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# Verdazyl Radicals as Substrates for Organic Synthesis: A Synthesis of 3-Methyl-5-aryl-1,3,4-oxadiazolones

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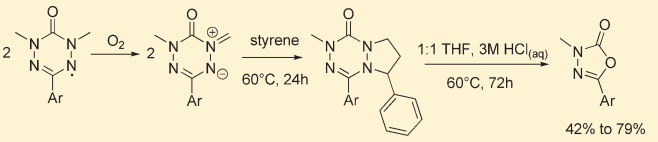
Supporting Information

**ABSTRACT:** The synthesis of oxadiazolones under hydrolytic conditions is described for a series of 3-methyl-5-aryl-1,3,4-oxadiazolone compounds. The unique starting materials for the hydrolysis reaction are obtained from efficient 1,3-dipolar cycloaddition reactions of styrene and azomethine imine dipoles derived from verdazyl radicals via a disproportionation reaction. A proposed mechanism for the formation of these biologically relevant oxadiazolones includes an opening of the tetrazinone ring followed by a 5-*exo*-*trig* ring closure. In support of the mechanism, in one case the ring-opened intermediate was isolated and subsequently treated with acid to give the relevant oxadiazolone.




A unique and valuable property of heterocyclic compounds is their ability to undergo a variety of rearrangements in one step to give new molecular architectures that would otherwise require a multistep sequence of involved reactions. Considering that most naturally occurring and synthetic biologically active compounds are heterocyclic, these rearrangements offer a sophisticated opportunity to enable the building of libraries of compounds with interesting motifs for new drug discoveries along the lines of the DOS concept.[1] We have recently shown that verdazyl radicals, as a result of their propensity to react with each other via a disproportionation reaction to form azomethine imines, can be used as substrates for the synthesis of a variety of heterocyclic compounds. This application goes beyond their traditional relevance as spin probes in ESR studies,[2] mediators for living radical polymerizations,[3] molecular magnets,[4] and polymerization inhibitors.[5] Thus, for example, 1,5-dimethyl-3-phenyl-6-oxoverdazyl radical has been shown to be a unique starting material for a series of tetrahydropyrazolotetrazinone compounds.[6] The key step in the reaction sequence is a regioselective 1,3-dipolar cycloaddition[7] of a variety of electron-deficient dipolarophiles, in particular, acrylates, methacrylates, acrylonitriles, and the slightly electron-rich styrene, with the azomethine imine derived from the disproportionation reaction between two verdazyl radicals. Alkyne dipolarophiles, on the other hand, provide dihydropyrazolotetrazinones, which upon heating at 150 °C rearrange in an interesting manner to afford pyrazolotriazinones.[8]

Herein, we report a further extension to the synthetic usefulness of verdazyl radicals as substrates for organic synthesis, specifically for the synthesis of 3-methyl-5-aryl-1,3,4-oxadiazolones. 1,3,4-Oxadiazolones have been shown to be important as ion channel inhibitors[9] and drugs for the treatment of malaria[10] and tuberculosis.[11] A common route for the synthesis of 3-methyl-5-aryl-1,3,4-oxadiazolones involves the reaction of potassium salts of substituted hydrazides with phosgene to give 5-aryl substituted oxadiazolones, which are subsequently N-methylated.[12] Reactions of 1,1-dimethyl-2-substituted hydrazides with acid chlorides provide another general route to these oxadiazolones.[13] As well, oxadiazolones have been made via the rearrangement which occurs upon methylation of a precursor heterocycle 2-alkoxy-substituted 1,3,4-oxadiazole.[14] This latter synthetic route, like the previous examples, still relies on appropriately substituted hyrazides.[15] The use of verdazyl radicals as starting materials to 1,3,4-oxadiazolones presents a completely different route to existing methodologies. Verdazyl radicals have been known for nearly 50 years,[16] and the chemistry of their synthesis has been well studied and for the most part is very straightforward.[17] The synthesis of the verdazyl radicals required to make the oxadiazolones presented herein all use the readily available N−N building block methyl hydrazine.[18]

It seemed reasonable to assume that exposure of cycloadduct **1**, obtained from the 1,3-dipolar cycloaddition reaction between the azomethine imine, derived from 1,5-dimethyl-3-phenyl-6-oxoverdazyl radical, with styrene, to acid hydrolysis conditions would lead at minimum to a ring-opening of the tetrazinone ring. What would happen after that occupied the realm of wild speculation. As expected, heating compound **1** in 1:1 THF/3 M $HCl_{aq}$ for 3 days at 60 °C resulted in the complete disappearance of the starting material, as evidenced by TLC. Fortuitously, the reaction was very clean with a single major product, whose $^{1}H$ NMR showed the presence of a phenyl ring and an *N*-methyl group but nothing more. The $^{13}C$ NMR spectrum added the fact that there were also two quaternary C's. Single-crystal X-ray crystallography provided the complete structure. Since the yield of the reaction was good (73%) and the reaction itself was simple and very straightforward, the scope and limitations of the reaction were investigated using the unique set of previously unreported cycloadducts **2**−**9** and **20**, **22**, **24**, and **26**. The results are summarized in Table 1. Yields of the oxadiazolones ranged typically from 42 to 79% with the exception of the 2-furyl

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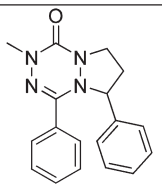
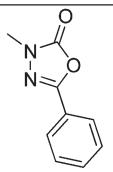
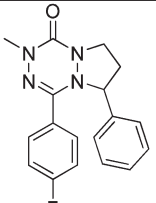
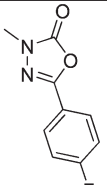
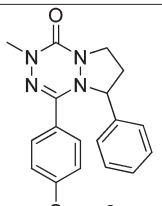
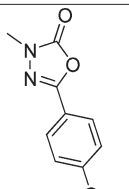
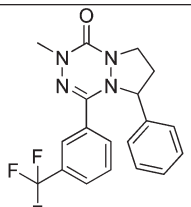
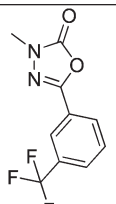
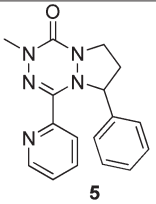
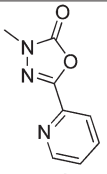
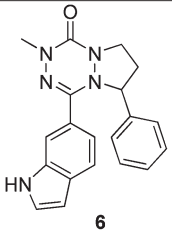
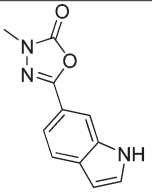
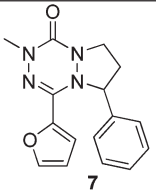
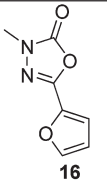
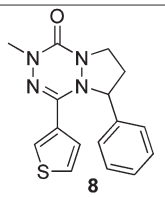
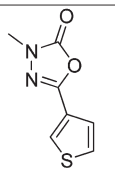
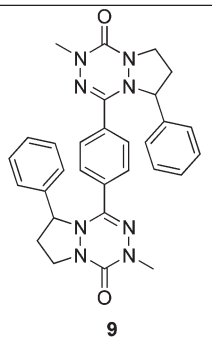
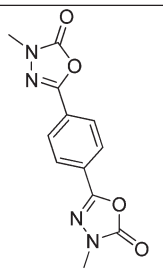
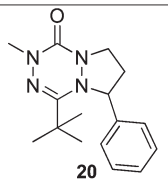
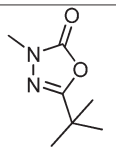
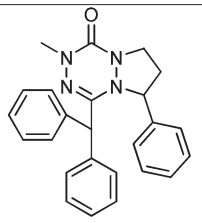
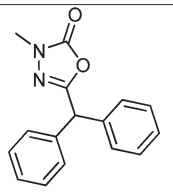
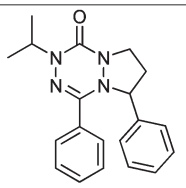
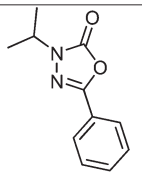
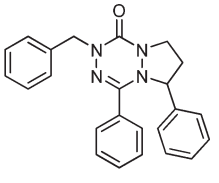
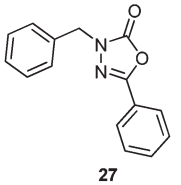
**Table 1. Cycloaddition Precursor Structures, 3-Methyl-5-aryl-1,3,4-oxadiazole Products, And Hydrolysis Reaction Yields**

| Entry | Cycloadduct precursor | Product | Yield |
|---|---|---|---|
| 1 |  **1** |  **10** | 73% |
| 2 |  **2** |  **11** | 64% |
| 3 |  **3** |  **12** | 68% |
| 4 |  **4** |  **13** | 79% |
| 5 |  **5** |  **14** | 78% |
| 6 |  **6** |  **15** | 42% |
| 7 |  **7** |  **16** | 7.7% |
| 8 |  **8** |  **17** | 46% |
| 9 |  **9** |  **18** | 64% |
| 10 |  **20** |  **21** Not observed | 0% |
| 11 |  **22** |  **23** Not observed | 0% |
| 13 |  **24** |  **25** | 61% |
| 14 |  **26** |  **27** | 62% |

derivative **16** that gave only a 7.7% yield. We suspect the lower yield for **16** is due to furan's susceptibility to hydrolysis under acidic conditions. Unexpectedly, the cycloaddition products of 5-alkyl substituted verdazyl radicals did not provide any oxadiazolones.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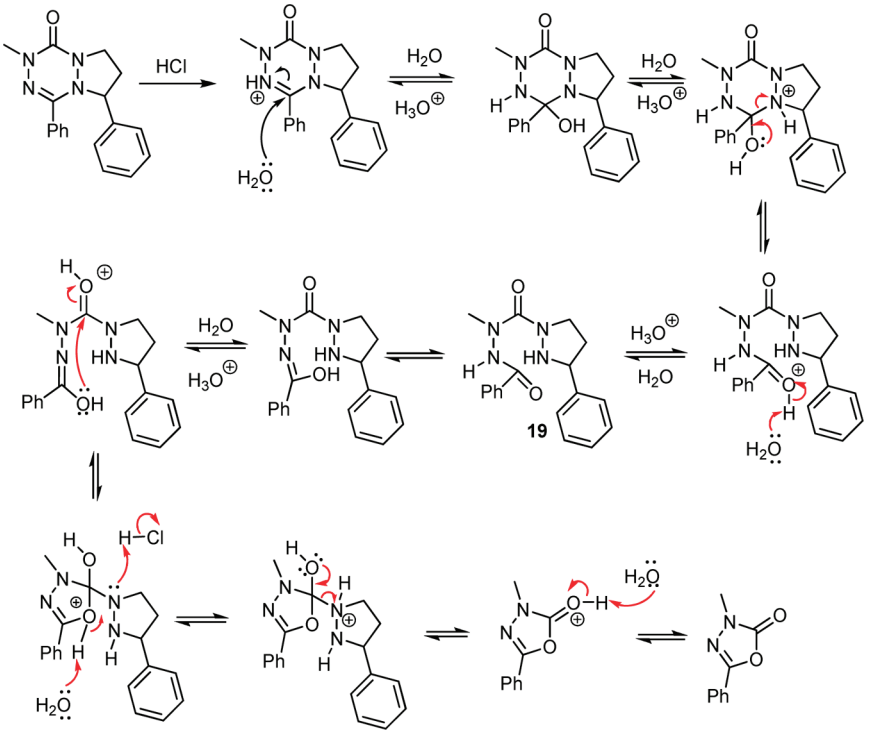
**Scheme 1. Proposed Mechanism for the Formation of 3-Methyl-5-phenyl-1,3,4-oxadiazolone**




A literature search reveals that some of the simple compounds in Table 1 have not been previously reported, specifically compounds **14**−**18**. Due to the biological relevance of these compounds it would seem that the synthesis of these compounds would be widespread enough to include these simple examples. Their absence, especially with those containing heterocycles at the 5-position, might imply a gap in current methodologies to make these compounds. Also, the synthesis of **18** from **9** demonstrates that this approach can be used to provide complex multioxadiazolone architectures that may not be trivial to make by other methods. Compounds **25** and **27** were synthesized to demonstrate that this methodology is compatible with substituents other than methyl at the 3 position.

It was found that using 1:1 THF and 3 M $HCl_{aq}$ at 60 °C for the hydrolysis reaction provides a reasonable balance between the rate of reaction and mild reaction conditions. At ambient temperature the reaction proceeds very slowly, requiring a week for all the starting material to disappear, while at 60 °C the reaction is complete after 72 h. The exceptions are **14**, **24**, and **26**, which require a temperature of 100 °C over 3 days to go to completion. Using these reaction conditions on 4-alkyl- as opposed to 4-aryl-substituted cycloadducts did not appear to yield any oxadiazolones. Compound **20** and **22** were subjected to the acid hydrolysis conditions; however, upon workup numerous spots were observed on TLC and column chromatography did not yield the expected products **21** and **23**, respectively, shown in Table 1. This could be due to the lack of conjugation experienced by the C═N bond in the alkyl case leaving the LUMO too high in energy for an efficient hydrolysis reaction to occur and leading instead to several unidentified decomposition products.

A proposed mechanism for the hydrolysis reaction is provided in Scheme 1. According to this mechanism, the 4-N position is protonated by HCl resulting in the formation of an iminium ion which is subsequently attacked by water. Following a series of protonation and deprotonation steps compound **19** is formed. Compound **19** undergoes a 5-*exo*-*trig* ring-closing reaction followed by a fragmentation reaction resulting in the oxadiazolone product. This fragmentation byproduct was never isolated. We suspect the isolation by our methods may be difficult because the fragment may break down into volatile compounds in the reaction or upon workup. In support of this mechanism, a small amount of compound **19** (16 mg) was able to be isolated from the hydrolysis reaction mixture of compound **1**. Acid hydrolysis of **19** gave compound **10** as confirmed by TLC and $^1$H NMR.

In conclusion, a novel synthesis complementary to existing methodologies has been developed for the synthesis of 3-methyl-5-aryl-1,3,4-oxadiazol-2(3*H*)-ones with yields typically ranging from 42 to 79%. Using appropriately 3-substituted verdazyl radicals, reacted with the inexpensive and readily available styrene dipolarophile, 4-aryl-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*][1,2,4,5]tetrazin-1-ones are prepared and subjected to acid hydrolysis conditions yielding 3-methyl-5-aryl-1,3,4-oxadiazol-2(3*H*)-ones. A mechanism is proposed, and as supporting evidence an intermediate was isolated and then shown to afford the final product when subjected to the hydrolytic conditions.

## EXPERIMENTAL SECTION

**General Methods.** Silica gel chromatography was performed with silica gel 60 (particle size 40−63 $\mu$m). Verdazyl radicals were previously synthesized according to published procedures.[16] NMR spectra were recorded at 23 °C, operating at 400 MHz for $^1$H NMR and 100 MHz for $^{13}$C NMR spectroscopy. Chemical shifts ($\delta$) are reported in parts per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million (ppm) referenced to tetramethylsilane ($\delta = 0$ ppm) for $^1$H NMR spectra and $CDCl_3$ ($\delta$ = 77.0 ppm) for $^{13}$C NMR spectroscopy. Coupling constants ($J$) are reported in hertz (Hz). Mass spectrometry was performed with an ESI source, MS/MS, and accurate mass capabilities, associated with a capillary LC system. X-ray data were collected on a diffractometer using monochromated Mo K$\alpha$ radiation, and measurements were made using a combination of $\Phi$ and $\omega$ scans with $\kappa$ offsets to fill the Ewald sphere. The structure was solved and refined for full-matrix least-squares refinement that was based on F2. All H atoms were included in the calculated positions and allowed to refine in the riding-motion approximation with Uiso tied to the carrier atom.

**General Cycloaddition Procedure.** 1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1 mmol) was dissolved in 2 mL of THF in a 10 mL round-bottom flask. Excess styrene (500 mg, 4.8 mmol) was added, and the solution was refluxed for 24 h. The reaction solution was cooled to ambient temperature, and the unreacted styrene was removed in vacuo. The product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes).

**General Hydrolysis Procedure.** The styrene cycloadduct (306 mg, 1 mmol) was dissolved in 5 mL of THF in a 10 mL round-bottom flask equipped with a condenser. A 5 mL solution of 3 M $HCl_{aq}$ was added, and the reaction was stirred and heated at 60 °C for 3 days. The reaction mixture was cooled to ambient temperature and extracted with 50 mL of dichloromethane 3 times. The dichloromethane extracts were combined, dried over sodium sulfate, and evaporated to give an oil. The product was isolated by silica gel column chromatography (1:2 ethyl acetate/hexanes).

*2-Methyl-4,6-diphenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,-4,5]tetrazin-1-one (**1**).* 1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg) was reacted according to the general procedure for cycloaddition yield a yellow waxy solid (257.3 mg, 84%): FT-IR ($\nu$, cm$^{-1}$, KBr) 2929, 1675, 1607, 1363, 757, 696; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.44−7.40 (d, $J$ = 7.2 Hz, 2H), 7.35−7.30 (t, $J$ = 7.2 Hz, 1H), 7.27−7.20 (t, $J$ = 8.0 Hz, 2H), 7.18−7.12 (m, 3H), 6.93−6.88 (m, 2H), 4.74−4.69 (m, 1H), 4.39−4.30 (m, 1H), 3.67−3.58 (m, 1H), 3.20 (s, 3H), 2.61−2.50 (m, 1H), 2.26−2.14 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.0 (C), 147.4 (C), 139.5 (C), 131.6 (C), 130.2 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.5 (CH), 127.2 (CH), 66.1 ($CH_3$), 44.8 ($CH_2$), 36.4 (CH), 33.3 ($CH_2$); HRMS (ESI) $m/z$ [M]$^+$ calcd for $C_{18}H_{19}N_4O$ 307.15589, found 307.15632.

*4-(4-Fluorophenyl)-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (**2**).* 1,5-Dimethyl-3-(4-fluoro)-phenyl-6-oxoverdazyl (300 mg) was reacted according to the general procedure for cycloaddition to yield a yellow waxy solid (311 mg, 71%): FT-IR ($\nu$, cm$^{-1}$, KBr) 3541, 3021, 2951, 1691, 1417, 1361; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.42−7.36 (m, 2H), 7.18−7.12 (m, 3H), 6.92−6.86 (m, 4H) 4.79−4.63 (m, 1H), 4.36−4.28 (m, 1H), 3.66−3.57 (m, 1H), 3.20 (s, 3H), 2.59−2.48 (m, 1H), 2.23−2.13 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 164.9−162.4 (d, $J$ = 249 Hz) (C), 154.9 (C), 146.4 (C), 139.2 (C), 129.4−129.3 (d, $J$ = 8.6 Hz) (CH), 128.2 (CH), 127.8 (CH), 127.70−127.67 (d, $J$ = 3 Hz) (C), 127.1 (CH), 115.2−114.9 (d, $J$ = 22 Hz), 66.2 (CH), 44.8 ($CH_2$), 36.3 ($CH_3$), 33.3 ($CH_2$); HRMS (ESI) $m/z$ [M]$^+$ calcd for $C_{18}H_{17}N_4OF$ 324.1386, found 324.1390.

*4-(4-Methoxyphenyl)-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (**3**).* 1,5-Dimethyl-3-(4-methoxy)-phenyl-6-oxoverdazyl (350 mg) was reacted according to the general procedure for cycloaddition to yield a yellow waxy solid (302.7 mg, 60%): FT-IR ($\nu$, cm$^{-1}$, KBr) 2937, 1665, 1607, 1514, 1357, 1252, 1028; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.33 (d, $J$ = 8.8 Hz, 2H), 7.18−7.14 (m, 3H), 6.93−6.88 (m, 4H) 6.78−6.73 (d, $J$ = 8.8 Hz, 2H), 4.72−4.67 (m, 1H), 3.39−3.31 (m, 1H), 3.79 (s, 3H), 3.64−3.56 (m, 1H), 3.18 (s, 3H), 2.60−2.50 (m, 1H), 2.25−2.15 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.3 (C), 155.3 (C), 147.4 (C), 139.7 (C), 129.1 (CH), 128.3 (CH), 127.8 (CH), 127.3 (CH), 124.1 (C), 113.6 (CH), 66.2 (CH), 55.2 ($CH_3$), 44.9 ($CH_2$), 36.4 ($CH_3$), 33.4 ($CH_2$); HRMS (ESI) $m/z$ [M]$^+$ calcd for $C_{19}H_{20}N_4O_2$ 336.1586, found 336.1577.

*2-Methyl-6-phenyl-4-(3-(trifluoromethyl)phenyl)-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (**4**).* 1,5-Dimethyl-3-(3-trifluoromethylphenyl)-6-oxoverdazyl (700 mg) was reacted according to the general procedure for cycloaddition yield a yellow waxy solid (612 mg, 63%): FT-IR ($\nu$, cm$^{-1}$, KBr) 3554, 3478, 2949, 1681, 1617, 1321, 1127; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.63−7.62 (s, 1H), 7.61−7.58 (d, $J$ = 8 Hz, 1H), 7.54−7.50 (d, $J$ = 8 Hz, 1H) 7.35−7.29 (t, $J$ = 8 Hz, 1H), 7.16−7.09 (m, 3H), 6.91−6.87 (m, 2H), 4.67−4.62 (m, 1H), 4.32−4.24 (m, 1H), 3.75−3.67 (m, 1H), 3.25 (s, 3H), 2.61−2.51 (m, 1H), 2.25−2.14 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.9 (C), 145.9 (C), 138.9 (C), 130.9−129.9 (q, $J$ = 32.4 Hz) (C), 130.4 (C), 128.5 (C), 128.3 (CH), 128.0 (C), 127.6−119.5 (q, $J$ = 271 Hz) (C), 127.2 (CH), 126.5−126.4 (q, $J$ = 3.6 Hz) (CH), 124.3−124.2 (q, $J$ = 3.8 Hz) (CH), 66.6 ($CH_3$), 45.0 ($CH_2$), 36.6 (CH), 33.4 ($CH_2$); HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{19}H_{18}N_4OF_3$ 375.1427, found 375.1423.

*2-Methyl-6-phenyl-4-(pyridin-2-yl)-2,6,7,8-tetrahydro-1H-pyrazolo-[1,2-a][1,2,4,5]tetrazin-1-one (**5**).* 1,5-Dimethyl-3-(2-pyridyl)-6-oxoverdazyl (800 mg) was reacted according to the general procedure for cycloaddition to yield a yellow waxy solid (885 mg, 74%); FT-IR ($\nu$, cm$^{-1}$, KBr) 3550, 3472, 2946, 1669, 1408, 1194; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.59−8.56 (dq, $J$ = 4.8 Hz, 0.8 Hz, 1H), 7.58−7.49 (dt, $J$ = 8 Hz, 1.6 Hz, 1H), 7.48−7.44 (dt, $J$ = 7.6 Hz, 0.8 Hz, 1H), 7.22−7.17 (ddd, $J$ = 7.3 Hz, 4.8 Hz, 1.6 Hz, 1H), 7.15−7.10 (m, 3H), 7.00−6.95 (m, 2H), 5.30−5.25 (m, 1H), 4.36−4.28 (m, 1H), 3.68−3.55 (m, 1H), 3.25 (s, 3H), 2.69−2.59 (m, 1H), 2.23−2.13 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.0 (C), 149.9 (C), 148.7 (CH), 145.9 (C), 140.0 (C), 136.1 (CH), 128.2 (CH), 127.6 (CH), 126.8 (CH), 124.1 (CH), 122.4 (CH), 65.3 ($CH_3$), 44.3 ($CH_2$), 36.6 (CH), 33.7 ($CH_2$); HRMS (ESI) $m/z$ [M]$^+$ calcd for $C_{17}H_{17}N_5O$ 307.1433, found 307.1445.

*4-(1H-Indol-6-yl)-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo-[1,2-a][1,2,4,5]tetrazin-1-one (**6**).* 1,5-Dimethyl-3-(6-indole)-6-oxoverdazyl (100 mg) was reacted according to the general procedure for cycloaddition to yield a beige solid (68 mg, 48%): mp 160−162 °C; FT-IR ($\nu$, cm$^{-1}$, KBr) FT-IR ($\nu$, cm$^{-1}$, KBr) 3049, 3250, 2938, 1652, 1598, 1421, 1168; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.20−8.02 (br, 1H), 7.95−7.91 (d, $J$ = 8 Hz, 1H), 7.34−7.30 (d, $J$ = 7.6 Hz, 1H), 7.25−7.13 (m, 5H), 7.10−7.08 (d, $J$ = 2.8 Hz, 1H), 7.02−6.98 (m, 2H), 4.79−4.73 (m, 1H), 4.23−4.08 (m, 1H), 3.90−3.82 (m, 1H), 3.25 (s, 1H), 2.61−2.50 (m, 1H), 2.28−2.19 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.9 (C), 144.5 (C), 140.5 (C), 136.2 (C), 128.3 (CH), 127.8 (CH), 127.4 (CH), 126.8 (CH), 125.0 (C), 123.0 (CH), 121.3 (CH), 121.2 (CH), 111.1 (CH), 109.2 (C), 66.0 (CH), 45.1 ($CH_2$), 36.7 ($CH_3$), 33.4 ($CH_2$); HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{20}H_{20}N_5O$ 346.1662, found 346.1657.

*4-(Furan-2-yl)-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo-[1,2-a][1,2,4,5]tetrazin-1-one (**7**).* 1,5-Dimethyl-3-(2-furyl)-6-oxoverdazyl (600 mg) was reacted according to the general procedure for cycloaddition to yield a yellow waxy solid (256 mg, 65%); FT-IR ($\nu$, cm$^{-1}$, KBr) 3548, 3475, 2926, 1679, 1375, 1018; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.36=7.34 (m, 1H), 7.25−7.18 (m, 3H), 7.09−7.05 (m, 2H) 6.45−6.42 (d, $J$ = 3.2 Hz, 1H), 6.29−6.26 (m, 1H), 4.90−4.84 (m, 1H), 4.20−4.10 (m, 1H), 3.72−3.62 (m, 1H), 3.21 (s, 3H), 2.60−2.48 (m, 1H), 2.22−2.11 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.4 (C), 144.6 (C), 143.8 (CH), 139.6 (C), 139.3 (C), 128.2 (CH), 127.7 (CH), 126.7 (CH), 112.6 (CH), 111.2 (CH), 65.7 (CH), 44.5 ($CH_2$), 36.3 ($CH_3$), 33.5 ($CH_2$); HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{16}H_{17}N_4O_2$ 297.1346, found 297.1348.

*2-Methyl-6-phenyl-4-(thiophene-3-yl)-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (**8**).* 1,5-Dimethyl-3-(3-thiophene)-6-oxoverdazyl (100 mg) was reacted according to the general procedure

for cycloaddition yield a yellow waxy solid (34.5 mg, 23%): FT-IR ($\nu$, $cm^{-1}$, KBr) 3298, 3102, 2956, 1659, 1595, 1371, 1034; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.33 (dd, $J$ = 3.2 Hz, 1.2 Hz, 1H), 7.22−7.18 (m, 3H), 7.17−7.14 (dd, $J$ = 4.8 Hz, 3.0 Hz, 1H), 7.06−7.03 (dd, $J$ = 5.2 Hz, 1.2 Hz, 1H), 7.02−6.97 (m, 2H), 4.78−4.72 (m, 1H), 4.25−4.17 (m, 1H), 3.75−3.67 (m, 1H), 3.18 (s, 3H), 2.60−2.49 (m, 1H), 2.25−2.15 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 155.1 (C), 143.8 (C), 139.8 (C), 133.8 (C), 128.4 (CH), 128.0 (CH), 127.3 (CH), 126.6 (CH), 126.3 (CH), 125.8 (CH), 66.4 ($CH_3$), 44.9 ($CH_2$), 36.5 (CH), 33.7 ($CH_2$); HRMS (ESI) $m/z$ $[M]^+$ calcd for $C_{16}H_{16}N_4OS$ 312.1045, found 312.1043.

*4,4′-(1,4-Phenylene)bis(2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one)* (***9***). 1,4-Bis-(1,5-dimethyl-6-oxoverdazyl)benzene (200 mg) was reacted according to the general procedure for cycloaddition to yield a yellow waxy solid (107 mg, 33%): mp 194−197 °C; FT-IR ($\nu$, $cm^{-1}$, KBr) 3550, 2941, 1673, 1617, 1364; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.37 (s, 2H), 7.37−7.36 (s, 2H), 7.22−7.12 (m, 6H), 6.92−6.84 (m, 4H), 4.70−4.66 (m, 2H), 4.46−4.35 (m, 2H), 3.65−3.51 (m, 2H), 3.20−3.19 (s, 3H), 3.19−3.18 (s, 3H), 2.64−2.52 (m, 2H), 2.28−2.16 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 155.0 (C), 146.35 (C), 146.31 (C), 139.31 (C), 139.27 (C), 133.48 (C), 133.44 (C), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.32 (CH), 127.28 (CH), 127.25 (CH), 66.32 ($CH_3$), 66.25 ($CH_3$), 45.0 ($CH_2$), 36.6 (CH), 33.22 ($CH_2$), 33.18 ($CH_2$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{30}H_{31}N_8O_2$ 535.2564, found 535.2561.

*3-Methyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one* (***10***). Compound **1** (306 mg) was reacted according to the general hydrolysis procedure to yield a white solid (129 mg, 73%): mp 64−65 °C; FT-IR ($\nu$, $cm^{-1}$, KBr) 3068, 1770, 1638, 1455, 1356, 1020; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.85−7.82 (m, 2H), 7.54−7.44 (m, 3H), 3.51 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.7 (C), 153.1 (C), 131.5 (CH), 128.9 (CH), 125.5 (CH), 123.8 (C), 32.7 ($CH_3$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_9H_9N_2O_2$ 177.0658, found 177.0665.

*5-(4-Fluorophenyl)-3-methyl-1,3,4-oxadiazol-2(3H)-one* (***11***). Compound **2** (311 mg) was reacted according to the general hydrolysis procedure to yield a white solid (119 mg, 64%): mp 86−88 °C; FT-IR ($\nu$, $cm^{-1}$, KBr) 3537, 3086, 1782, 1611, 1508, 1225, 1015; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.84−7.80 (m, 2H), 7.18−7.13 (m, 2H), 3.50 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 165.8 (C), 163.2 (C), 153.5−152.3 (d, $J$ = 127 Hz) (C), 127.8−127.7 (d, $J$ = 8.8 Hz) (CH), 120.1−120.0 (d, $J$ = 3.2 Hz) (C), 116.4−116.2 (d, $J$ = 22.2 Hz) (CH), 32.7 ($CH_3$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_9H_8N_2O_2F$ 195.0564, found 195.0562.

*5-(4-Methoxyphenyl)-3-methyl-1,3,4-oxadiazol-2(3H)-one* (***12***). Compound **3** (303 mg) was reacted according to the general hydrolysis procedure to yield a white solid (126 mg, 68%): mp 133−135 °C; FT-IR ($\nu$, $cm^{-1}$, KBr) 2976, 2847, 1785, 1618, 1513, 1260, 1021; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.77−7.72 (d, $J$ = 8.8 Hz, 2H), 6.98−6.94 (d, $J$ = 8.8 Hz, 2H), 3.86 (s, 3H), 3.47 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 162.1 (C), 153.7 (C), 153.1 (C), 127.2 (CH), 116.1 (C), 114.3 (CH), 55.3 ($CH_3$), 32.5 ($CH_3$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{10}H_{11}N_2O_3$ 207.0764, found 207.0767.

*3-Methyl-5-(3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2(3H)-one* (***13***). Compound **4** (600 mg) was reacted according to the general hydrolysis procedure to yield a white solid (310 mg, 79%): mp 38−39 °C; FT-IR ($\nu$, $cm^{-1}$, KBr) 3555, 2950, 1782, 1612, 1577, 1180; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.09 (s, 1H), 8.01−7.97 (d, $J$ = 8 Hz, 1H) 7.78−7.74 (d, $J$ = 8 Hz, 1H), 7.65−7.59 (t, $J$ = 8 Hz, 1H) 3.53 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.2 (C), 151.7 (C), 132.1−131.1 (q, $J$ = 33 Hz) (C), 129.6 (CH), 128.5 (CH), 127.9−127.8 (q, $J$ = 3.6 Hz) (CH), 124.7−119.3 (q, $J$ = 271 Hz) (C), 124.6 (C), 122.4−122.3 (q, $J$ = 3.9 Hz) (CH), 32.7 ($CH_3$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{10}H_8N_2O_2F_3$ 245.0532, found 245.0543.

*3-Methyl-5-(pyridin-2-yl)-1,3,4-oxadiazol-2(3H)-one* (***14***). Compound **5** (700 mg) was reacted according to the general hydrolysis procedure to yield a white solid (313 mg, 78%): mp 75−76 °C; FT-IR ($\nu$, $cm^{-1}$, KBr) 3057, 1774, 1562, 1362, 1247, 1022; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.77−8.73 (d, $J$ = 4.8 Hz, 1H), 7.90−7.82 (m, 2H) 7.46−7.43 (m, 1H), 3.56 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.3 (C), 151.9 (C), 150.4 (CH), 142.8 (C), 137.1 (CH), 125.6 (CH), 121.4 (CH), 32.8 ($CH_3$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_8H_8N_3O_2$ 178.0611, found 178.0610.

*5-(1H-Indol-6-yl)-3-methyl-1,3,4-oxadiazol-2(3H)-one* (***15***). Compound **6** (60 mg) was reacted according to the general hydrolysis procedure to yield a brownish solid (16 mg, 42%): mp 185−186 °C; FT-IR ($\nu$, $cm^{-1}$, KBr) 3551, 3252, 2942, 1764, 1633, 1449, 998; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.80−8.60 (br, NH), 8.12−8.08 (d, $J$ = 7.6 Hz, 1H) 7.73−7.72 (d, $J$ = 2.8 Hz, 1H), 8.47−8.43 (d, $J$ = 7.2 Hz, 1H), 7.34−7.26 (m, 2H) 3.52 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.6 (C), 151.4 (C), 136.1 (C), 126.0 (CH), 123.8 (CH), 123.7 (C), 122.0 (CH), 121.0 (CH), 111.7 (CH), 101.8 (C), 32.7 ($CH_3$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{11}H_{10}N_3O_2$ 216.0778, found 216.0779.

*5-(Furan-2-yl)-3-methyl-1,3,4-oxadiazol-2(3H)-one* (***16***). Compound **7** (256 mg) was reacted according to the general hydrolysis procedure to yield a white solid (11 mg, 7.7%): mp 91−93 °C; FT-IR ($\nu$, $cm^{-1}$, KBr) 3138, 2924, 1779, 1645, 1471, 1225, 1016; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.60−7.58 (m, 1H), 6.98−6.96 (d, $J$ = 3.6 Hz, 2H), 6.57−6.55 (dd, J= 3.6 Hz, 2 Hz 1H) 3.50 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 152.8 (C), 146.6 (C), 145.6 (CH), 138.9 (C), 113.5 (CH), 111.9 (CH), 32.9 ($CH_3$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_7H_7N_2O_3$ 167.0451, found 167.0454.

*3-Methyl-5-(thiophene-3-yl)-1,3,4-oxadiazol-2(3H)-one* (***17***). Compound **8** (34.5 mg) was reacted according to the general hydrolysis procedure to yield a white solid (9.2 mg, 46%): mp 68−70 °C; FT-IR ($\nu$, $cm^{-1}$, KBr) 3475, 3131, 2922, 1774, 1619, 1310, 1107; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.86−7.84 (dd, $J$ = 2.8 Hz, 1.2 Hz, 1H), 7.47−7.45 (dd, $J$ = 5.2 Hz, 1.2 Hz, 1H) 7.44−7.41 (dd, $J$ = 5.2 Hz, 3.2 Hz, 1H), 3.48 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.4 (C), 150.4 (C), 127.5 (CH), 126.7 (CH), 125.3 (C), 124.6 (CH), 32.7 ($CH_3$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_7H_7N_2O_2S$ 183.0222, found 183.0221.

*5,5′-(1,4-Phenylene)bis(3-methyl-1,3,4-oxadiazol-2(3H)-one)* (***18***). Compound **9** (107 mg) was reacted according to the general hydrolysis procedure to yield a white solid (35 mg, 64%): mp 278−282 °C; FT-IR ($\nu$, $cm^{-1}$, KBr) 3548, 3475, 1781, 1617, 1413, 1112; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.93 (s, 4H), 3.53 (s, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.4 (C), 152.1 (C), 126.3 (C), 126.1 (CH), 32.9 ($CH_3$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{12}H_{11}N_4O_4$ 275.0774, found 275.0783.

*N′-Benzoyl-N-methyl-3-phenylpyrazolidine-1-carbohydrazide* (***19***). Compound **1** (260 mg) was reacted according to the general hydrolysis procedure to yield a clear oil (19 mg, 7.7%): FT-IR ($\nu$, $cm^{-1}$, KBr) 3191, 2958, 2872, 1729, 1689, 1620, 1289; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.36 (br, 1H), 7.90−7.84 (d, $J$ = 7.6 Hz, 2H), 7.54−7.48 (t, $J$ = 7.2 Hz, 1H), 7.33−7.38 (t, $J$ = 8.0 Hz, 2H), 7.32−7.22 (m, 5H), 5.00−4.30 (br, 1H), 4.20−4.14 (t, $J$ = 7.6 Hz, 1H), 3.84−3.76 (m, 1H), 3.66−3.56 (m, 1H), 3.25 (s, 3H), 2.48−2.37 (m, 1H), 2.14−2.00 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 165.4 (C), 161.3 (C), 138.0 (C), 132.1 (C), 131.0 (C), 128.60 (CH), 128.57 (CH), 127.9 (CH), 127.3 (CH), 126.8 (CH), 63.0 ($CH_3$), 47.9 ($CH_2$), 38.3 (CH), 34.0 ($CH_2$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{18}H_{21}N_4O_2$ 325.16645, found 325.16524.

*4-tert-Butyl-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo-[1,2-a][1,2,4,5]tetrazin-1-one* (***20***). 1,5-Dimethyl-3-(*tert*-butyl)-6-oxoverdazyl (183 mg) was reacted according to the general procedure for cycloaddition yield a yellow solid (217.1 mg, 76%): FT-IR ($\nu$, $cm^{-1}$, KBr) 3173, 3142, 2988, 2954, 1595, 1351; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.33−7.27 (m, 2H), 7.25−7.19 (m, 3H), 4.92−4.86 (m, 1H), 4.10−4.02 (m, 1H), 3.38−3.28 (m, 1H), 3.12 (s, 3H), 2.56−2.45 (m, 1H), 2.07−1.96 (m, 1H), 1.05 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$

156.9 (C), 156.4 (C), 140.8 (C), 128.4 (CH), 127.6 (CH), 126.4 (CH), 65.6 ($CH_3$), 43.6 ($CH_2$), 36.3 (CH), 35.9 (C), 35.4 ($CH_2$), 28.7 ($CH_3$); HRMS (ESI) $m/z$ $[M]^+$ calcd for $C_{16}H_{23}N_4O$ 287.18719, found 287.18720.

*4-Benzhydryl-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo-[1,2-a][1,2,4,5]tetrazin-1-one* (**22**). 1,5-Dimethyl-3-benzhydryl-6-oxo-verdazyl (110 mg) was reacted according to the general procedure for cycloaddition yield a yellow solid (96 mg, 65%): mp 144−146 °C; FT-IR ($\nu$, $cm^{-1}$, KBr) 3025, 2901, 1684, 1619, 1493, 1384; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.44−7.25 (m, 10H), 7.15−7.06 (m, 3H), 6.80−6.74 (m, 2H), 4.57 (s, 1H), 4.44−4.37 (t, $J$ = 7.2 Hz, 1H), 3.68−3.53 (m, 2H), 3.14 (s, 3H), 2.35−2.25 (m, 1H), 2.04−1.92 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 157.1 (C), 151.5 (C), 140.6 (C), 139.6 (C), 138.6 (C), 129.07 (CH), 129.06 (CH), 128.81 (CH), 128.76 (CH), 128.2 (CH), 127.7 (CH), 127.3 (CH), 126.4 (CH), 126.1 (CH), 61.7 ($CH_3$), 51.8 (CH), 43.0 ($CH_2$), 36.3 (CH), 35.3 ($CH_2$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{25}H_{25}N_4O$ 397.20284, found 397.20295.

*2-Isopropyl-4,6-diphenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a]-[1,2,4,5]tetrazin-1-one* (**24**): yellow waxy solid; FT-IR ($\nu$, $cm^{-1}$, KBr) 3062, 3030, 2973, 2933, 1719, 1671, 1450, 1384; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.65−7.59 (t, $J$ = 7.2 Hz, 1H), 7.50- 7.46 (m, 2H), 7.38−7.33 (t, $J$ = 7.6 Hz, 2H), 7.20−7.10 (m, 3H), 6.90−6.85 (d, $J$ = 6.8 Hz, 2H), 4.74−4.68 (m, 1H), 4.64−4.47 (m, 2H), 3.56−3.48 (m, 1H), 2.64−2.52 (m, 1H), 2.29−2.20 (m, 1H), 1.21−1.16 (d, $J$ = 6.8 Hz, 3H), 0.97−0.93 (d, $J$ = 6.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 154.2 (C), 146.5 (C), 139.3 (C), 133.0 (C), 130.0 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 66.0 ($CH_3$), 47.2 ($CH_2$), 44.8 ($CH_2$), 32.9 ($CH_2$), 19.8 ($CH_3$), 19.6 ($CH_3$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{20}H_{23}N_4O$ 335.18719, found 335.18793.

*3-Isopropyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one* (**25**). Compound **24** (25 mg) was reacted according to the general hydrolysis procedure to yield a white solid (9.2 mg, 61%): mp 45−47 °C; FT-IR ($\nu$, $cm^{-1}$, KBr) 2983, 2938, 2877, 1767, 1614, 1356; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.88−7.87 (dd, $J$ = 7.6 Hz, 1.2 Hz, 2H), 7.53−7.43 (m, 3H), 4.46−4.35 (sept, $J$ = 6.8 Hz, 1H), 1.46−1.41 (d, $J$ = 6.8 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.0 (C), 152.8 (C), 131.2 (CH), 128.7 (CH), 125.5 (CH), 124.0 (C), 48.1 (CH), 20.7 ($CH_3$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{11}H_{13}N_2O_2$ 205.09770, found 205.09738.

*2-Benzyl-4,6-diphenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,-4,5]tetrazin-1-one* (**26**): yellow solid; mp 99−101 °C; FT-IR ($\nu$, $cm^{-1}$, KBr) 3060, 3029, 2925, 1674, 1604, 1384; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.35 (d, $J$ = 7.2 Hz, 2H), 7.34−7.20 (m, 8H), 7.12−7.06 (t, $J$ = 7.2 Hz, 1H), 7.01−7.94 (t, $J$ = 8.0 Hz, 2H), 6.79−6.75 (d, $J$ = 7.2 Hz, 2H), 4.98−4.92 (d, $J$ = 14.8 Hz, 1H), 4.74−4.68 (m, 1H), 4.63−4.56 (d, $J$ = 15.2 Hz, 1H) 4.49−4.42 (m, 1H), 3.59−3.53 (m, 1H), 2.62−2.51 (m, 1H), 2.23−2.12 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 154.7 (C), 147.1 (C), 139.4 (C), 137.4 (C), 131.8 (C), 130.2 (CH), 128.25 (CH), 128.19 (CH), 128.17 (CH), 128.1 (CH), 127.7 (CH), 127.5 (CH), 127.1 (CH), 127.0 (CH), 66.3 ($CH_3$), 52.6 ($CH_2$), 44.8 ($CH_2$), 33.5 ($CH_2$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{24}H_{23}N_4O$ 383.18719, found 383.18844.

*3-Benzyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one* (**27**). Compound **26** (130 mg) was reacted according to the general hydrolysis procedure to yield a white solid (53.2 mg, 62%): mp 96−98 °C; FT-IR ($\nu$, $cm^{-1}$, KBr) 3063, 3032, 2925, 2853, 1767, 1612, 1571; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.84−7.80 (dd, $J$ = 8.0 Hz, 1.2 Hz, 2H), 7.51−7.30 (m, 8H), 4.95 (s, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.4 (C), 153.2 (C), 134.8 (C), 131.4 (CH), 128.8 (CH), 128.7 (CH), 128.23 (CH), 128.17 (CH), 125.6 (CH), 123.7 (C), 49.6 ($CH_2$); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{15}H_{13}N_2O_2$ 253.09770, found 253.09834.

## ■ ASSOCIATED CONTENT

**Supporting Information.** $^1H$ and $^{13}C$ NMR spectra; X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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