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MONONUCLEAR HETEROCYCLIC REARRANGEMENT: SYNTHESIS OF [5:5] BICYCLIC [*c*]-FUSED 3-AMINOPYRAZOLES *via* THE *N-N* BOND FORMATION STRATEGY

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Abstract – The formation of [5:5] bicyclic heterocyclic ring systems containing [*c*]pyrazoles, *i.e.* imidazo[4,5-*c*]pyrazole, pyrazolo[3,4-*c*]pyrazole, pyrrolo-[2,3-*c*]pyrazole, and pyrazolo[3,4-*d*][1,2,3]triazole, was accomplished by mononuclear heterocyclic rearrangement (MHR). The core pyrazole ring was formed based on a *N-N* bond formation strategy. The ring transformation of 5-substituted 3-(2-aminoaryl)-1,2,4-oxadiazoles (**14**, **15a-b**, **16b** and **33**) under thermal conditions to the corresponding [5:5] bicyclic [*c*]-fused 3-aminopyrazole ring systems (**17a**, **18a-b**, **20** and **34** respectively) was promoted by sodium hydride in DMF or DMSO. The ring transformation by MHR has provided a practical and general synthetic method for the derivatives of 3-aminoimidazo-[4,5-*c*]pyrazole (**4**), 3-aminopyrazolo[3,4-*c*]pyrazole (**5**), 3-aminopyrrolo[2,3-*c*]-pyrazole (**6**) and 6-aminopyrazolo[3,4-*d*][1,2,3]triazole (**7**).

INTRODUCTION

Naturally occurring [6:5] bicyclic heterocycles, *i.e.* purines, indoles, benzimidazoles *et al*., and [6:6] bicyclic heterocycles, *i.e.* pteridines, quinazolines *et al.*, have received significant attention in the past half century because of their chemical and especially their biological properties.[1] A number of ring-structural analogs have also been discovered in nature or synthesized in various laboratories.[2] Many of these analogs have demonstrated interesting biological activities and stimulated interest in the preparation of other bicyclic heterocycles.[3-5] Most of the studies have involved modifications of the

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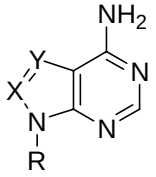
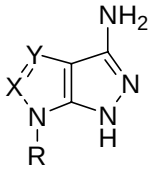
heterocyclic ring system by replacing ring carbon atoms with nitrogen atoms, or *vice versa*, to form the bicyclic ring analogs.[2,6,7]

In contrast to the [6:5] and [6:6] bicyclic heterocycles, the ring-contracted [5:5] bicyclic aromatic rings, with the same number of π-electrons, have significant differences in the distribution of ring electron densities as well as in spatial orientation. These properties could change the binding affinity of these compounds to the biological targets as well as alter their biological responses. The [5:5] azapentalene [*c*]pyrazole ring systems were of special interest to us because of their close structural resemblance to the [6:5] ring systems (**1**, **2** and **3**) and the inherent potential for biological activities.[8-12] Based on the chemical and biological interest in this series of heterocycles, we initiated studies to investigate feasible synthetic strategies to prepare the [5:5] bicyclic [*c*]-fused 3-aminopyrazole ring systems (**4**, **5**, **6** and **7**).

Figure 1 [6:5] bicyclic heterocycles and proposed [5:5] azapentalene [*c*]pyrazole ring systems



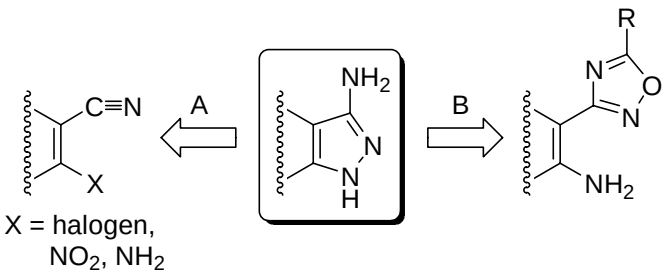
1 X = CH, Y = N
adenine
2 X = N, Y = CH
4-aminopyrazolo[3,4-*d*]pyrimidine
3 X = Y = CH
4-aminopyrrolo[2,3-*d*]pyrimidine



4 X = CH, Y = N
3-aminoimidazo[4,5-*c*]pyrazole
5 X = N, Y = CH
3-aminopyrazolo[3,4-*c*]pyrazole
6 X = Y = CH
3-aminopyrrolo[2,3-*c*]pyrazole
7 X = Y = N
6-aminopyrazolo[3,4-*d*][1,2,3]triazole

A literature survey showed a paucity of feasible routes for the synthesis of the [5:5] bicyclic [*c*]-fused 3-aminopyrazole ring systems.[13-18] Two general pathways may be amenable for the construction of the [*c*]-fused 3-aminopyrazole ring system from existing 5-membered heterocycles.[19,20] (**Scheme 1**)

Scheme 1 Synthetic Strategies for [*c*]-fused 3-aminopyrazoles



X = halogen, NO_2, NH_2

A. hydrazine annulation; B. *N-N* bond formation

The most straightforward approach involves a condensation of hydrazine with a heterocycle possessing a cyano group and an adjacent leaving group to afford the fused pyrazole rings. This approach has been widely utilized in the synthesis of fused pyrazoles from various aromatic rings (**A**).[21] However, its application toward the [5:5] bicyclic [*c*]-fused 3-aminopyrazole ring systems was rarely reported in the literature. Our preliminary studies resulted in no success with the hydrazine annulation methods. We then elected to study an alternative approach (**B**) based on the mononuclear heterocyclic rearrangement (MHR) (or Boulton-Katritzky rearrangement).[22] It has been reported that the [*c*]-fused 3-aminopyrazole ring can be prepared by the ring transformation of an aromatic ring bearing adjacent 5-substituted 1,2,4-oxadiazol-3-yl and amino groups.[18-20,23-26] This approach was initially used on π-electron deficient heterocyclic and carbocyclic aromatic ring systems to furnish the [*c*]-fused 3-aminopyrazoles. Korbonits *et al.* demonstrated that 5-amino-1-phenyl-4-(5-phenyl-1,2,4-oxadiazol-3-yl)pyrazole would undergo the MHR to give the bicyclic pyrazolo[3,4-*c*]pyrazole ring.[18] This was the only azapentalene congener which has been synthesized *via* the MHR of an appropriately substituted pyrazole derivative. We reasoned that the ring transformation, in this case, was facilitated by the electron withdrawing property of the phenyl groups. Therefore, the generality of this methodology has still remained unexploited. Our group has previously used this approach to synthesize 3-aminopyrazolo[3,4-*c*]pyrazole nucleosides as [5:5] bicyclic adenosine analogs.[17] Herein, we wish to report our studies which were designed to expand the application of this methodology for the preparation of a series of azapentalene derivatives including 3-amino-imidazo[4,5-*c*]pyrazole (**4**), 3-aminopyrazolo[3,4-*c*]pyrazole (**5**), 3-aminopyrrolo[2,3-*c*]pyrazole (**6**) and 6-aminopyrazolo[3,4-*d*][1,2,3]triazole (**7**).

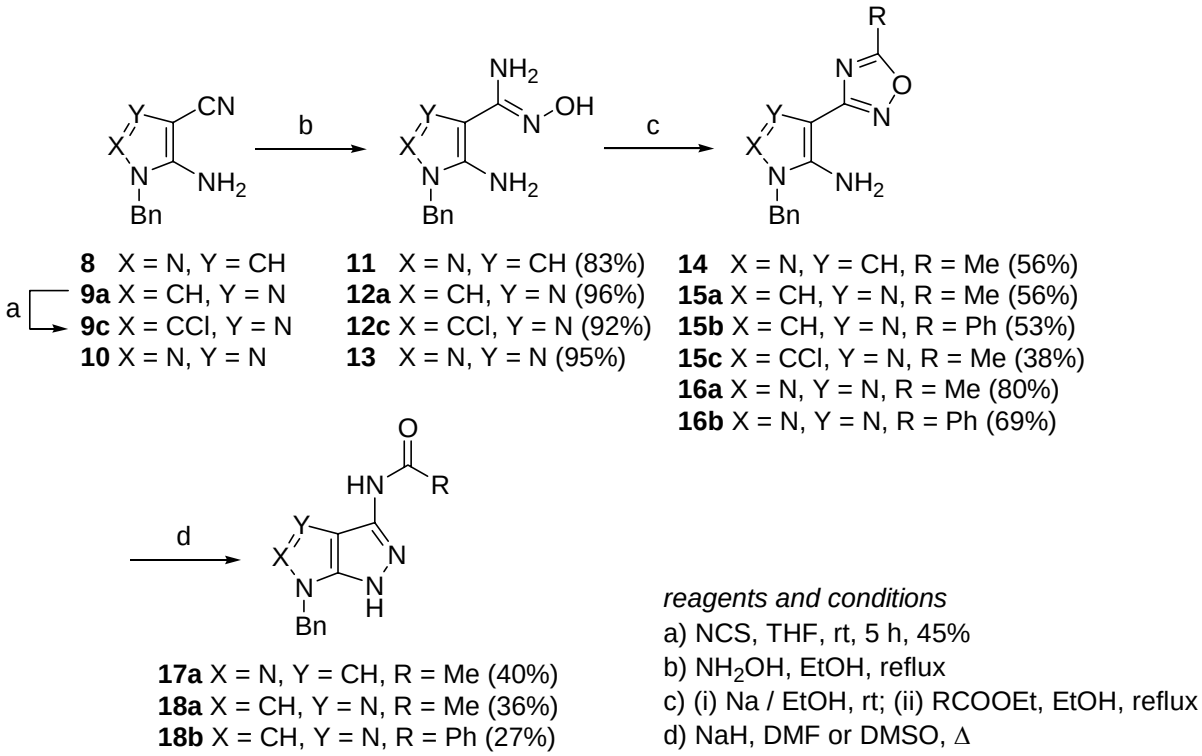
RESULTS AND DISCUSSION

The 5-substituted 3-(2-aminoaryl)-1,2,4-oxadiazole derivatives of 5-membered heterocycles were synthesized to explore and establish the reaction conditions. 1-Benzylated 5-membered heterocyclic 1,2-aminonitriles (**8**,[27] **9a**,[28,29] **9c**,[30] and **10**[31]) which were prepared by literature procedures, were selected for the initial investigation. Reactions of the 1,2-aminonitriles (**8**, **9a**, **9c** and **10**) with hydroxylamine in ethanol at reflux temperature gave the carboxamidoximes (**11**, **12a**, **12c** and **13**[32]) in excellent yields. Treatment of the carboxamidoximes (**11**, **12a**, **12c** and **13**) with ethyl acetate or ethyl benzoate in an ethanolic solution of sodium ethoxide at reflux temperature afforded the 3-(2-aminoaryl)-1,2,4-oxadiazoles (**14**, **15a-c**, and **16a-b**).

Several attempts to treat **14**, **15a-c**, and **16a-b** under the reported conditions[18,20,23,25] were unsuccessful in obtaining the desired [5:5] bicyclic products. These attempts included various reaction conditions such as different bases (KOH, NaOH, NaOEt), different solvents (MeOH, EtOH, DMF) and different reaction temperatures (75 ^{o}C, 100 ^{o}C, 150 ^{o}C). However, it was subsequently found that the rearrangement would

proceed with sodium hydride as a base.[17] The pyrazole derivative (**14**) was treated with sodium hydride in *N*,*N*-dimethylformamide at 100 ^{o}C to give the ring-transformed 3-acetamido-6-benzylpyrazolo[3,4-*c*]-pyrazole (**17a**) in 40% yield. A similar set of reaction conditions was then applied to the imidazole derivatives (**15a-c**). When **15a-c** was treated with sodium hydride in DMF, only **15a** underwent the rearrangement to give the desired 3-acetamido-6-benzylimidazo[4,5-*c*]pyrazole (**18a**) in 36% yield. It was of some interest that the chemical shifts for the methyl groups had significant upfield shifts in the ^{1}H NMR spectrum from 2.58 and 2.60 ppm for **14** and **15a** to 2.07 and 2.03 ppm for **17a** and **18a**, respectively. These shifts indicated that the exocyclic methyl groups of the 1,2,4-oxadiazoles were transformed to the corresponding acetyl groups. The amide NH resonances of **17a** and **18a** were also observed approximately at 11 – 12 ppm by ^{1}H NMR spectrum. The rearrangement of **15b** was facilitated by using sodium hydride in dimethyl sulfoxide at 120 ^{o}C and afforded 3-benzamido-6-benzylimidazo-[4,5-*c*]pyrazole (**18b**) in 27% yield. (**Scheme 2**)

Scheme 2

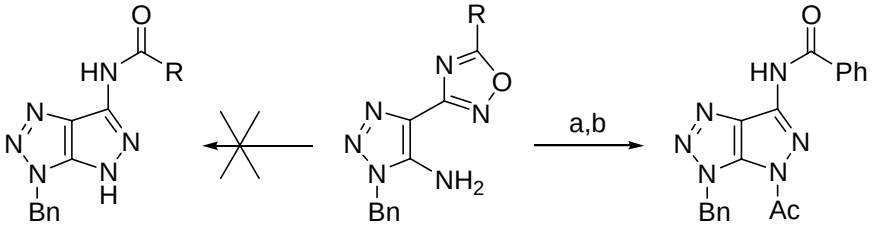


The triazole derivatives (**16a-b**) were also subjected to a wide variety of reaction conditions but did not form the desired rearranged products (**19a-b**). However, when the 5-amino group of **16b**[32] was first acetylated and then the compound was treated with sodium hydride in DMF, it did undergo the MHR to form 3-benzyl-4-acetyl-6-benzamidopyrazolo[3,4-*d*][1,2,3]triazole (**20**) in 42% yield. (**Scheme 3**)

Studies designed to explore the chemical behavior of azapentalene (**17a**) were also investigated. Compound (**17a**) was readily brominated with *N*-bromosuccinimide to give 3-acetamido-6-benzyl-4-

bromopyrazolo[3,4-*c*]pyrazole (**17b**) in 91% yield. Bromination occurred exclusively at the 4-position of the bicyclic heterocycle as determined by ^{1}H NMR spectrum. Debenzylation of **17a** was accomplished by dissolving metal reduction to give 3-acetamidopyrazolo[3,4-*c*]pyrazole (**22**).[14,33] The acetyl group in **22** was removed by acid hydrolysis to afford 3-aminopyrazolo[3,4-*c*]pyrazole hydrochloride (**23**).[14,33] (**Scheme 4**)

Scheme 3



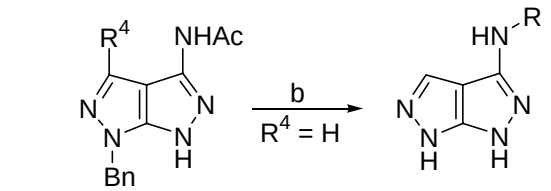
19a R = Me
19b R = Ph

16a R = Me
16b R = Ph

20

reagents and conditions
a) Ac_2O, *cat.* DMAP, pyridine, 100 ^oC, 7 h
b) NaH, DMF, 100 ^oC, 35 min, 42% from **16b**

Scheme 4



a → **17a** R^4 = H; **17b** R^4 = Br

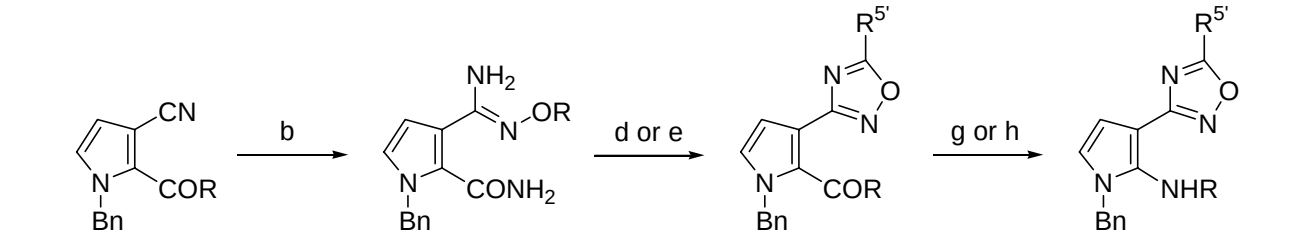
c → **22** R = Ac; **23** R = H (HCl salt)

reagents and conditions
a) NBS, THF, rt, 2 h, 91%
b) Na / NH_3, -50 ^oC - rt, 49%
c) 1N HCl, reflux, 2 h, 69%

Our initial approach for the synthesis of the bicyclic pyrrolo[2,3-*c*]pyrazole ring system was based on the successful synthesis of some pyrazolo[3,4-*c*]pyrazoles and imidazo[4,5-*c*]pyrazoles. However, the anticipated carboxamidoxime was not obtained when 2-amino-1-benzyl-3-cyanopyrrole[34] was treated with hydroxylamine. This result prompted us to look for a different route to prepare the 5-substituted 3-(2-aminopyrrol-3-yl)-1,2,4-oxadiazole derivatives. Instead of the 1,2-aminonitrile approach, ethyl 1-benzyl-3-cyanopyrrole-2-carboxylate[35] (**24**) was selected as the starting material. The carboxylate was first converted to the amide (**25**) with ammonia. Compound **25** was then reacted with hydroxylamine in ethanol to give 2-carboxamido-1-benzylpyrrole-3-carboxamidoxime (**26**) in 54% yield. Formation of the 1,2,4-oxadiazoles (**28a-b**) from **26** was accomplished by a base-promoted condensation with ethyl acetate, or acylated at the oxime oxygen by *p*-nitrobenzoyl chloride followed by an acid-catalyzed condensation. The amides were hydrolyzed by nitrosylsulfuric acid to give the corresponding carboxylic acids (**29a-b**).

Compound (**29a**) was treated with ethyl chloroformate in the presence of triethylamine followed by sodium azide to form the acyl azide *in situ*. The acyl azide underwent a Curtius rearrangement and was subsequently trapped with ethanol to afford the carbamate (**30a**) in 19% yield. An improved procedure was also developed. Compound (**29b**) was treated with diphenylphosphoryl azide followed by heating with methanol to give the carbamate (**30b**) in 46% yield. (**Scheme 5**)

Scheme 5



a → **24** R = OEt; **25** R = NH_2

c → **26** R = H; **27** R = *p*-$NO_2C_6H_4CO$

f → **28a** $R^{5'}$ = Me, R = NH_2 (90%); **29a** $R^{5'}$ = Me, R = OH (50%)

f → **28b** $R^{5'}$ = *p*-nitrophenyl, R = NH_2 (55%); **29b** $R^{5'}$ = *p*-nitrophenyl, R = OH (57%)

30a $R^{5'}$ = Me, R = CO_2Et (19%)

30b $R^{5'}$ = *p*-nitrophenyl, R = CO_2Me (46%)

reagents and conditions

a) NH_3, 100 ^oC, 4 days, 96%

b) NH_2OH, MeOH, reflux, 18 h, 93%

c) *p*-nitrobenzoyl chloride, Et_3N, THF, rt, 5 h, 54%

d) (i) Na / EtOH, rt; (ii) EtOAc, EtOH, reflux, 18 h, 90%

e) (i) *p*-nitrobenzoyl chloride, Et_3N, THF, rt, 5 h; (ii) AcOH, toluene, reflux, 16 h, 55% from **26**

f) nitrosylsulfuric acid, AcOH, rt

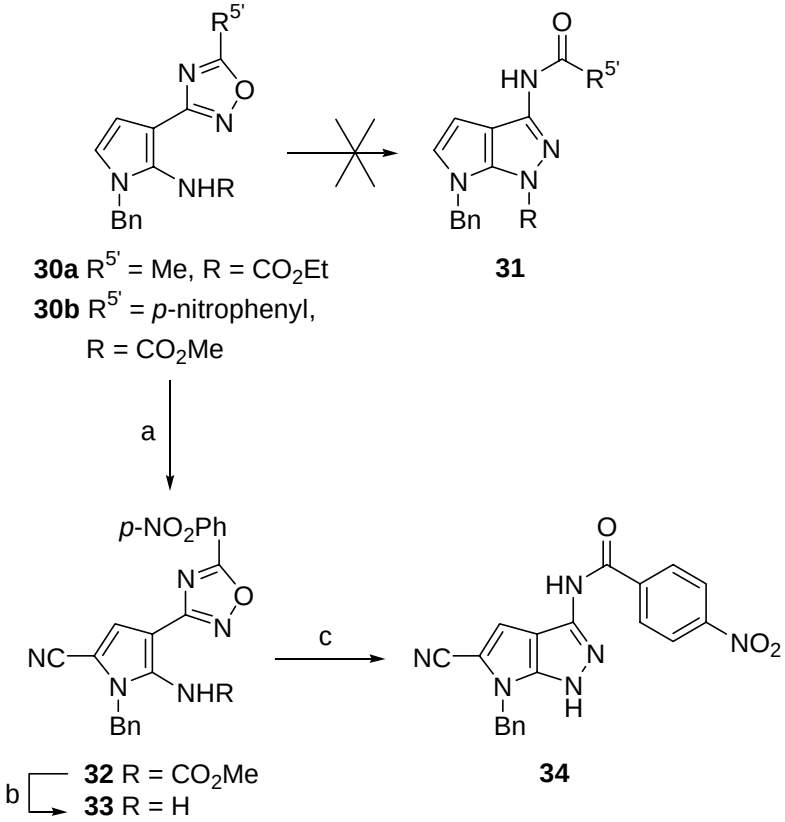
g) (i) ClCOOEt, Et_3N, DMF, rt, 2 h; (ii) NaN_3, 3 h, rt; (ii) EtOH, 85 ^oC, 2 h, 19% from **29a**

h) (i) diphenylphosphoryl azide, DMF, rt, 70 min; (ii) MeOH, 65 ^oC, 70 min, 46% from **29b**

Ring transformations of **30a-b** under various basic conditions were unsuccessful. It was noticeable that **30a-b** were completely consumed in the reaction when the compounds were heated with sodium hydride in DMF or DMSO. We interpreted that the ring transformations might occur but the highly electronegative rings may cause the decomposition of the unstable products. Therefore, a cyano group was introduced to the pyrrole ring in order to reduce the electron density and stabilize the [5:5] bicyclic ring. Compound (**30b**) was treated with chlorosulfonyl isocyanate followed by quenching with *N,N*-dimethylformamide to afford **32** in 66% yield. The position of the cyano group on the pyrrole ring was determined by extensive NMR spectroscopic studies including ^1H, ^{13}C, DEPT135, proton coupled ^{13}C, HETCOR, and COLOC NMR. A long-range coupling between the methylene protons of the benzyl group and C-5 on the pyrrole ring was observed while the proton-coupled ^{13}C NMR spectrum showed multiplet splitting at C-5 position due to the three-bond coupling. This long range coupling was also

confirmed by the 2D COLOC NMR spectroscopy. (**Table 1**) Attempts to catalyze the ring transformation of **32** to the [5:5] bicyclic ring also failed. While exploring possible conditions for the rearrangement, it was found that treatment of **32** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in anisole at reflux resulted in a clean removal of the methoxycarbonyl group to afford **33**. Compound (**33**) was then subjected to sodium hydride in DMSO at 125 ^{o}C to give the desired product (**34**) in 29%. (**Scheme 6**)

Scheme 6



reagents and conditions

a) (i) chlorosulfonyl isocyanate, MeCN, 0 ^{o}C - rt, 16 h;
(ii) 1 eq. DMF, MeCN, reflux, 2 h, 66% from **30b**

b) DBU, anisole, reflux, 1.5 h, 70%

c) NaH, DMSO, 15 min, 29%

CONCLUSION

This investigation has successfully extended the use of the mononuclear heterocyclic rearrangement to the [5:5] bicyclic [*c*]-fused pyrazole ring systems which were not achievable by the widely used hydrazine annulation approach. Our success has established a viable route toward several derivatives of the [5:5] bicyclic [*c*]-fused 3-aminopyrazole ring systems. Our efforts, thus far, in the removal of the acyl groups from the ring-transformed products (**17a**, **18a-b**, **20** and **34**) have been unsuccessful. We have attributed

this to the fact that these [5:5] bicyclic [*c*]-fused 3-aminopyrazole derivatives are relatively unstable due to the highly π-electron excess properties on the ring atoms. In certain examples, such as **20** and **34**, the heterocycles required some stabilization by extra electron-withdrawing substituents.

Table 1 ^{13}C NMR Spectral Assignments for **30b**, **32**, and **33**

Assignment		**30b**	**32**	**33**
Pyrrole[b,c]	2-	128.0	132.8	145.9
	3-	105.0	106.8	90.3
	4-	107.5[a]	119.7[a]	120.1[a]
	5-	120.9[a]	102.7	97.4
Benzyl	CH_2[a]	49.4	49.1	47.6
	1-[b,d]	138.4	136.5	137.2
	2-[a,b]	128.3	127.9	127.5
	3-[a,b]	129.3	129.6	129.6
	4-[a]	128.3	128.8	128.5
CN[d]		-----	113.5	115.5
Methoxycarbonyl	C=O[d]	156.6	156.0	-----
	MeO[a]	53.0	53.4	-----
p-Nitrophenyl	1-[d]	129.8	129.4	129.6
	2-,3-[d]	130.0, 125.5	130.1, 125.6	130.4, 125.4
	4-[d]	150.7	150.8	150.8
1,2,4-Oxadiazole	3-,5-[d]	166.0, 173.1	164.6, 173.8	165.4, 173.1

The peak was assigned by: [a)]DEPT135 NMR and 2D HETCOR NMR; [b)]Proton-coupled ^{13}C NMR; [c)]2D COLOC NMR; [d)]Empirical and/or Calculation

EXPERIMENTAL

General chemical procedures. Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. NMR spectra were obtained by Bruker WP270SY, DPX300, or DRX500 instruments. The chemical shift values are reported in δ values (parts per million, ppm) relative to the standard chemical shift of tetramethylsilane (TMS). The coupling constant values are expressed in Hertz (Hz). UV spectra were recorded on a Hewlett-Packard model 8450A UV/VIS spectrophotometer. IR spectra were recorded on a Nicolet 5DXB FT-IR spectrophotometer. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, or by the Analytical Laboratory, Department of Chemistry, University of Michigan, MI. MS spectrometry was performed by the Analytical Laboratory, Department of Chemistry, University of Michigan, MI. TLC was performed on silica gel GHLF-254 plates (Merck Reagents). Compounds on TLC were visualized by illumination under UV light (254 nm), or dipped into 10% methanolic sulfuric acid followed by charring on a hot plate. Solvent systems are expressed as a percentage of the more polar component with respect to total volume (v/v%). E. Merck silica gel (230 - 400 mesh) was used for flash column chromatography and this technique has been described by Still *et al.*[36] The reported yields have not been optimized. Evaporations

were carried out under reduced pressure (water aspirator) with the bath temperature below 50 °C unless specified otherwise. Materials obtained from commercial suppliers were used without further purification.

5-Amino-1-benzylpyrazole-4-carboxamidoxime (11)

A solution of 5-amino-1-benzylpyrazole-4-carbonitrile[27] (**8**, 31.7 g, 0.16 mol) and hydroxylamine[37] (8.3 g, 0.25 mol) in ethanol (650 mL) was heated at reflux temperature under nitrogen for 4.5 h. The mixture was concentrated under reduced pressure to give the crude product. This material was recrystallized from acetonitrile to give **11** (30.6 g, 0.13 mol, 83%). mp 134 – 137 °C; IR (KBr, cm^{-1}) 3480 – 3000, 1637, 1602, 1574; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 8.90 (s, 1 H, OH), 7.58 (s, 1 H, 3-H), 7.38 - 7.22 (m, 3 H, Ph), 7.20 – 7.10 (m, 2 H, Ph), 5.95 (br s, 2 H, NH_2), 5.60 (br s, 2 H, NH_2), 5.13 (s, 2 H, CH_2); UV λ_{max} nm (ε) (MeOH): 248 (9270). Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 56.93; H, 5.63; N, 30.25.

5-Amino-1-benzylimidazole-4-carboxamidoxime (12a)

Compound (**12a**) (12.58 g, 54.41 mmol, 89%) was prepared from 5-amino-1-benzylimidazole-4-carbonitrile[28,29] (**9a**, 12.14 g, 61.25 mmol) using 50%*wt* aqueous hydroxylamine solution (5.6 mL, containing 3.04 g of hydroxylamine (91.88 mmol)) and ethanol (300 mL) by the method described for **11**, and purified by recrystallization. mp 184 – 189 °C (decomp) (EtOH / H_2O) [*lit.*,[38] 193 – 201 °C (decomp)]; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.88 (s, 1 H, OH), 7.38 – 7.19 (m, 5 H, Ph), 7.22 (s, 1 H, 2-H), 5.37 (br s, 2 H, NH_2), 5.31 (br s, 2 H, NH_2), 5.07 (s, 2 H, CH_2). Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 56.98; H, 5.73; N, 30.66.

5-Amino-1-benzyl-2-chloroimidazole-4-carboxamidoxime (12c)

Compound (**12c**) (5.54 g, 20.85 mmol, 92%) was prepared from 5-amino-1-benzyl-2-chloroimidazole-4-carbonitrile[30] (**9c**, 5.25 g, 22.56 mmol) using 50%*wt* aqueous hydroxylamine solution (2.3 mL, containing 1.24 g of hydroxylamine (37.5 mmol)) and ethanol (175 mL) by the method described for **11**, and purified by recrystallization. mp 145 °C (decomp) (EtOH); IR (KBr, cm^{-1}) 3493, 3458 - 1946, 1637, 1616, 1574; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 8.95 (s, 1 H, OH), 7.40 – 7.10 (m, 5 H, Ph), 5.60 (br s, 2 H, NH_2), 5.35 (br s, 2 H, NH_2), 5.10 (s, 2 H, CH_2); UV λ_{max} nm (ε) (MeOH): 263 (11200). Anal. Calcd for $C_{11}H_{12}N_5OCl$: C, 49.72; H, 4.55; N, 26.36. Found: C, 49.56; H, 4.50; N, 26.12.

5-Amino-1-benzyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)pyrazole (14)

Compound (**11**) (9.50 g, 41.1 mmol) was added to an ethanolic solution of sodium ethoxide (9.50 g of sodium (413.2 mmol) in 300 mL ethanol) followed by the addition of EtOAc (10.1 mL, 9.09 g, 103.2

mmol). The mixture was heated at reflux temperature under nitrogen for 2 h. After the reaction mixture was cooled to rt, the solution was neutralized with acetic acid, and then concentrated under reduced pressure. The resulting residue was partitioned between $CHCl_3$ and H_2O. The organic partition was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure to give the crude product. This material was recrystallized in acetonitrile to give **14** (5.90 g, 23.1 mmol, 56%). mp 146 – 148 ^oC; IR (KBr, cm^{-1}) 3480, 3222, 1630, 1600, 1560; ^1H NMR (DMSO-d_6, 270 MHz) δ 7.59 (s, 1 H, 3-H), 7.32 - 7.24 (m, 3 H, Ph), 7.17 – 7.15 (m, 2 H, Ph), 6.11 (br s, 2 H, NH_2), 5.22 (s, 2 H, CH_2), 2.58 (s, 3 H, CH_3); UV λ_{max} nm (ε) (MeOH): 264 (6535). Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.16; H, 5.13; N, 27.43. Found: C, 61.19; H, 5.04; N, 27.80.

5-Amino-1-benzyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)imidazole (15a)

Compound (**15a**) (7.79 g, 30.5 mmol, 56%) was prepared from **12a** (12.58 g, 54.41 mmol) using sodium ethoxide (3.13 g of sodium (136.02 mmol) in 500 mL of ethanol) and then EtOAc (81 mL, 71.9 g, 816 mmol) by the method described for **14**, and purified by recrystallization from ethanol. mp 198 – 200 ^oC; IR (KBr, cm^{-1}) 3416, 3282, 1630, 1595; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.42 – 7.35 (m, 3 H, Ph), 7.30 (s, 1 H, 2-H), 7.21 – 7.19 (m, 2 H, Ph), 5.07 (s, 2 H, CH_2), 4.36 (br s, 2 H, NH_2), 2.60 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.7, 165.2, 139.7, 135.2, 133.2 (CH), 129.7 (CH), 128.9 (CH), 127.2 (CH), 110.9, 48.1 (CH_2), 12.6 (CH_3); UV λ_{max} nm (ε) (MeOH): 280 (9530). MS (CI, NH_3) *m/z* 91 (100), 256 (75) (M + 1); HRMS (CI) Calcd for $C_{13}H_{14}N_5O$ (M + 1): 256.1198. Found: 256.1199. Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.16; H, 5.13; N, 27.43. Found: C, 61.07; H, 5.38; N, 27.50.

5-Amino-1-benzyl-4-(5-phenyl-1,2,4-oxadiazol-3-yl)imidazole (15b)

Compound (**15b**) (7.25 g, 22.9 mmol, 53%) was prepared from **12a** (10.0 g, 43.24 mmol) using sodium ethoxide (2.5 g of sodium (108.7 mmol) in 225 mL of ethanol) and then ethyl benzoate (15.0 mL, 15.7 g, 104.4 mmol) by the method described for **14**, and purified by recrystallization from ethanol. mp 205 – 240 ^oC (decomp); IR (KBr, cm^{-1}) 3420, 3280, 1630, 1600, 1545; ^1H NMR (DMSO-d_6, 270 MHz) δ 8.20 (m, 2 H), 7.80 – 7.60 (m, 2 H), 7.40 – 7.20 (m, 7 H), 5.87 (br s, 2 H, NH_2), 5.2 (s, 2 H, CH_2); UV λ_{max} nm (ε) (MeOH): 266 (31450). Anal. Calcd for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07. Found: C, 68.05; H, 4.81; N, 21.97.

5-Amino-1-benzyl-2-chloro-4-(5-methyl-1,2,4-oxadiazol-3-yl)imidazole (15c)

Compound **15c** (830 mg, 2.86 mmol, 38%) was prepared from **12c** (2.0 g, 7.53 mmol) using sodium ethoxide (0.50 g of sodium (21.7 mmol) in 150 mL of ethanol) and then EtOAc (40.0 mL, 36.0 g, 408.6 mmol) by the method described for **14**, and purified by recrystallization from methanol. mp 184 – 187 ^oC;

IR (KBr, cm^{-1}) 3423, 3310, 1616, 1567, 1553, 1454; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 7.40 – 7.10 (m, 5 H, Ph), 6.00 (br s, 2 H, NH_2), 5.20 (s, 2 H, CH_2), 2.57 (s, 3 H, CH_3); UV λ_{max} nm (ε) (MeOH): 247 (8540), 281 (10200). Anal. Calcd for $C_{13}H_{12}N_5OCl$: C, 53.89; H, 4.17; N, 24.17. Found: C, 54.03; H, 4.26; N, 24.05.

5-Amino-1-benzyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)-1,2,3-triazole (16a)

Compound (**16a**) (17.6 g, 68.7 mmol, 80%) was prepared from 5-amino-1-benzyl-1,2,3-triazole-4-carboxamidoxime[32] (**13**, 20.0 g, 86.1 mmol) using sodium ethoxide (20 g of sodium (0.87 mol) in 600 mL ethanol) and then EtOAc (25 mL, 22.6 g, 0.256 mmol) by the method described for **14**, and purified by recrystallization from ethanol and H_2O. mp 236 - 239 ^{o}C; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 7.39 - 7.30 (m, 3 H, Ph), 7.25 – 7.22 (m, 2 H, Ph), 6.37 (br s, 2 H, NH_2), 5.49 (s, 2 H, CH_2), 2.64 (s, 3 H, CH_3). MS (EI, 70 eV) *m/z* 91 (43), 137 (43), 185 (47), 227 (44), 256 (100) (M^+); HRMS (EI) Calcd for $C_{12}H_{12}N_6O$ (M): 256.1073. Found: 256.1075.

3-Acetamido-6-benzylpyrazolo[3,4-*c*]pyrazole (17a)

Compound (**14**) (5.0 g, 19.6 mmol) was added to a mixture of sodium hydride (50% in mineral oil, 2.0 g, 41.7 mmol) in *N*,*N*-dimethylformamide (100 mL). The mixture was heated at 100 ^{o}C under nitrogen for 45 min. The mixture was then cooled (ice bath) and concentrated *in vacuo*. The resulting residue was dissolved in water (50 mL) and neutralized with acetic acid. The precipitate was collected by filtration. This material was recrystallized from ethanol to give **17a** (2.0 g, 7.8 mmol, 40%). mp 212 – 215 ^{o}C; IR (KBr, cm^{-1}) 3320, 1705, 1550, 1485; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 11.44 (br s, 1 H, NH), 11.39 (br s, 1 H, NH), 7.32 - 7.19 (m, 5 H, Ph), 7.15 (s, 1 H, 4-H), 5.29 (s, 2 H, CH_2), 2.07 (s, 3 H, CH_3); UV λ_{max} nm (ε) (MeOH): 264 (16720). Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.16; H, 5.13; N, 27.43. Found: C, 61.06; H, 5.12; N, 27.28.

3-Acetamido-6-benzyl-4-bromopyrazolo[3,4-*c*]pyrazole (17b)

To a solution of **17a** (0.25 g, 1.0 mmol) in tetrahydrofuran (20 mL) was added *N*-bromosuccinimide (220 mg, 1.2 mmol) and the mixture was stirred at rt for 2 h. The solution was concentrated under reduced pressure and the resulting residue was purified by column chromatography (EtOAc) to give **17b** (303 mg, 0.91 mmol, 91%). mp 240 – 243 ^{o}C (EtOAc); IR (KBr, cm^{-1}) 3311, 3057, 2755, 1764, 1694, 1574, 1518; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 11.92 (br s, 1 H, NH), 11.45 (br s, 1 H, NH), 7.34 - 7.21 (m, 5 H, Ph), 5.27 (s, 2 H, CH_2), 2.08 (s, 3 H, CH_3); Anal. Calcd for $C_{13}H_{12}N_5OBr$: C, 46.72; H, 3.62; N, 20.96. Found: C, 46.80; H, 3.64; N, 20.76.

3-Acetamido-6-benzylimidazo[4,5-*c*]pyrazole (18a)

Sodium hydride (60% in mineral oil, 0.16 g, 4 mmol) was placed in a 100 mL round bottom flask equipped with a rubber septum and an inert gas (argon) inlet. *N*,*N*-Dimethylformamide (20 mL) was added and the mixture was stirred at rt. The suspension mixture was heated in a 75 ^{o}C oil bath and **15a** (0.511 g, 2 mmol) was added to the mixture. The reaction temperature was gradually raised to 100 ^{o}C in 15 min. The reaction was then cooled to rt and neutralized with acetic acid (0.12 mL, 0.12 g, 2 mmol). The solvent was evaporated *in vacuo*. The residue was partitioned between $CHCl_3$ (150 mL) and H_2O (50 mL). The aqueous layer was further extracted with $CHCl_3$ (2 x 150 mL). The organic partitions were washed with saturated aqueous NaCl solution, combined, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The crude product was recrystallized in ethanol to give **18a** (0.183 g, 0.72 mmol, 36%). mp 207 - 210 ^{o}C (decomp); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.70 (br s, 1 H, NH), 11.09 (br s, 1 H, NH), 7.52 (s, 1 H, 5-H), 7.35 – 7.27 (m, 5 H, Ph), 5.24 (s, 2 H, CH_2), 2.03 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 168.8, 141.5, 137.8, 134.8 (CH), 134.1, 133.4, 129.0 (CH), 128.1 (CH), 128.0 (CH), 48.8 (CH_2), 23.3 (CH_3); MS (CI, NH_3) *m/z* 91 (33), 256 (100) (M + 1); UV λ_{max} nm (ε) (MeOH): 202 (21383), 272 (14566), 279 (14489). HRMS (CI) Calcd for $C_{13}H_{14}N_5O$ (M + 1): 256.1198. Found: 256.1206. Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.16; H, 5.13; N, 27.43. Found: C, 61.08; H, 5.17; N, 27.38.

3-Benzamido-6-benzylimidazo[4,5-*c*]pyrazole (18b)

Sodium hydride (50% in mineral oil, 480 mg, 10.0 mmol) was added to dimethyl sulfoxide (50 mL) and the mixture was heated at 75 ^{o}C until a cessation of hydrogen gas evolution. Compound **15b** (1.50 g, 4.73 mmol) was added and the mixture was heated at 100 ^{o}C under argon for 15 min. The solvent was removed by distillation and the resulting residue was added to ice / water. The precipitated solid was collected by filtration. This material was purified by column chromatography (acetone) to give **18b** (410 mg, 1.29 mmol, 27%). mp 200 – 240 ^{o}C (decomp) (acetone); IR (KBr, cm^{-1}) 3557 – 2579, 3275, 1672, 1602, 1574; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 12.02 (br s, 1 H, NH), 11.45 (br s, 1 H, NH), 8.00 (m, 2 H), 7.60 – 7.40 (m, 4 H), 7.30 – 7.20 (m, 5 H), 5.25 (s, 2 H, CH_2); UV λ_{max} nm (ε) (MeOH): 228 (15250), 307 (13410); MS (EI) *m/z* 212, 317 (M^+); Anal. Calcd for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07. Found: C, 68.08; H, 5.01; N, 22.15.

3-Benzyl-4-acetyl-6-benzamidopyrazolo[3,4-*d*][1,2,3]triazole (20)

To a mixture of 5-amino-1-benzyl-4-(5-phenyl-1,2,4-oxadiazol-3-yl)-1,2,3-triazole[32] (**16b**, 0.50 g, 1.57 mmol) and *N*,*N*-dimethylaminopyridine (19.2 mg, 0.157 mmol) in pyridine (20 mL) was added acetic anhydride (0.30 mL, 0.321 g, 3.14 mmol). The reaction mixture was heated at 100 ^{o}C for 7 h. The solvent

was evaporated under reduced pressure. The residue was dissolved in EtOAc and the solution was washed with H_2O, saturated aqueous NaCl solution, and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude product of 5-acetamido-1-benzyl-4-(5-phenyl-1,2,4-oxadiazol-3-yl)-1,2,3-triazole that was used without further purification. This compound was added to a mixture of sodium hydride (50% in mineral oil, 0.10 g, 2.08 mmol) in *N*,*N*-dimethylformamide (5 mL). The mixture was heated at 100 ^oC under nitrogen for 35 min. The mixture was then cooled (ice bath), neutralized with acetic acid, and then poured onto ice. The resulting precipitate was collected by filtration. This material was recrystallized from methanol to give **20** (0.24 g, 0.67 mmol, 42% from **16b**). mp 192 - 196 ^oC; ^1H NMR (DMSO-d_6, 270 MHz) δ 10.50 (br s, 1 H, NH), 8.20 (m, 2 H, Ph), 7.80 - 7.60 (m, 3 H, Ph), 7.40 – 7.20 (m, 5 H, Ph), 5.55 (s, 2 H, CH_2), 2.10 (s, 3 H, CH_3). Anal. Calcd for $C_{19}H_{16}N_6O_2$: C, 63.32; H, 4.48; N, 23.32. Found: C, 63.02; H, 4.46; N, 23.11.

3-Acetamidopyrazolo[3,4-*c*]pyrazole (22)

To a solution of **17a** (2.0 g, 7.83 mmol) in liquid ammonia (125 mL) at –50 ^oC was added sodium portionwise with vigorous stirring until a blue color persisted. Ammonia was allowed to evaporate and the resulting residue was placed under vacuum to remove a trace amount of ammonia. Methanol (100 mL) was added and the solution was neutralized with acetic acid. The precipitate was collected, washed with water, methanol and ether, and then dried *in vacuo* to give **22** (640 mg, 3.88 mmol, 49%). The compound was recrystallized from 75% aqueous ethanol to give the analytical sample of **22** (100 mg, 0.61 mmol, 8%). mp 297 - 300 ^oC (decomp); IR (KBr, cm^{-1}) 3663 - 2389, 3360, 2938, 1686, 1602, 1525; ^1H NMR (DMSO-d_6, 270 MHz) δ 12.40 - 11.00 (br s, 3 H, 3 x NH), 7.30 (s, 1 H, 4-H), 2.14 (s, 3 H, CH_3); MS (EI) *m/z* 165 (65), 123 (100) ($M^+ - CH_3CO$); Anal. Calcd for $C_6H_7N_5O \cdot 0.25\ H_2O$: C, 42.48; H, 4.46; N, 41.28. Found: C, 42.45; H, 4.23; N, 40.89.

3-Aminopyrazolo[3,4-*c*]pyrazole hydrochloride (23)

A solution of **22** (473 mg, 2.9 mmol) in 1 N HCl (25 mL) was heated at reflux temperature for 2 h. The solution was concentrated under reduced pressure and the residue was coevaporated with ethanol. The crude product was recrystallized from ethanol, washed with ether, and then dried *in vacuo* at 100 ^oC overnight to give **23** (323 mg, 2 mmol, 69%). mp 282 – 285 ^oC (decomp); ^1H NMR (DMSO-d_6, 270 MHz) δ 13.65 (br s, 1 H, NH), 12.00 (br s, 1 H, NH), 8.35 (br s, 2 H, NH_2), 7.58 (d, 1 H, 4-H); ^{13}C NMR (DMSO-d_6, 68 MHz) δ 154.9, 146.0, 114.8, 110.5 (4-CH); MS (El): *m/z* 43 (100), 123 (84) (M^+); Anal. Calcd for $C_4H_5N_5 \cdot HCl$: C, 30.11; H, 3.79; N, 43.89. Found: C, 30.17; H, 3.73; N, 43.73.

1-Benzyl-3-cyanopyrrole-2-carboxamide (25)

To ethyl 1-benzyl-3-cyanopyrrole-2-carboxylate[35] (**24**, 20.0 g, 78.7 mmol) in a high-pressure vessel was added liquid ammonia (300 mL). The vessel was sealed and heated at 100 ^{o}C for 4 days. The pressure vessel was allowed to cool to rt with venting to release the ammonia. The solid residue was suspended in ether and the solid was collected by filtration to give **25** (17.0 g, 75.5 mmol, 96%). mp 141 – 145 ^{o}C (EtOAc); IR (KBr, cm^{-1}) 3400, 3300, 3250, 3200, 2224, 1665, 1610, 1480; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 8.00 - 7.70 (d, 2 H, NH_2), 7.40 - 7.15 (m, 6 H), 6.56 (d, 1 H), 5.45 (s, 2 H, CH_2); UV λ_{max} nm (ε) (MeOH): 244 (7020), 265 (6820). Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.29; H, 4.83; N, 18.79.

1-Benzyl-2-carboxamidopyrrole-3-carboxamidoxime (26)

Compound **25** (45.0 g, 200 mmol) was added to a solution of sodium methoxide (54.0 g, 1.0 mol) in methanol (1 L) and the solution was stirred for 30 min. Hydroxylamine sulfate (82.8 g. 0.50 mol) was added to the solution portionwise with stirring and then the mixture was heated at reflux temperature under argon for 18 h. The solids were removed by filtration and the filtrate was concentrated under reduced pressure to approx. 250 mL. This solution was poured onto ice (500 g) with stirring and the pH was adjusted to 6 with acetic acid. The mixture was stirred for 30 min, and the precipitate formed was collected by filtration, washed with cold water and dried to give **26** (48.0 g, 186 mmol, 93%). mp 144 – 147 ^{o}C (H_2O); IR (KBr, cm^{-1}) 3528 - 2657, 3458, 1651, 1588, 1496; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 9.55 (s, 1 H, OH), 9.50 (br s, 2 H, NH_2), 7.40 – 7.10 (m, 6 H), 6.38 (d, 1 H), 5.90 (br s, 2 H, NH_2), 5.62 (s, 2 H, CH_2); UV λ_{max} nm (ε) (MeOH): 267 (7230); Anal. Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.69. Found: C, 60.27; H, 5.32; N, 21.70.

1-Benzyl-3-(5-methyl-1,2,4-oxadiazol-3-yl)pyrrole-2-carboxamide (**28a**)

Compound **28a** (6.88 g, 24.4 mmol, 90%) was prepared from **26** (7.0 g, 27.1 mmol) using sodium ethoxide (610 mg of sodium (26.5 mmol) in 250 mL of ethanol) and then EtOAc (7.6 mL, 6.86 g, 77.8 mmol) by the method described for **14**, and purified by recrystallization from acetonitrile. mp 141 – 144 ^{o}C; IR (KBr, cm^{-1}) 3370, 3190, 1645, 1622, 1587, 1562; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 8.10 (br s, 1 H, NH), 7.54 (br s, 1 H, NH), 7.34 - 7.24 (m, 3 H), 7.16 - 7.13 (m, 3 H), 6.52 (d, 1 H), 5.00 (s, 2 H, CH_2), 2.60 (s, 3 H, CH_3); UV λ_{max} nm (ε) (MeOH): 261 (4340), 277 (sh, 3760). Anal. Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85; O, 11.34. Found: C, 63.68; H, 4.92; N, 19.96.

1-Benzyl-3-[5-(*p*-nitrophenyl)-1,2,4-oxadiazol-3-yl]pyrrole-2-carboxamide (28b)

To a mixture of **26** (10.0 g, 38.7 mmol) and triethylamine (30 mL, 21.6 g, 213 mmol) in THF (800 mL) was added *p*-nitrobenzoyl chloride (9.2 g, 49.6 mmol). The mixture was stirred at rt for 5 h. The solvent

was removed under reduced pressure. The resulting residue was dissolved in EtOAc (200 mL). The solution was washed with H_2O (100 mL), saturated aqueous NaCl solution (100 mL), dried over anhydrous Na_2SO_4, and then evaporated to dryness. The resulting solid was recrystallized from acetonitrile to give **27** (8.5 g, 20.9 mmol, 54%) that was used without further characterization. Anal. Calcd for $C_{20}H_{17}N_5O_5 \cdot H_2O$: C, 56.47; H, 4.50; N, 16.46. Found: C, 56.57; H, 4.54; N, 16.39.

A mixture of **27** (obtained from 38.7 mmol of **26**) and acetic acid (1 mL) in toluene (300 mL) was heated at reflux temperature for 16 h in a flask equipped with a Dean-Stark apparatus. The solution was concentrated under reduced pressure to approx. 250 mL. The solution was placed in the freezer (0 ^oC) overnight. Crystals were collected by filtration and washed with pentane to give **28b** (8.3 g, 21.3 mmol, 55% from **26**). mp 215 - 219 ^oC (toluene); IR (KBr, cm^{-1}) 3381, 3205, 1658, 1623, 1567, 1525; ^1H NMR (DMSO-d_6, 270 MHz) δ 8.45 - 8.35 (m, 4 H, *p*-$NO_2C_6H_4$), 7.93 (br s, 1 H, NH), 7.60 (br s, 1 H, NH), 7.38 - 7.20 (m, 6 H), 6.60 (d, 1 H), 5.45 (s, 2 H, CH_2); UV λ_{max} nm (ε) (MeOH): 274 (34070). Anal. Calcd for $C_{20}H_{15}N_5O_4$: C, 61.69; H, 3.88; N, 17.99. Found C, 61.79, H, 4.14, N, 18.04.

1-Benzyl-3-(5-methyl-1,2,4-oxadiazol-3-yl)pyrrole-2-carboxylic Acid (29a)

To a solution of nitrosylsulfuric acid (3.1 g, 24.4 mmol) in acetic acid (50 mL) was added **28a** (4.13 g, 14.6 mmol) portionwise with vigorous stirring. After 1 h, the room temperature solution was diluted with ether (50 mL) and the precipitated white solid was collected by filtration. This material was dried and then a solution of sodium acetate (1.20 g, 14.6 mmol) in water was added. The mixture was stirred for 30 min. The crude product was collected and dried, and then suspended in ether to remove the reddish impurities. The solid was collected by filtration to give **29a** (2.06 g, 7.27 mmol, 50%). mp 154 – 156 ^oC (acetone); IR (KBr, cm^{-1}) 3600 - 2400, 2938, 2593, 1700, 1596, 1510; ^1H NMR (DMSO-d_6, 270 MHz) δ 12.75 (br s, 1 H, CO_2H), 7.37 - 7.20 (m, 5 H), 7.10 (s, 1 H), 6.40 (d, 1 H), 5.55 (s, 2 H, CH_2), 2.57 (s, 3 H, CH_3); UV λ_{max} nm (ε) (MeOH): 266 (9630). Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.71; H, 4.51; N, 15.08.

1-Benzyl-3-[5-(*p*-nitrophenyl)-1,2,4-oxadiazol-3-yl]pyrrole-2-carboxylic Acid (29b)

Compound **29b** (570 mg, 1.46 mmol, 57 %) was prepared from **28b** (1.0 g, 2.57 mmol) using nitrosylsulfuric acid (560 mg, 4.4 mmol) and acetic acid (40 mL) by the method described for **29a**, and purified by recrystallization from acetone. mp 232 – 235 ^oC; IR (KBr, cm^{-1}) 3600 - 2400, 1715, 1574, 1539; ^1H NMR (DMSO-d_6, 270 MHz) δ 12.85 (br s, CO_2H), 8.45 - 8.35 (m, 4 H, *p*-$NO_2C_6H_4$), 7.38 - 7.11 (m, 6 H), 6.53 (d, 1 H), 5.58 (s, 2 H, CH_2); MS (EI) *m/z* 91 (100), 374, 391 (M + 1); UV λ_{max} nm (ε) (MeOH): 273 (19060). Anal. Calcd for $C_{20}H_{14}N_4O_5 \cdot 0.5\ H_2O$: C, 60.15; H, 3.79; N, 14.03. Found: C, 60.10; H, 3.84; N. 14.15.

1-Benzyl-2-ethoxycarbonylamino-3-(5-methyl-1,2,4-oxadiazol-3-yl)pyrrole (30a)

To a solution of **29a** (1.0 g, 3.53 mmol) and triethylamine (0.5 mL, 0.36 g, 3.56 mmol) in *N*,*N*-dimethylformamide (75 mL) was added ethyl chloroformate (0.84 mL, 0.95 g, 8.79 mmol) in one portion with vigorous stirring. After 2 h, sodium azide (0.34 g, 5.23 mmol) was added and the mixture was stirred for an additional 3 h. Ethanol (20 mL) was added and the mixture was heated at 85 ^{o}C for an additional 2 h. The dark mixture was then concentrated under reduced pressure and the residue was partitioned between H_2O (40 mL) and EtOAc (50 mL). The organic layer was washed with H_2O, concentrated to dryness and then purified by column chromatography (toluene / EtOAc = 10 : 3) to give **30a** (216 mg, 0.66 mmol, 19%). mp 156 – 160 ^{o}C (ether). IR (KBr, cm^{-1}) 3233, 3198, 3142, 3121, 2980, 1700, 1580; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 9.00 and 8.75 (both br s, total = 1 H, NH), 7.35 - 7.15 (m, 5 H), 6.80 (d, 1 H), 6 43 (d, 1 H), 5.00 (s, 2 H, CH_2), 4.05 and 3.80 (both br s, total = 2 H, CH_2), 2.57 (s, 3 H, CH_3), 1.15 and 0.85 (both br s, total = 3 H, CH_3); UV λ_{max} nm (ε) (MeOH): 241 (8920), 262 (sh, 6305). Anal. Calcd for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62 49; H, 5.36; N, 16.96.

1-Benzyl-2-methoxycarbonylamino-3-[5-(*p*-nitrophenyl)-1,2,4-oxadiazol-3-yl]pyrrole (30b)

To a solution of **29b** (7.44 g, 19.1 mmol) and triethylamine (3.5 mL, 2.52 g, 24.9 mmol) in *N*,*N*-dimethylformamide (300 mL) was added diphenylphosphoryl azide (6.54 g, 23.7 mmol) and the solution was stirred at rt for 70 min. MeOH (65 mL) was added and the mixture was heated at 65 ^{o}C for an additional 70 min. The reaction mixture was concentrated under reduced pressure to afford a dark solid residue. The crude product was purified by column chromatography (toluene : EtOAc = 7 : 3) to give the product which was contaminated by a trace amount of orange impurity. This material was recrystallized from EtOAc to give **30b** (3.65 g, 8.7 mmol, 46%). mp 187 - 192.5 ^{o}C; IR (KBr, cm^{-1}) 3282, 1707, 1567, 1532; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.24 (br s, 0.7 H, NH), 8.99 (br s, 0.3 H, NH), 8.48 (d, J = 8.7 Hz, 2 H, *p*-$NO_2C_6H_4$ 3-H), 8.37 (d, J = 8.7 Hz, 2 H, *p*-$NO_2C_6H_4$ 2-H), 7.36 – 7.33 (m, 2 H, Ph 3-H), 7.30 – 7.27 (m, 1 H, Ph 4-H), 7.24 – 7.22 (m, 2 H, Ph 2-H), 6.89 (br s, 1 H, pyrrole 5-H), 6.60 (d, J = 3.1 Hz, 1 H, pyrrole 4-H), 5.09 (s, 2 H, CH_2), 3.68 (br s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 173.1 (oxadiazole 5-C), 166.0 (oxadiazole 3-C), 156.6 (C=O), 150.7 (*p*-$NO_2C_6H_4$ 4-C), 138.4 (Ph 1-C), 130.0 (*p*-$NO_2C_6H_4$ 2-CH), 129.8 (*p*-$NO_2C_6H_4$ 1-C), 129.3 (Ph 3-CH), 128.3 (Ph 2- and 4-CH), 128.0 (pyrrole 2-C), 125.5 (*p*-$NO_2C_6H_4$ 3-CH), 120.9 (pyrrole 5-CH), 107.5 (pyrrole 4-CH), 105.0 (pyrrole 3-C), 53.0 (CH_3), 49.4 (CH_2); UV λ_{max} nm (ε) (MeOH): 276 (23700). Anal. Calcd for $C_{21}H_{17}N_5O_5$: C, 60.14; H, 4.09; N, 16.70. Found: C, 60.42; H, 4.04; N, 16.47.

1-Benzyl-2-methoxycarbonylamino-3-[5-(*p*-nitrophenyl)-1,2,4-oxadiazol-3-yl]pyrrole-5-carbonitrile (32)

To a solution of **30b** (0.10 g, 0.24 mmol) in acetonitrile (15 mL) in an ice bath was added a solution of chlorosulfonyl isocyanate (24 μL, 39 mg, 0.27 mmol) in acetonitrile (5 mL) dropwise with stirring. The ice bath was removed after the addition was completed and the reaction mixture was allowed to stir for an additional 16 h at rt. *N*,*N*-Dimethylformamide (22 μL, 20 mg, 0.27 mmol) was added and the mixture was heated at reflux temperature for an additional 2 h. The solvent was removed under reduced pressure and the resulting residue was suspended in EtOAc (2 mL). The yellow solid was collected by filtration and then recrystallized from methanol to give **32** (70.0 mg, 0.16 mmol, 66%). mp 198 – 201 ^{o}C (MeOH); IR (KBr, cm^{-1}) 3250, 2227, 1743, 1708, 1602, 1567; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.85 (br s, 1 H, NH), 8.47 (d, *J* = 8.9 Hz, 2 H, *p*-$NO_2C_6H_4$ 3-CH), 8.36 (d, *J* = 8.9 Hz, 2 H, *p*-$NO_2C_6H_4$ 2-CH), 7.57 (s, 1 H, pyrrole 4-H), 7.40 – 7.37 (m, 2 H, Ph 3-CH), 7.34 – 7.31 (m, 1 H, Ph 4-CH), 7.21 – 7.20 (m, 2 H, Ph 2-CH), 5.32 (s, 2 H, CH_2), 3.71 (br s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 173.8 (oxadiazole 5-C), 164.6 (oxadiazole 3-C), 156.0 (C=O), 150.8 (*p*-$NO_2C_6H_4$ 4-C), 136.5 (Ph 1-C), 132.8 (pyrrole 2-C), 130.1 (*p*-$NO_2C_6H_4$ 2-CH), 129.6 (Ph 3-CH), 129.4 (*p*-$NO_2C_6H_4$ 1-C), 128.8 (Ph 4-CH), 127.9 (Ph 2-CH), 125.6 (*p*-$NO_2C_6H_4$ 3-CH), 119.7 (pyrrole 4-CH), 113.5 (CN), 106.8 (pyrrole 3-C), 102.7 (pyrrole 5-C), 53.4 (CH_3), 49.1 (CH_2); UV λ_{max} nm (ε) (MeOH): 274 (29500). Anal. Calcd for $C_{22}H_{16}N_6O_5 \cdot 0.5\ H_2O$: C, 58.28; H, 3.78; N, 18.53. Found: C, 58.17; H, 4.00; N, 18.25.

2-Amino-1-benzyl-3-[5-(*p*-nitrophenyl)-1,2,4-oxadiazol-3-yl]pyrrole-5-carbonitrile (33)

To a solution of **32** (150 mg, 0.34 mmol) in anisole (10 mL) was added 1,8-diazabicyclo-[5.4.0]undec-7-one (15 μL, 40.0 mg, 0.26 mmol) and the mixture was heated at reflux temperature for 1.5 h. The reaction mixture was concentrated *in vacuo* to afford a solid residue. This material was recrystallized from methanol to give **33** (92 mg, 0.24 mmol, 70%). mp 245 – 250 ^{o}C (decomp); IR (KBr, cm^{-1}) 3430, 3346, 2207, 1623, 1525; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.45 (s, 4 H, *p*-$NO_2C_6H_4$), 7.41 – 7.38 (m, 2 H, Ph 3-CH), 7.35 (s, 1 H, pyrrole 4-H), 7.33 – 7.30 (m, 1 H, Ph 4-CH), 7.18 – 7.16 (m, 2 H, Ph 2-CH), 6.67 (s, 2 H, NH_2), 5.27 (s, 2 H, CH_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 173.1 (oxadiazole 5-C), 165.4 (oxadiazole 3-C), 150.8 (*p*-$NO_2C_6H_4$ 4-C), 145.9 (pyrrole 2-C), 137.2 (Ph 1-C), 130.4 (*p*-$NO_2C_6H_4$ 2-CH), 129.6 (2 C, *p*-$NO_2C_6H_4$ 1-C + Ph 3-CH), 128.5 (Ph 4-CH), 127.5 (Ph 2-CH), 125.4 (*p*-$NO_2C_6H_4$ 3-CH), 120.1 (pyrrole 4-CH), 115.5 (CN), 97.4 (pyrrole 5-C), 90.3 (pyrrole 3-C), 47.6 (CH_2); MS (EI) *m/z* 386 (100) (M^+); UV λ_{max} nm (ε) (MeOH): 306 (29100), 275 (sh, 22150). Anal. Calcd for $C_{20}H_{14}N_6O_3$: C, 62.17; H, 3.65; N, 21.75. Found: C, 62.41; H, 3.81; N, 21.58.

6-Benzyl-5-cyano-3-(*p*-nitrobenzamido)pyrrolo[2,3-*c*]pyrazole (34)

To a suspension of sodium hydride (50% in mineral oil, 62 mg, 1.29 mmol) in dimethyl sulfoxide (40 mL) was added **33** (0.50 g, 1.29 mmol) and the mixture was heated at 75 °C under argon for 15 min. The reaction mixture was then cooled (ice bath) to rt and neutralized with acetic acid (80 mg, 1.33 mmol). The solvent was removed by distillation to give a dark residue. The residue was partitioned between EtOAc (150 mL) and H_2O (100 mL). The organic layer was washed with saturated aqueous NaCl solution, and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (toluene / EtOAc = 3 : 1) to give a dark orange solid. The solid was suspended in a small amount of ether and then collected by filtration to give **34** (146 mg, 0.38 mmol, 29%). mp 245 – 250 ^oC (decomp) (EtOAc); IR (KBr, cm^{-1}) 3346, 3297, 2214, 1680, 1602, 1546; ^1H NMR (DMSO-d_6, 270 MHz) δ 12.34 (br s, 1 H, NH), 12.03 (br s, 1 H, NH), 8.34 - 8.22 (m, 4 H, *p*-$NO_2C_6H_4$), 7.36 - 7 18 (m, 5 H), 6.78 (s, 1 H, 4-H), 5.30 (s, 2 H, CH_2); MS (FAB) *m/z* 91 (100), 150, 386 (7) (M^+). Anal. Calcd for $C_{20}H_{14}N_6O_3$: C, 62.17; H, 3.65; N, 21.75. Found. C, 62.11; H, 3.87; N, 21.51.

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