investigated compounds showed better inhibitory profiles compared to AZA, a clinically used CA inhibitor. In addition, CA II is often associated with several diseases such as glaucoma, osteoporosis, and renal tubular acidosis. The hCA II was also efficiently inhibited by the novel pyrazoline compound (**1–6**) derivatives investigated here. These compounds appeared to strongly inhibit hCA II, with K_i values ranging from 6.08 to 93.21 nM. These values are better than those of the clinically used drug AZA (K_i = 370 nM). All the investigated novel pyrazoline compound (**1–6**) derivatives demonstrated marked inhibition against hCA II, but the compound **1** showed excellent inhibitions profile against cytosolic hCA II with a K_i value of 6.08 nM (Table 1). Considering the data of Table 1, the amino or hydroxyl substituents on phenyl ring A and nitrogen atoms of pyrazoline ring could easily be predicted to be involved in making hydrogen bonds with the active site, as observed in classical hCA I/II sulfonamide inhibitors (Scheme 1). It is clear from the results that all molecules were found to act as low-nanomolar hCA I–II inhibitors. According to the experimental findings, new pyrazoline compounds used in this study had better inhibition constants than the clinically used inhibitor AZA.

TABLE 1 Human carbonic anhydrases (hCA) I and II inhibition data for pyrazolines **1–6**

Compound No.	K_i (nM)[a]	
	hCA I	hCA II
1	26.5	6.08
2	20.0	33.42
3	16.4	93.21
4	66.4	49.51
5	205.9	44.59
6	81.5	35.57
Acetazolamide	36,200	370

[a]Mean from at least three determinations. Errors in the range of 3–8% of the reported value (data not shown).

In a recent study, it was reported that different pyrazoline derivatives, a simple compound lacking the sulfonamide, sulfamate, or related functional groups that are typically found in all known CA inhibitors, act as CA I and CA II inhibitors and could represent the starting point for a new class of inhibitors that may have advantages for patients with sulfonamide allergies.[13,14] However, it is critically important to explore further classes of potent CAIs to detect compounds with a different inhibition profile as compared to the sulfonamides and their bioisosteres and to find novel applications for the inhibitors of these widespread enzymes. CAIs possess an active Zn^{2+} ion region, which is coordinated by three histidine residues (His 94, His 96, and His 119) and H_2O molecule. The CAIs belong to four main classes and two of them (a) phenols (such as the simple phenol C_6H_5OH), which bind to the zinc-coordinated water molecule/

hydroxide ion from the active site, through a network of two hydrogen bonds (Figure 2a), (b) the polyamines, such as spermine, spermidine and congeners, which bind rather similarly but not identically to phenols, that is, by anchoring to the water molecule/hydroxide ion coordinated to Zn(II) (Figure 2b).[13,14] They are quite similar in these small groups of pyrazoline, phenolic, and aniline rings in new compounds, considering the structure of drugs used as reference for CAs. These rings could easily be predicted to be involved in making hydrogen bonds with the active site as observed in classical hCA I and II inhibitors.[13] These data suggested that these compounds showed hCA I and II inhibitory activity due to the presence of the pyrazoline, phenolic and aniline groups in compounds. The proposed mechanisms for enzymes inhibition are given in Figure 2.

3 | CONCLUSION

To summarize, design, synthesis, and characterization of some new pyrazolines containing hydroxyl, amine and fluorine functional groups were reported for the first time and their cytosolic CA forms (hCA I and II) inhibitions were examined. Most of the synthesized compounds showed against both hCA I and II inhibitory activity. Though pyrazoline derivative **3** demonstrated the most powerful hCA I isoenzyme inhibition properties with K_i values of 16.4 nM, pyrazoline **1** showed excellent inhibitions profile against cytosolic hCA II with K_i value of 6.08 nM. As a result of study, new pyrazoline analogues showed inhibition at the nanomolar levels against these enzymes. These results showed that newly synthesized pyrazolines have the potential for hCA I and II inhibition.

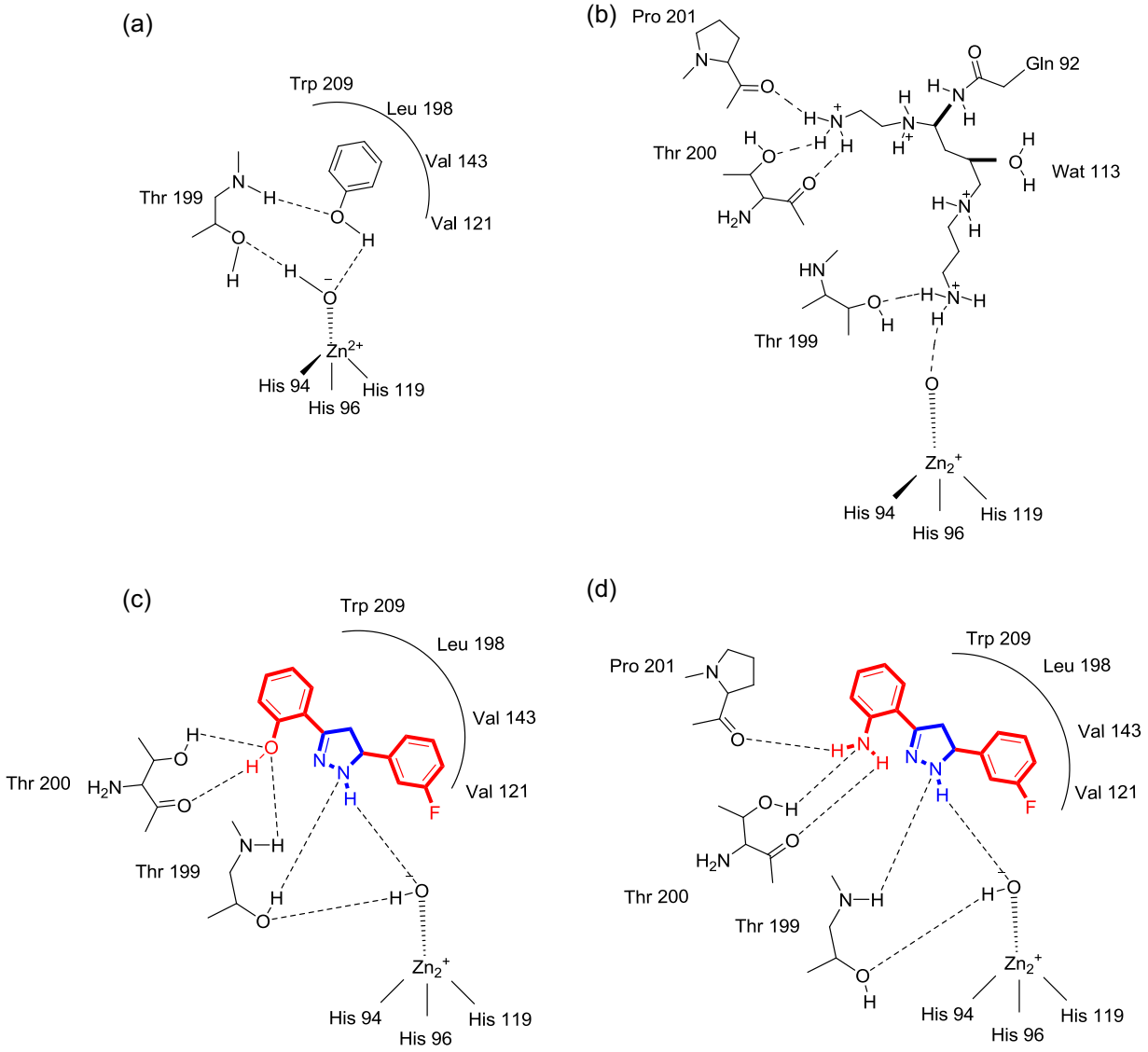


FIGURE 2 CA (carbonic anhydrases) inhibition with phenol (a) and spermine (b) compounds. (c, d) Proposed hCA I inhibition mechanism by pyrazolines **2** and **5**

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

All reagents and solvents were of reagent grade quality and were obtained from commercial suppliers. All solvents were dried and purified as described by Armarego and Perrin.[25] Sulfanilamide, Sepharose 4B, protein assay reagents, and 4-nitrophenylacetate were obtained from Sigma-Aldrich Co. All other chemicals were analytical grade and obtained from Merck. hCA I and II were purified from human erythrocytes according to the literature.[21]

The InChI codes of the investigated compounds are provided as Supporting Information.

4.1.2 | General methods for the synthesis of the pyrazoline derivatives 1–6

To a stirred solution of chalcone (1 mmol) in ethanol, hydrazine hydrate (80% aqueous solution, 10 mmol) was added. The mixture was then refluxed for 18 hr, monitored by thin-layer chromatography. Upon completion, the solution was cooled to room temperature. Water was added to the reaction mixture. The products were extracted from the one-third concentrated solution of reaction mixture using chloroform. The organic layer was then evaporated to yield the required crude 4,5-dihydro pyrazoline derivatives. Residues obtained were purified by column chromatography to afford pure 4,5-dihydropyrazoline derivatives.

*2-(5-(2-Fluorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol (**1**)*
Yield: 45%. m.p. 137–139°C. IR (ATR), ν cm^{-1}: 3,370 (–OH), 1,615 (C═N), 1,485 (N–N), and 1,222 (C–N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.03 (1H, dd, J = 14–16 Hz), 3.30 (1H, dd, J = 11–14 Hz), 5.38 (1H, t, J = 9.6 Hz), 6.85 (1H, d, J = 7.6 Hz), 6.91 (1H, d, J = 8 Hz), 7.06 (1H, t, J = 9.6 Hz), 7.18 (2H, t, J = 6.8 Hz), 7.28 (1H, m), 7.45 (1H, d, J = 7.6 Hz), and 7.63 (1H, t, J = 6.8 Hz). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 160.5 (d, J = 210), 158.2, 154.8, 131.4 (d, J = 13.6 Hz), 129.7, 129.0 (d, J = 8.3 Hz), 126.8 (d, J = 4.4 Hz), 126.4 (d, J = 2.3 Hz), 124.4 (d, J = 3.3 Hz), 119.4, 118.7, 117.0, 115.2 (d, J = 21.7 Hz), 67.0, and 34.1. Anal. calcd. for $C_{15}H_{13}FN_2O$: C, 70.30; H, 5.11; N, 10.93. Found: C, 70.32; H, 5.10; N, 10.90. MS (ESI, *m/z*) for $C_{15}H_{13}FN_2O$ [M+H_2O+H]$^+$: 275.1216.

*2-(5-(3-Fluorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol (**2**)*
Yield: 52%. m.p. 122–124°C. IR (ATR), ν cm^{-1}: 3,369 (–OH), 1,615 (C═N), 1,449 (N–N), and 1,286 (C–N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.01 (1H, dd, J = 14.4-3.2 Hz), 3.31 (1H, dd, J = 14.4–9.6 Hz), 5.03 (1H, t, J = 3.2–3.2 Hz), 6.83 (1H, d, J = 7.2 Hz), 6.88 (1H, d, J = 8 Hz), 6.97 (1H, m), 7.19 (1H, m), 7.23 (1H, m), and 7.29–7.36 (3H, m). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 164.2 (d, J = 244 Hz), 158.4, 154.1, 147.3 (d, J = 7 Hz), 130.1 (d, J = 8), 129.5, 126.2, 120.9 (d, J = 11.2 Hz), 119.4, 118.5, 116.9, 114.4 (d, J = 21 Hz), 112.2 (d, J = 22 Hz), 77.2 (d, J = 2 Hz), and 35.1. Anal. calcd. for $C_{15}H_{13}FN_2O$: C, 70.30; H, 5.11; N, 10.93. Found: C, 70.33; H, 5.10; N, 10.92. MS (ESI, *m/z*) for $C_{15}H_{13}FN_2O$ [M+H_2O]$^+$: 274.2769.

*2-(5-(2-Fluorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol (**3**)*
Yield: 50%. m.p. 135–137°C. IR (ATR), ν cm^{-1}: 3,370 (–OH), 1,602 (C═N), 1,446 (N–N), and 1,216 (C–N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.95 (1H, dd, J = 14.0–2.8 Hz), 3.28 (1H, m), 4.98 (1H, m), 6.80 (1H, m), 6.89 (1H, m), 7.02 (1H, m), 7.15 (1H, m), 7.24 (1H, m), and 7.40 (2H, m). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 163.5 (d, J = 244 Hz), 158.6, 154.4, 139.9 (d, J = 3.1 Hz), 129.8, 127.0 (d, J = 9 Hz), 126.1, 119.2, 118.5, 117.3, 115.6 (d, J = 21 Hz), 72.8 (d, J = 11 Hz), and 35.1. Anal. calcd. for $C_{15}H_{13}FN_2O$: C, 70.30; H, 5.11; N, 10.93. Found: C, 70.33; H, 5.10; N, 10.89. MS (ESI, *m/z*) for $C_{15}H_{13}FN_2O$ [M+H_2O]$^+$: 274.2761.

*2-(5-(2-Fluorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)aniline (**4**)*
Yield: 48%. Oil. IR (ATR), ν cm^{-1}: 3,317 and 3,299 NH_2, 1,607 (C═N), 1,486 (N–N), and 1,224 (C–N). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.17 (1H, dd, J = 16,0–9.4 Hz), 3.70 (1H, dd, J = 16.0–10.6 Hz), 5.14 (1H, t, J = 9.6 Hz), 5.90 (2H, –NH_2), 6.0 (1H, –NH), 6.75–6.66 (2H, m), 7.29–7.03 (5H, m), 7.51 (1H, t, J = 7.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 161.6 (d, J = 244 Hz), 154.0, 146.7, 129.4, 129.1 (d, J = 8.1 Hz), 128.9, 127.4 (d, J = 3.9 Hz), 124.5 (d, J = 3.4 Hz), 116.3, 115.6, 115.5 (d, J = 21.6 Hz), 114.8, 55.7 (d, J = 2.7 Hz), and 41.2. Anal. calcd. for $C_{15}H_{14}FN_3$: C, 70.57; H, 5.53; N, 16.46. Found: C, 70.55; H, 5.51; N, 16.42. MS (ESI, *m/z*) for $C_{15}H_{13}FN_2O$ [M+H_2O+H]$^+$: 274.2726.

*2-(5-(3-Fluorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)aniline (**5**)*
Yield: 55%. m.p. 73–75°C. IR (ATR), ν cm^{-1}: 3,346 and 3,308 NH_2, 1,607 (C═N), 1,449 (N–N), and 1,262 (C–N). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.14 (1H, dd, J = 16.0–9.4 Hz), 3.60 (1H, dd, J = 16.0–10.6 Hz), 4.77 (1H, t, J = 10 Hz), 5.81 (2H, –NH_2), 6.76–6.87 (2H, m), 6.97–7.17 (5H, m), and 7.30 (1H, t, J = 6.4). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.1 (d, J = 244 Hz), 153.3, 146.4, 145.1 (d, J = 6 Hz), 130.1 (d, J = 8 Hz), 129.2, 128.6, 121.9 (d, J = 3 Hz), 116.1, 115.4, 114.4, 114.4 (d, J = 19 Hz), 113.4 (d, J = 21 Hz), 61.9, and 42.5. Anal. calcd. for $C_{15}H_{14}FN_3$: C, 70.57; H, 5.53; N, 16.46. Found: C, 70.54; H, 5.51; N, 16.43. MS (ESI, *m/z*) for $C_{15}H_{13}FN_2O$ [M+H_2O+H]$^+$: 274.2732.

*2-(5-(4-Fluorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)aniline (**6**)*
Yield: 56%. m.p. 115–117°C. IR (ATR), ν cm^{-1}: 3,345 and 3,309 NH_2, 1,608 (C═N), 1,495 (N–N), and 1,228 (C–N). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.11 (1H, dd, J = 16,4–9.4 Hz), 3.56 (1H, dd, J = 16.0–10.6 Hz), 4.74 (1H, t, J = 9.8 Hz), 5.99 (2H, –NH_2), 6.70–6.79 (2H, m), and 7.05–7.40 (6H, m). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 164.1 (d, J = 243 Hz), 153.2, 146.3, 138.1 (d, J = 3.3 Hz), 129.0, 128.5, 128.1, 127.8 (d, J = 8 Hz), 115.9, 115.2 (d, J = 20 Hz), 114.3, 61.6, and 42.3. Anal. calcd. for $C_{15}H_{14}FN_3$: C, 70.57; H, 5.53; N, 16.46. Found: C, 70.55; H, 5.50; N, 16.43. MS (ESI, *m/z*) for $C_{15}H_{13}FN_2O$ [M+H_2O+H]$^+$: 274.2730.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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