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Functional Group Transformations in Derivatives of 6-Oxoverdazyl

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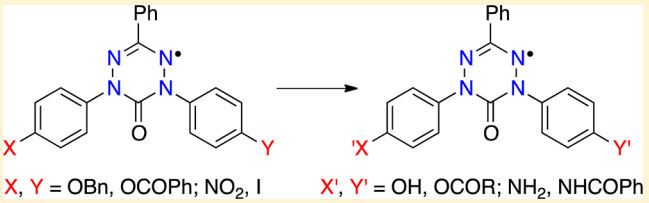
Supporting Information

ABSTRACT: Transformations of functional groups, such as OCH_2Ph, OCOPh, NO_2 and I, in 1,3,5-triphenyl-6-oxoverdazyls **1a**−**1e** were investigated in order to expand the range of synthetic tools for incorporation of the verdazyl system into more complex molecular architectures and to increase spin delocalization. Thus, Pd-catalyzed debenzylation of the OCH_2Ph group or basic hydrolysis of the OCOPh group gave the phenol functionality, which was acylated, but could not be alkylated. Orthogonal deprotection of diphenol functionality was also demonstrated in radical **1c**. Pt-catalyzed reduction of the NO_2 group led to the aniline derivative, which was acylated. Attempted C−C coupling reactions to iodophenyl derivatives **1e** and **5e** were unsuccessful. Selected verdazyl radicals were characterized by EPR and electronic absorption spectroscopy, and results were analyzed with the aid of DFT computational methods.



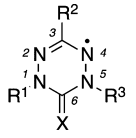
INTRODUCTION

π-Delocalized stable radicals have become important structural elements of contemporary advanced materials for technological and biological applications.[1,2] For instance, redox active radicals have been explored for rechargeable battery applications,[3] solar cells,[4] in vivo oximetry,[5] as polarizing agents for dynamic nuclear polarization (DNP),[6−8] and have been investigated in the context of spintronics.[9] Recently, we demonstrated photocurrent generation in columnar discotic radicals[10,11] as the first step toward photovoltaic applications. Further expansion of the use of such radicals for functional materials requires the presence of reactive functional groups and development of functional group transformations in the presence of the radical center.

Verdazyls are among a handful of classes of stable radicals that are often used in the design of functional low molecular weight and polymeric materials;[12,13] however, there are relatively few reports of functional group transformations in this class of radicals. Arguably, amino derivatives of 1,3,5-triphenylverdazyl, such as **Ia** obtained by selective reduction of the corresponding nitro derivative,[14,15] are the most investigated and used in synthesis of functional verdazyl derivatives. It has been demonstrated that the amino group can be acylated, condensed with aldehydes, and arylated with picryl chloride.[14] Also, the amino group was used to build a maleoimide group in a triarylverdazyl for anionic polymerization.[15] Another polyradical was obtained by acylation of **Ia** with poly(4-vinylbenzoyl chloride).[16]

An interesting transformation was demonstrated for verdazyl derivatives **Ib** that were obtained from formazane of *O*-acetylated carbohydrates. The acetyl groups in **Ib** were removed by treatment with ammonia or NaOMe in MeOH giving the corresponding polyhydroxy derivatives in high yields.[17] The 6-oxoverdazyl system appears to be stable also to acidic conditions; 1,3,5-triphenyl-6-oxoverdazyl was sulfonylated giving water-soluble trisulfonium acid **Ic**.[18]

Carboxyphenyl[19] and hydroxyphenyl[20] derivatives **Id**−**If** and **Ig**, respectively, were deprotonated, and their solubility in aqueous basic solutions was demonstrated. More recently the formation of reactive primary bromide **Ih** and its reaction with pyridine to form the corresponding pyridinium salt was reported.[21] It should be mentioned that verdazyls with the carbethoxy,[22] nitro[14] and 4-methoxycarbonylphenyl[23] substituents in the C(3) position were reported, but their transformations were not investigated.



I

a: $R^1 = R^3 = Ph$, $R^2 = C_6H_4\text{-}NH_2$, $X = H_2$
b: $R^1 = R^3 = Ph$, $R^2 = (CHOAc)_nCH_2OAc$, $X = H_2$
c: $R^1 = R^2 = R^3 = C_6H_4\text{-}4\text{-}SO_3H$, X = O
d: $R^1 = R^3 = Ph$, $R^2 = C_6H_4\text{-}4\text{-}COOH$, $X = H_2$
e: $R^1 = R^2 = Ph$, $R^3 = C_6H_4\text{-}4\text{-}COOH$, $X = H_2$
f: $R^1 = Ph$, $R^2 = R^3 = C_6H_4\text{-}4\text{-}COOH$, $X = H_2$
g: $R^1 = R^3 = i\text{-}Pr$, $R^2 = C_6H_4\text{-}OH$, X = O
h: $R^1 = R^3 = Ph$, $R^2 = C_6H_4\text{-}4\text{-}(CH_2)_8Br$, X = O

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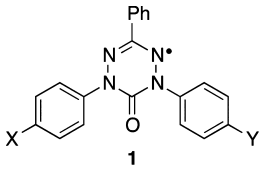
Majority of functional groups investigated to date are placed in the nodal position C(3) of the verdazyl skeleton, where they do not participate in spin delocalization. We are interested in functionalization of benzene rings attached at the positive spin density of the N(1) and N(5) positions, and reactivity of such groups in the context of construction of functional materials. In this report we focus on the 1,3,5-triaryl-6-oxoverdazyl substituted with typical functional groups, such as OH, NH_2, COOH, and halogen, and their transformations. For this purpose, we envisioned a series of radicals **1a**−**1g** containing the OH functionality, protected as OBn and OCOPh, NH_2 accessible from the NO_2 group, and also COOH and I groups (Figure 1). Further transformations of these groups should provide access to ether, ester, amide, or carbon−carbon coupling products, respectively.



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a: X= OBn; Y= OBn
b: X= OCOPh; Y= OCOPh
c: X= OBn; Y= OCOPh
d: X= NO_2; Y= OBn
e: X= NO_2; Y= I
f: X= NO_2; Y= COOH
g: X= OBn; Y= COOH

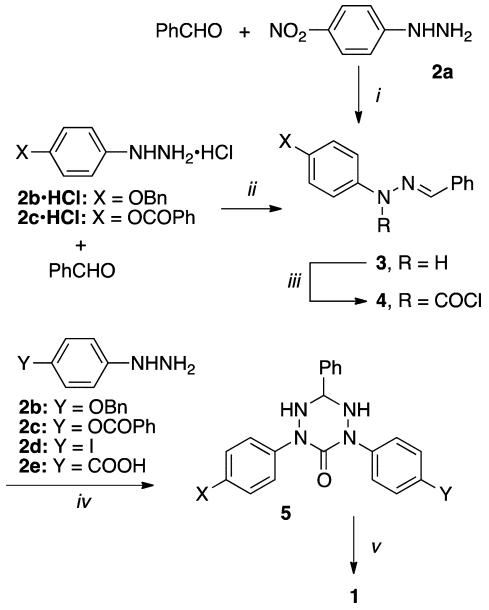
Figure 1. Target radicals for functional group transformation studies.

Here we report the preparation of radicals **1a**−**1e**, generation of the OH and NH_2 functionalities and investigation of their chemical transformations. We also characterize selected radicals **1** by spectroscopic methods and briefly investigate the effect of a substituent on the phenyl ring on electronic absorption and EPR spectra. Experimental results are discussed in the context of DFT calculations.

RESULTS AND DISCUSSION

Synthesis of Radicals 1. Radicals **1** were prepared according to the Milcent method[23] (Scheme 1) using substituted phenylhydrazines **2** and benzaldehyde. Thus, condensation of 4-nitrophenylhydrazine (**2a**) with benzaldehyde gave hydrazone **3a**, while hydrazones **3b** and **3c** were conveniently obtained directly from hydrochlorides of 4-benzyloxyphenylhydrazine (**2b·HCl**), and 4-benzoyloxyphenylhydrazine (**2c·HCl**), respectively. The resulting hydrazones **3** were reacted with triphosgene to give carbonyl chlorides **4**. Subsequent reactions of the chlorides with hydrazines **2b**−**2d** in ethanol in the presence of Et_3N gave tetrazines **5a**−**5e** in yields >70%. In preparation of **5a**−**5d** hydrazines **2b** and **2c** were generated in situ from the corresponding hydrochlorides by using additional equivalents of Et_3N. Tetrazines **5f** and **5g** were obtained in about 30% yield from **4a** and **4b**, respectively, in a similar way with an additional equivalent of Et_3N to neutralize the carboxyl group in 4-hydrazinobenzoic acid (**2e**). The observed lower yield for **5f** and **5g** than for **5a**−**5e** is presumably related to regioselectivity of N-acylation of the arylhydrazine by chloride **4**,[23] which is governed by relative nucleophilicity of the two nitrogen atoms. Also the choice of solvent may dictate the mode of aggregation of the two reactants (head-to-head or head-to-tail) and affect the regiochemistry of acylation.[10] Tetrazines **5a** and **5d** were purified by column chromatography using eluents containing small amounts of Et_3N to passivate the silica gel. The remaining tetrazines were purified by recrystallization or washing with solvents.

Scheme 1. Synthesis of Radicals 1[a]

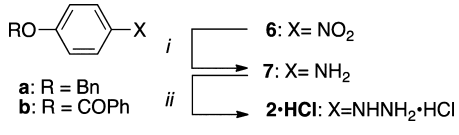


[a]Reagents and conditions: (i) 2 M H_2SO_4 rt, 3 h; (ii) EtOH, rt; (iii) $CO(CCl_3)_2$, py, CH_2Cl_2; (iv) Et_3N, EtOH, 60 °C, 3 h; (v) Method A: $K_3Fe(CN)_6$, 0.5 M Na_2CO_3, $[NBu_4]^+Br^-$ cat, CH_2Cl_2, 1−3 days; Method B: $NaIO_4$, $[NBu_4]^+Br^-$ cat, CH_2Cl_2/H_2O, 1−2 days.

Oxidation of tetrazines **5a**−**5e** with $K_3Fe(CN)_6$ or $NaIO_4$ gave the corresponding radicals **1a**−**1e** in moderate to very good yields. Tetrazine **5f** also underwent oxidation with $NaIO_4$ in the presence of aq Na_2CO_3, as evident from dark red color of the reaction mixture characteristic for **1**. The color changed to brown after 20 h, which indicated significant loss of the radical. Quenching of the reaction mixture after 2 h permitted isolation of a wine-red, unstable product, presumably radical **1f**. Similar irreproducible results were obtained when **5f** was oxidized with PbO_2 in hot acetic acid. Therefore, the preparation of **1f** and **1g** was not pursued further; instead, tetrazine **5g** was first converted to an ester before oxidation to the radical (vide infra).

Hydrazine hydrochlorides **2b·HCl** and **2c·HCl** were obtained from 4-benzyloxynitrobenzene[24] (**6b**) and 4-benzoyloxynitrobenzene[25] (**6c**), respectively, according to a general literature procedure[26] (Scheme 2). The nitro group was reduced either catalytically (H_2 and PtO_2) at 50 psi (**6b**) or by $SnCl_2·2H_2O$ in isopropanol (**6b** and **6c**) giving the corresponding anilines **7**. The former method is more efficient,

Scheme 2. Synthesis of Substituted Phenylhydrazines 2[a]



[a]Reagents and conditions: (i) H_2 50 psi, PtO_2, or $SnCl_2·2H_2O$ in *i*-PrOH; (ii) $NaNO_2$, HCl.

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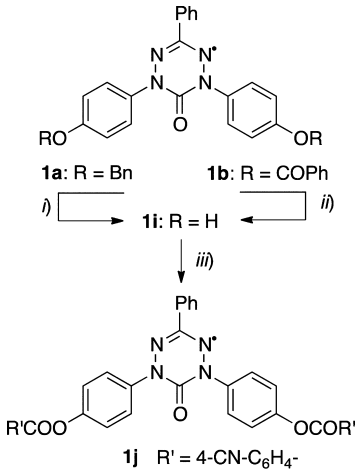
and **7b** was isolated in 86% yield, which compares to 70% yield obtained in the $SnCl_2$ method. The resulting anilines **7** were then diazotized with $NaNO_2$/HCl, and the diazonium salts were reduced with $SnCl_2{\cdot}2H_2O$ to give the corresponding hydrazines isolated in about 70% yield as hydrochlorides **2b·HCl** and **2c·HCl**.

Functional Group Transformations in Radicals 1. Deprotection of the phenolic functionality and formation of the diphenol **1i** was investigated by debenzylation of **1a** under reductive conditions (Scheme 3). Thus, reactions run in several

Scheme 3. Transformations of the OH Groups in 1a and 1b[a]



[a]Reagents and conditions: (i) H_2 50 psi, 10% Pd/C, EtOH/THF, rt; (ii) KOH (2 equiv), MeOH/CH_2Cl_2, rt; (iii) 4-CN-C_6H_4COCl, Et_3N, CH_2Cl_2, rt.

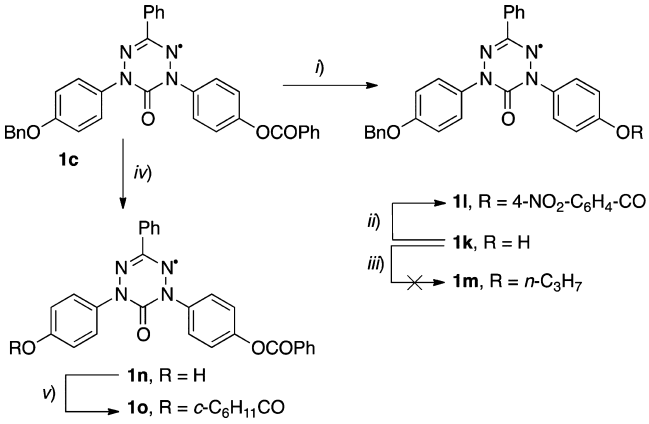
solvents under atmospheric pressure of H_2 and 10% Pd/C required several days for the starting material to be consumed and gave mainly decomposition products with only traces of the desired radical **1i**. A similar reaction conducted under 50 psi of H_2 in a EtOH/THF mixture was completed in 24 h, and bisphenol **1i** was isolated in 51% yield after aerial oxidation of the *leuco* form. As expected, in all cases the reaction proceeded stepwise, and the monodeprotected intermediate was observed on TLC as a colored spot of intermediate polarity between that for **1a** and **1i**.

An alternative route to **1i** involves basic hydrolysis of the bis-benzoate **1b**. Thus, treatment of radical **1b** with stoichiometric amounts of KOH in MeOH/CH_2Cl_2 at ambient temperature, followed by workup with a mild acid gave the desired diphenol **1i** in somewhat lower yields of about 40%. The product exhibits limited stability to storage and elevated temperature. Therefore, all solutions containing **1i** were kept at ambient temperature for minimum amounts of time, and the bis-phenol was quickly converted into ester **1j** (Scheme 3).

The benzyloxy and benzoyloxy substituents in radical **1c** can typically be removed under orthogonal conditions, and offer a potential access to unsymmetric derivatives of bis-phenol **1i**. Thus, the benzoate group in **1c** was removed under basic conditions (KOH in MeOH/CH_2Cl_2) giving phenol **1k** in 80% yield (Scheme 4). The phenol can be stored dry at low temperature for a limited time. Treatment of phenol **1k** with 4-nitrobenzoyl chloride gave ester **1l** in 82% yield.

Attempts to alkylate phenol **1k** with 1-iodopropane under basic conditions (K_2CO_3/DMF, rt) to form propyloxy derivative **1m** led to rapid decolorization of the solution,

Scheme 4. Transformations of the OH Groups in 1c[a]



[a]Reagents and conditions: (i) KOH (1 equiv), MeOH/CH_2Cl_2, rt; (ii) 4-NO_2-C_6H_4COCl, Et_3N, CH_2Cl_2, rt; (iii) NaH, MeCN, *n*-PrI; (iv) H_2 50 psi, 10% Pd/C, EtOH/THF, rt; (v) *c*-C_6H_{11}COCl, py, CH_2Cl_2, rt.

indicating loss of the radical. Investigation of the stability of the phenolate anion $\mathbf{1k}^-$ generated from **1k** with 1 equiv of KOH in MeOH/CH_2Cl_2 mixture demonstrated that it is moderately stable in the absence of air, and after 6 h only about 15% decomposition was observed by TLC. It appears that exclusion of light further enhances stability of the phenolate anion. In another attempt to prepare **1m**, phenol **1k** was treated with 1 equiv of KOH in MeOH/CH_2Cl_2 in the absence of air and light, followed by addition of 1 equiv of 1-iodopropane. No expected product **1m** was detected; instead, fast decoloration, within minutes, was observed. Also, treatment of a dark blue solution of anion $\mathbf{1k}^-$ (generated from **1k** with NaH in dry MeCN in the absence of light and air) with 1 equiv of *n*-PrI led to rapid change of color. TLC analysis of the reaction mixture revealed that the expected product **1m** could have formed in trace amounts.

The removal of the benzyl group in **1c** and formation of phenol **1n** was more difficult than in the case of **1a**, and full conversion of the starting **1c** took 3 days. The phenol **1n** was isolated in 85% yield and acylated with cyclohexanecarbonyl chloride to form ester **1o** in 86% yield (Scheme 4).

The transformation of the nitro group in 6-oxoverdazyls was demonstrated using radical **1d**. Thus, reduction of **1d** with H_2 at 50 psi in the presence of PtO_2 was completed in 2 h and after exposure to air yielded a mixture of *leuco* **8** and radical **1p**, resulting from oxidation of **8**, in 82% yield. An attempt to oxidize the *leuco* derivative **8** with $K_3Fe(CN)_6$ to **1p** or to purify on silica gel led to extensive decomposition, as evident from TLC analysis.

The crude mixture of **8** and **1p** was quickly reacted with benzoyl chloride in the presence of a base, followed by treatment with $K_3Fe(CN)_6$ to furnish pure amide **1q** isolated by chromatography in 55% overall yield based on **1d** (Scheme 5).

The subsequent removal of the benzyl group in **1q** was accomplished using a catalytic hydrogenation reaction in the presence of Pd/C at 50 psi in THF. The resulting crude phenol **1r** was obtained in 57% yield after oxidation of the *leuco* form **9** with air and passing through a silica gel plug. A similar deprotection reaction under atmospheric pressure took several days for the starting material to be consumed and gave only a low yield of **1r** due to extensive decomposition. The crude phenol was treated with PhCOCl, and the resulting ester **1s** was

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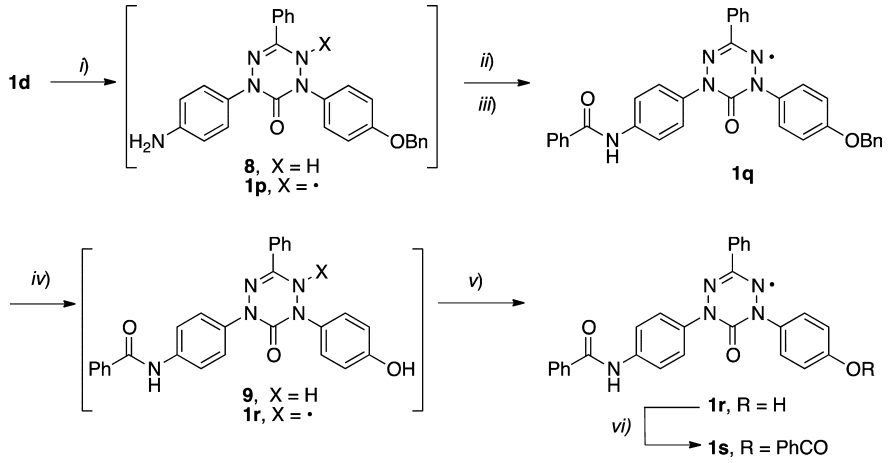
Scheme 5. Transformations of the OH and NO_2 Groups in 1d[a]

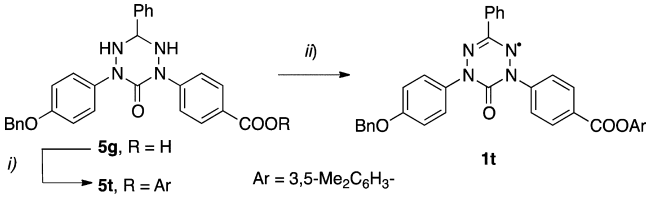


[a]Reagents and conditions: (i) H_2 50 psi, PtO_2 cat, EtOH; (ii) PhCOCl, Et_3N, CH_2Cl_2; (iii) $K_3Fe(CN)_6$, CH_2Cl_2, 0.5 M Na_2CO_3, $[NBu_4]^+Br^-$ cat; (iv) H_2 50 psi, Pd/C, EtOH/THF; (v) air; (vi) PhCOCl, Et_3N, CH_2Cl_2.

isolated in 42% overall yield based on **1q**. Thus, amide ester **1s** was obtained in 6 steps and 23% overall yield based on radical **1d**.

Since 6-oxoverdazyls containing a carboxyl group, such as **1f**, appear to be unstable (vide supra), tetrazine **5g** was first converted into ester **5t** and then oxidized to the corresponding radical **1t** in 56% overall yield (Scheme 6). The esterification of

Scheme 6. Synthesis of Radical 1t[a]

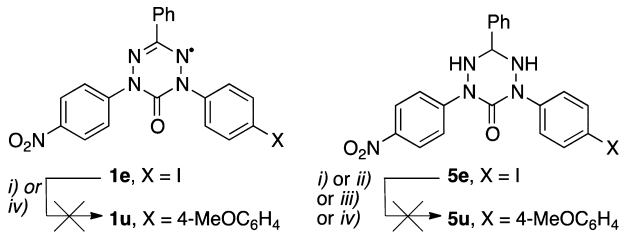


[a]Reagents and conditions: (i) 3,5-$Me_2C_6H_3OH$, DCC, DMAP cat, DMF; (ii) $K_3Fe(CN)_6$, CH_2Cl_2, 0.5 M Na_2CO_3, $[NBu_4]^+Br^-$ cat.

5g was accomplished using 4.5× excess 3,5-dimethylphenol in the presence of DCC[27] and 20 mol % of DMAP. Under these conditions tetrazine **5t** was isolated in 56% after 3 days. Fewer equivalents of the phenol led to lower yield of **5t** (15%), while significant amounts of a byproduct, presumably *N*-acylated *N*,*N*′-dicyclohexylurea, was formed.[28]

The synthetic utility of the iodine in iodophenyl radical **1e** and also in tetrazine **5e** was investigated in Suzuki[29−31] and Negishi-type[32,33] C−C coupling reactions with organometallic derivatives of anisole (Scheme 7). Reactions of tetrazine **5e** under Suzuki conditions with or without ligand gave no reaction at ambient temperature overnight, and a complex mixture, presumably decomposition products, was formed after heating at about 55 °C, according to TLC analysis. Attempted Suzuki C−C coupling reactions of radical **1e** using the Molander or Suzuki conditions gave either no reaction or a complex mixture of products and was not investigated further. Sonogashira reaction of **5e** also did not yield the expected product. These results are in sharp contrast to those obtained for similar reactions of iodo derivatives of benzo[1,2,4]triazinyl, which undergo smooth Pd-catalyzed Suzuki,[34,35] Stille,[34] and

Scheme 7. Attempted C−C Coupling Reactions in 1e and 5e[a]



[a]Reagents and conditions: (i) $[MeOC_6H_4BF_3]^-K^+$, Cs_2CO_3, $PdCl_2(PPh_3)_2$, toluene/H_2O 4:1; (ii) $MeOC_6H_4B(OH)_2$, $Pd(OAc)_2$ 5% mol, $[Chx_3PH]^+$ $[BF_4]^-$, K_2CO_3, THF, 6 h rt, 50 °C 16 h; (iii) $MeOC_6H_4B(OH)_2$, $PdCl_2$ 10% mol, K_2CO_3, EtOH/THF/H_2O, 1:1:1, 12 h rt, 60 °C 12 h; (iv) $MeOC_6H_4ZnCl$/LiCl, Pd_2dba_3 5% mol, $[Chx_3PH]^+$ $[BF_4]^-$, THF.

Sonogashira[35] reactions, and indicate a more fragile nature of the verdazyl when compared to benzo[1,2,4]triazinyl.

Electronic Absorption Spectroscopy. All investigated radicals **1** are brown-red in solutions. UV−vis spectroscopic analysis of four selected radicals, **1a**, **1c**, **1d** and **1t**, revealed similar medium intensity absorption band at about 350 nm and broad low intensity bands in the visible range with a well-defined maximum at about 570 nm, as shown for **1t** in Figure 2.

TD-DFT computational analysis of three model derivatives **1v**−**1x** revealed that the lowest energy excitation is largely due to the *β*-HOMO−*β*-LUMO transition with a small contribution from the *α*-HOMO−*α*-LUMO transition, and it is calculated at 554 nm (**1v**, X = OMe), 558 nm (**1w**, X = COOMe) and 573 nm (**1x**, X = NO_2) with the oscillator strength of about $f = 0.10$. The excitation due mainly to the *α*-HOMO−*α*-LUMO transition is calculated at 456 nm (**1v**, X = OMe), 449 and 428 nm (**1w**, X = COOMe), and 498 and 485 nm (**1x**, X = NO_2). These transitions are shifted to lower energies in the phenolate anion **1y**. Thus, for the anion **1y** the lowest energy excitation is calculated at 870 nm ($f = 0.26$) and involves the *β*-HOMO−*β*-LUMO transition, while the *α*-HOMO−*α*-LUMO transition is calculated at 634 nm ($f = 0.04$).

The distribution of density of orbitals involved in the low energy excitations in two derivatives **1v** and **1x** is different

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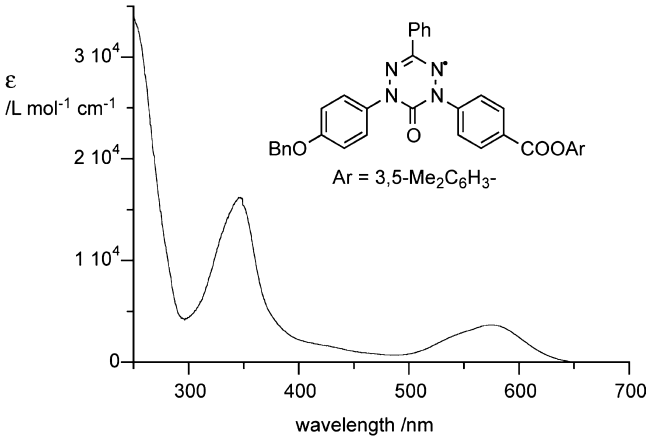
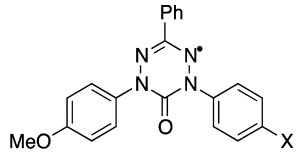


Figure 2. Electronic absorption spectrum for **1t** (dioxane).



1v, X = OMe
1w, X = NO_2
1x, X = COOMe
1y, X = O^-
1z, X = NH_2

because of the different character of the substituent X. In the dimethoxy derivative **1v** the β-HOMO is delocalized over all four rings, while the β-LUMO is largely localized on the nitrogen atoms. The α-HOMO is also mostly concentrated on the nitrogen atoms, while the α-LUMO is localized on the most electron-poor benzene ring at the C(3) position. The replacement of one OMe group in **1v** with the NO_2 group in **1w** changes electron distribution in the molecule, and both HOMOs involve the methoxyphenyl ring, while both LUMOs involve the nitrophenyl group (Figure 3).

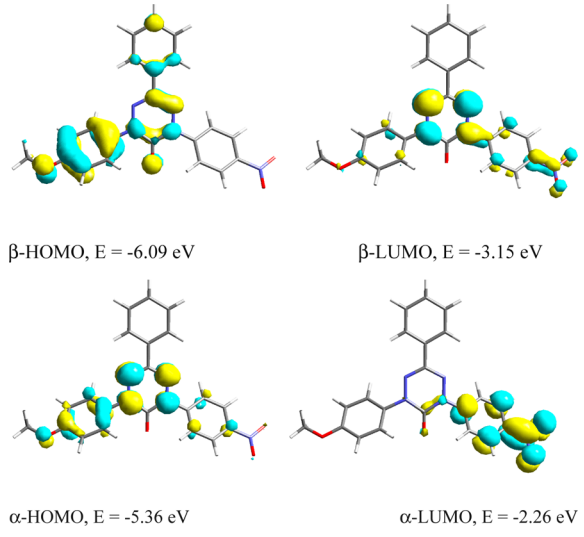


Figure 3. B3LYP/6-31G(2d,p)-derived contours and energies of frontier molecular orbitals for **1w**.

EPR Spectroscopy. EPR spectrum of the symmetric dibenzyloxy derivative **1a** exhibits 9 principal lines due to coupling to four quadrupolar ^{14}N nuclei broadened by minor coupling to ^{1}H's of the benzene rings (Figure 4, top). The EPR spectrum of **1c** is similar to that of **1a**, while further electronic dissymmetrization of radical **1a** has a marked effect on EPR spectra. Thus, replacement of one of the BnO groups in **1a** with

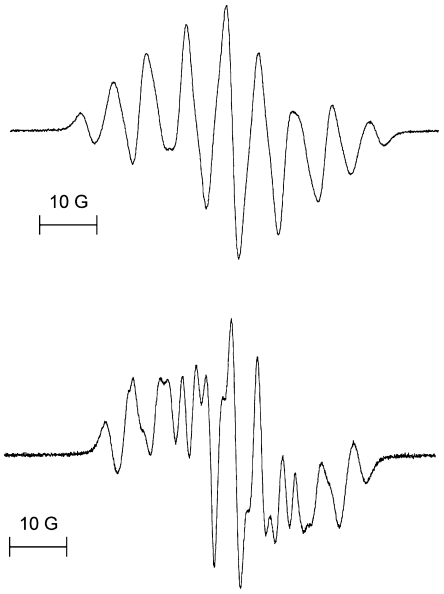


Figure 4. EPR spectra of **1a** (upper) and **1t** (lower) recorded in benzene.

an electron-withdrawing COOAr (**1t**) or NO_2 group (**1d**) significantly alters the spin population on the nitrogen atoms and results in a complex pattern of the EPR spectra (Figure 4, bottom).

Simulation of the experimental spectra aided with DFT calculations demonstrates that the highest *hfcc* values, about 6.3 G, are associated with the N(2) and N(4) atoms in all four radicals, while the values for the N(1) and N(5) atoms vary between 4.0 and 4.7 G (Table 1). Analysis of the results in Table 1 shows that the $a_{N(5)}$ values decrease with increasing electron-withdrawing nature of the substituent X and roughly correlate with the σ_p parameter of the substituent. Values for a_H are smaller than 1 G and the largest, in range of 0.6−0.8 G, can be ascribed to the *ortho* and *meta* positions of the benzene rings at the N(1) and N(5) positions. These *hfcc* values are consistent with the calculated total spin density maps (Figure 5a), which show, in agreement with general trends in the verdazyl system, highest spin concentration on the tetrazine fragment with modest delocalization onto benzene rings in the N(1) and N(5) positions. As expected, very little spin density is delocalized on the phenyl group located at the nodal C(3) position.

The relative a_N values and consequently spin densities on the nitrogen atoms in **1** are consistent with the general resonance structures for the verdazyl system. The nonpolar structures, those that give spin densities on atoms N(2) and N(4), are more favorable than the dipolar structures, responsible for spin density in positions N(1) and N(5) (Figure 6), which results in $a_{N(2,4)} > a_{N(1,5)}$. The dipolar structures are further disfavored by electron-withdrawing groups in the N(1) and N(5) positions, which include phenyl substituted with an electron-withdrawing group X. Conversely, electron-donating groups stabilize the dipolar resonance structures and expand the spin delocalization. For instance, the hfcc $a_{N(5)}$ calculated for the amino derivative **1z** is greater than that for the methoxy analogue **1v** (3.63 vs 3.53 G), and, as expected, the spin density on the NH_2 group's nitrogen atom in **1z** is greater than that for the NO_2 group in **1w** (+0.013 vs −0.002). An extreme example of an electron-donating group at the N(5) position is the phenoxide anion in

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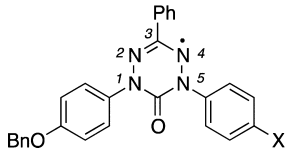
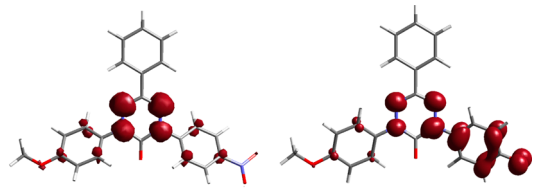
Table 1. Hyperfine Coupling Constants (G) for Selected Radicals



compound	$a_{N(1)}$[a]	$a_{N(2)}$[a]	$a_{N(4)}$[a]	$a_{N(5)}$[a]	a_H	a_H	a_H	a_H	a_H	a_H	a_H	g
1a (X = BnO)	4.69	6.26	6.26	4.69	0.81	0.52	0.36	0.30	0.03	–	–	2.0039
1c (X = OCOPh)	4.57	6.33	6.33	4.57	0.86	0.75	0.52	0.48	0.35	0.32	0.14	2.0042
1d (X = NO_2)	4.60	6.32	6.32	4.00	0.83	0.78	0.55	0.46	0.43	0.40	0.08	2.0037
1t (X = COOAr)	4.59	6.40	6.40	4.22	0.81	0.61	0.59	0.57	0.51	0.35	0.10	2.0039

[a]Assigned on the basis of B3LYP/EPR-II//B3LYP/6-31G(2d,p) results.



a) b)

Figure 5. Total spin density calculated for (a) **1w** and (b) **1y**.

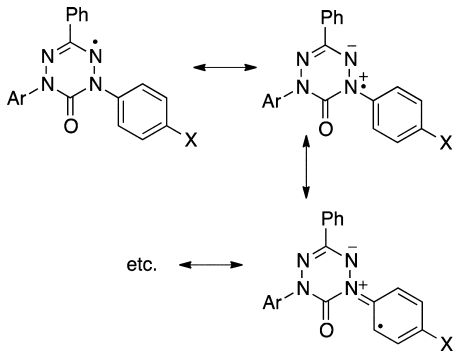


Figure 6. Selected resonance structures for **1**.

radical **1y**, in which significant spin density (+0.189) is localized on the phenolic oxygen atom, according to the DFT calculations (Figure 5b). Such significant spin concentration on the phenoxide oxygen and amine nitrogen atoms results in low stability of anion $\mathbf{1k}^-$ and amine **1p**, which is observed experimentally. Also, large spin concentration on the phenoxide coincides with delocalization of the negative charge in the tetrazine ring and increased nucleophilicity of the nitrogen atoms (Figure 7), which may be the reason for failed attempts to prepare **1m** (Scheme 4).

CONCLUSION

Substituted 1,3,5-triaryl-6-oxoverdazyls **1a**–**1e** were readily prepared in 4 steps using the Milcent method in overall yields of 30–55%. The last step, oxidation of the tetrazines to verdazyls, can conveniently be accomplished using mild oxidants such as $K_3Fe(CN)_6$ or $NaIO_4$ under phase transfer conditions. However, oxidation of tetrazines containing the carboxylic group was highly problematic and unreliable. The latter method of oxidation is preferred for further magnetochemical studies.

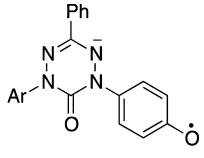


Figure 7. A resonance structure for **1y** with spin on the phenoxide oxygen atom.

Functional groups in radicals **1a**–**1e**, which include OCH_2Ph, OCOPh, NO_2, and I, were placed in the *para* positions of the benzene ring substituted at the high positive spin density positions, N(1) and N(5), of the verdazyl ring. A stable radical with the COOH group (**1f**) could not be obtained by oxidation of the corresponding tetrazine **5f**; instead, the COOH group was converted to an ester at the tetrazine stage prior to oxidation to **1**.

During functional group transformations, we have demonstrated that 6-oxoverdazyl skeleton is stable under mild Pd- or Pt-catalyzed hydrogenation, basic hydrolysis, and acylation conditions used for deprotection of the OH functionality, reduction of the NO_2 group, and acylation of the OH and NH_2 groups, respectively. During catalytic hydrogenation, the 6-oxoverdazyl undergoes 1 e^- reduction to the colorless *lecuo* form, which is reoxidized to the radical upon exposure to atmospheric oxygen. Attempts to alkylate the phenol functionality under basic conditions led to decomposition of the radical. Also attempts at C–C coupling reactions (Suzuki, Negishi, Sonogashira) using iodophenyl functionality in tetrazine **5e** or in radical **1e** were unsuccessful. Radicals containing the OH and NH_2 groups exhibit limited stability to light and oxygen due to their participation in spin delocalization.

The presented results expand the range of chemical transformations in the presence of the verdazyl radical, provide important intermediates, such as diphenol **1i**, and open up possibilities for incorporation of the verdazyl system into more complex molecular structures by ester or amide bond formation at the positive spin density position. Further work and development of C–C coupling methods for the verdazyls are necessary for more synthetic versatility and synthesis of materials with expanded spin delocalization.

EXPERIMENTAL SECTION

Computational Details. Quantum-mechanical calculations were carried out at the UB3LYP/6-31G(2d,p) level of theory using Gaussian 09 suite of programs.[36] Geometry optimizations were undertaken using tight convergence limits and without symmetry constraints. No conformational search for **1v**–**1z** was attempted. Electronic excitation energies for **1v**–**1x** in a vacuum were obtained at

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the UB3LYP/6-31G(2d,p) level using the time-dependent DFT method[37] supplied in the Gaussian package.

General Information. NMR spectra were obtained at 400 or 600 MHz (^{1}H) and 150 MHz (^{13}C) field in $CDCl_3$ and referenced to the solvent, unless otherwise specified. IR spectra were taken in KBr pallets. UV−vis spectra were recorded in spectroscopic grade dioxane at concentration of 1−10 × 10^{-5} M. Extinction coefficients were obtained by fitting the maximum absorbance at about 350 nm against concentration in agreement with Beer's law. HRMS measurements were performed using double focusing analyzed (BE geometry), unless specified otherwise.

X-band ESR spectra were taken typically using modulation amplitude 0.20 G and spectral width of 100 G. Solutions in distilled benzene were degassed by three freeze/pump/thaw cycles. The *g* values for radicals were obtained from the experimental parameters using WinEPR Sinfonia 1.26 program. Simulation of the EPR spectra was done with the PEST program (EPR-WinSim.2002 version 0.98 for Windows; available at http://www.niehs.nih.gov/research/resources/software/tox-pharm/tools/index.cfm) using results of B3LYP/EPR-II//B3LYP/6-31G(2d,p) for initial input. The resulting *hfcc* values were perturbed until the global minimum for the fit was achieved. Spectra used for simulation were generated by reflection of the left half of each spectrum.

6-Oxoverdazyls 1a−1e. General Procedure. *Method A.* A mixture of tetrazine **5** (0.5 mmol), $K_3Fe(CN)_6$ (3 mmol), 0.5 M Na_2CO_3 (10 mL), $[NBu_4]^+Br^-$ or $[NEt_4]^+Br^-$ (10−20 mol %) in CH_2Cl_2 (10 mL) was vigorously stirred at rt for 1−2 days until tetrazine **5** is no longer visible on TLC. The deeply colored CH_2Cl_2 layer was separated and dried (Na_2SO_4), solvent was evaporated, and the crude product was purified by column chromatography (SiO_2, hexane/CH_2Cl_2) followed by recrystallization.

Method B. A mixture of tetrazine **5** (0.216 mmol), CH_2Cl_2 (5 mL), H_2O (5 mL), $NaIO_4$ (0.238 mmol), and $[NBu_4]^+Br^-$ or $[NEt_4]^+Br^-$ (10−20 mol %) was stirred overnight at rt. The organic layer was separated, and radical **1** was isolated and purified as in Method A.

*1,5-bis(4-Benzyloxyphenyl)-3-phenyl-6-oxoverdazyl (**1a**).* Method A, yield 58%. Deep-violet crystals: mp 164−165 °C (EtOAc); IR (KBr) ν 1699 (C═O), 1505, 1246 (C−O) cm^{-1}; UV−vis (dioxane) λ_{max} (log ε) 337 (4.10), 435 (3.30), 453 (3.30), 550 sh (3.54), 574 (3.61) nm; ESI-MS *m*/*z* 559 (100, $[M + H_3O]^+$); EI, *m*/*z* 539(M, 12), 449(8), 91(100); EI-HRMS, calcd. for $C_{34}H_{27}N_4O_3$ $[M]^+$ *m*/*z* 539.2083, found *m*/*z* 539.2098. Anal. Calcd for $C_{34}H_{27}N_4O_3$: C, 75.68; H, 5.04; N, 10.38. Found: C, 75.73; H, 5.12; N, 10.23.

*1,5-bis(4-Benzoyloxyphenyl)-3-phenyl-6-oxoverdazyl (**1b**).* Method A, yield 91%. Deep-violet crystals: mp 209−210 °C (EtOAc); IR (KBr) ν 1743 (C═O), 1693 (C═O), 1263 (C−O), 1208 (C−O) cm^{-1}; EI-HRMS, calcd. for $C_{34}H_{23}N_4O_5$ $[M]^+$ *m*/*z* 567.1668, found *m*/*z* 567.1660. Anal. Calcd for $C_{34}H_{23}N_4O_5$: C, 71.95; H, 4.08; N, 9.87. Found: C, 72.03; H, 4.12; N, 9.91.

*1-(4-Benzoyloxyphenyl)-5-(4-benzyloxyphenyl)-3-phenyl-6-oxoverdazyl (**1c**).* Method A, yield 78%. Violet crystals: mp 217−218 °C (EtOAc); IR (KBr) 1732 (C═O), 1698 (C═O), 1504, 1263 (C−O), 1204 (C−O) cm^{-1}; UV−vis (dioxane) λ_{max} (log ε) 330 (4.11), 426 (3.22), 450 sh (3.19), 548 sh (3.50), 570 (3.56) nm; EI-HRMS, calcd for $C_{34}H_{25}N_4O_4$ $[M]^+$ *m*/*z* 553.1876, found *m*/*z* 553.1890. Anal. Calcd for $C_{34}H_{25}N_4O_4$: C, 73.77; H, 4.55; N, 10.12. Found: C, 73.49; H, 4.81; N, 9.95.

*1-(4-Benzyloxyphenyl)-5-(4-nitrophenyl)-3-phenyl-6-oxoverdazyl (**1d**).* Method A, yield 86%; Method B, yield 96%. Dark purple-brown crystals: mp 167−169 °C (MeCN); UV−vis (dioxane) λ_{max} (log ε) 359 (3.97), 475 (3.49), 579 (3.53). Anal. Calcd for $C_{27}H_{20}N_5O_4$: C, 67.77; H, 4.21; N, 14.64. Found: C, 67.88; H, 4.28; N, 14.72.

*1-(4-Iodophenyl)-5-(4-nitrophenyl)-3-phenyl-6-oxoverdazyl (**1e**).* Method A; yield 85%. Dark purple-brown crystals: mp >260 °C (EtOAc). Anal. Calcd for $C_{20}H_{13}IN_5O_3$: C, 48.21; H, 2.63; N, 14.06. Found: C, 48.07; H, 2.63; N, 13.93.

*Attempted Preparation of 1-(4-Carboxyphenyl)-5-(4-nitrophenyl)-3-phenyl-6-oxoverdazyl (**1f**).* Tetrazine **5f** (100 mg) was oxidized according to Method B in the presence of stoichiometric amounts of Na_2CO_3. After 2 h TLC analysis demonstrated nearly complete conversion of **5f**. The red-brown reaction mixture was carefully acidified with 1% HCl, the CH_2Cl_2 layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were dried (Na_2SO_4), and solvent was evaporated. The residue (30 mg) was separated on a short silica gel column (CH_2Cl_2, CH_2Cl_2/MeCN 5:1) to give 4 mg of a red-wine solid mixture of 3 products with similar polarity and containing the expected radical **1f**: ESI-HRMS-TOF, calcd. for $C_{21}H_{14}N_5O_5$ $[M]^+$ *m*/*z* 416.1000, found *m*/*z* 416.0995.

Oxidation of **5f** with PbO_2 in hot AcOH (10 min), followed by usual workup and chromatographic separation gave **1f** in 12% yield as a red-wine solid, which slowly decolorized.

*1-(4-Benzyloxyphenyl)-5-(4-(3,5-dimethylphenyloxycarbonyl)-phenyl)-3-phenyl-6-oxoverdazyl (**1t**).* Method A, yield 97%. Black-purple crystals: mp 166−167 °C (EtOAc/EtOH); IR (KBr) ν 1736 (C═O), 1698 (C═O), 1504, 1259 (C−O) cm^{-1}; UV−vis (dioxane) λ_{max} (log ε) 346 (4.21), 425 sh (3.20), 575 (3.56) nm; EI-HRMS, calcd. for $C_{36}H_{29}N_4O_4$ $[M]^+$ *m*/*z* 581.2189, found *m*/*z* 581.2194. Anal. Calcd for $C_{36}H_{29}N_4O_4$: C, 74.34; H, 5.03; N, 9.63. Found: C, 74.45; H, 5.11; N, 9.46.

6-Oxoverdazyls 1i−1s through Functional Groups Transformations. *1,5-bis(4-Hydroxyphenyl)-3-phenyl-6-oxoverdazyl (**1i**). Method A.* To a suspension of 10% Pd/C (87 mg) in EtOH (30 mL) a solution of bis-benzyloxy verdazyl **1a** (324 mg, 0.60 mmol) in THF (23 mL) was added, and the resulting mixture was hydrogenated at 50 psi for 24 h. The mixture was oxidized with air for ca. 20 min (TLC monitoring, CH_2Cl_2/EtOAc, 10:1) and filtered through Celite, solvents were removed under reduced pressure (*cold bath*!), and the crude mixture was purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc, 8:1) to afford **1i** (110 mg, 51% yield) as black-violet crystals.

Method B. To a solution of radical **1b** (177 mg, 0.312 mmol) in dry CH_2Cl_2 (20 mL), a solution of KOH in MeOH (0.086 M, 7.28 mL, 0.624 mmol) was added dropwise under vigorous stirring at rt, and the reaction progress was monitored on TLC (SiO_2, CH_2Cl_2/EtOAc 20:1). After neither starting material nor intermediate monophenol radical could be detected (ca. 1 h), brine (40 mL) followed by EtOAc were added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 15 mL), combined organics were dried ($MgSO_4$) and filtered, and solvents were removed under reduced pressure (*cold bath*!). Resulting residue was washed with small portions of CH_2Cl_2 (ca. 3 × 5 mL) to yield crude radical **1i** (44 mg, 39% yield) as a black solid: mp 202−203 °C; IR (KBr) ν 3440 (O−H), 1674 (C═O), 1511, 1218 (C−O) cm^{-1}. Anal. Calcd for $C_{20}H_{15}N_4O_3$: C, 66.85; H, 4.21; N, 15.59. Calcd for $C_{20}H_{15}N_4O_3 \cdot 1/4H_2O$: C, 66.02; H, 4.29; N, 15.40. Found: C, 66.01; H, 4.02; N, 15.03.

*1,5-bis(4-(4-Cyanobenzoyloxy)phenyl)-3-phenyl-6-oxoverdazyl (**1j**).* To a solution of diphenol radical **1i** (35 mg, 0.10 mmol) in a mixture of dry CH_2Cl_2 and Et_3N (1:1, 4.0 mL), a solution of *p*-cyanobenzoyl chloride (40 mg, 0.24 mmol) in CH_2Cl_2 (3 mL) was added dropwise under vigorous stirring at rt. After 10 min the reaction mixture was diluted with CH_2Cl_2 (15 mL), and the organic layer was washed with H_2O (2 × 10 mL). The organic layer was dried ($MgSO_4$), and the solvents were removed. Crude product was triturated with acetone, filtered, and washed with 3 portions of acetone to give the diester **1j** (49 mg, 82% yield) as a wine-red solid: mp 291−293 °C (EtOAc); IR (KBr) ν 2232 (CN), 1735 (C═O), 1695 (C═O), 1499, 1263, and 1200 (C−O) cm^{-1}. Anal. Calcd for $C_{36}H_{21}N_6O_5$: C, 70.01; H, 3.43; N, 13.61. Found: C, 69.79; H, 3.38; N, 13.64.

*1-(4-Benzyloxyphenyl)-5-(4-hydroxyphenyl)-3-phenyl-6-oxoverdazyl (**1k**).* Radical **1c** (0.11 g, 0.20 mmol) was dissolved in a mixture of CH_2Cl_2 (10 mL) and MeOH (3 mL), and a solution of KOH in MeOH (2.4 mL, 0.0857 M, 0.2 mmol KOH) was added dropwise under vigorous stirring at rt. The mixture was stirred at rt until all starting **1c** was consumed (about 1 h), diluted with CH_2Cl_2 (10 mL), washed with water (3 × 3 mL), and dried ($MgSO_4$). The solvent was removed to leave 0.080 g (89% yield) of crude solid product that was recrystallized (EtOAc) to give purple microcrystals: mp 224−226 °C; IR (KBr) ν 3420 (H−O), 1694 (C═O), 1511, 1246 (C−O) cm^{-1}.

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Anal. Calcd for $C_{27}H_{21}N_4O_3$: C, 72.15; H, 4.71; N, 12.46. Found: C, 72.05; H, 4.82; N, 12.18.

*1-(4-Benzyloxyphenyl)-5-(4-(4-nitrobenzoyloxy)phenyl)-3-phenyl-6-oxoverdazyl (**1l**).* To a solution of monophenol verdazyl **1k** (45 mg, 0.10 mmol) in CH_2Cl_2 (7.5 mL), Et_3N (33 mg, 32.7 mmol, 45 μL) was added followed by a solution of *p*-nitrobenzoyl chloride (17 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL). After ca. 10 min resulting mixture was washed with H_2O (3 × 5 mL), dried ($MgSO_4$), and filtered, and solvents were removed to yield crude verdazyl **1l** (49 mg, 82% yield). Analytically pure sample was obtained by recrystallization from hot EtOAc: mp 230−231 °C; IR (KBr) ν 1740 (C═O), 1687 (C═O), 1529, 1501, 1200 (C−O) cm^{-1}. Anal. Calcd for $C_{34}H_{24}N_5O_6$: C, 68.22; H, 4.04; N, 11.70. Found: C, 68.09; H, 4.25; N, 11.34.

*1-(4-Benzoyloxyphenyl)-5-(4-hydroxyphenyl)-3-phenyl-6-oxoverdazyl (**1n**).* The benzyl group in radical **1c** was removed under hydrogenation conditions in the presence of 10% Pd/C (54 h) as described for preparation of **1i** by debenzylation of **1a**. Crude hydroxyphenyl radical **1n** was purified by chromatography (SiO_2, CH_2Cl_2/EtOAc 20:1) and obtained in 85% yield as a deep violet solid: mp 163−143 °C (dec); HRMS-TOF, calcd for $C_{27}H_{19}N_4O_4$ $[M + H]^+$ *m*/*z* 463.1401, found *m*/*z* 463.1415.

*1-(4-Benzoyloxyphenyl)-5-(4-(cyclohexylcarbonyloxy)phenyl)-3-phenyl-6-oxoverdazyl (**1o**).* Hydroxyphenyl radical **1n** (71.0 mg, 0.15 mmol) was esterified with cyclohexanecarbonyl chloride (26.4 mg, 24 μL, 0.18 mmol) in CH_2Cl_2 in the presence of pyridine (37 mg, 35 μL, 0.42 mmol) as described for the preparation of **1j**. Crude ester was purified by chromatography (SiO_2, CH_2Cl_2) to give 76 mg (86% yield, mp 205−207 °C) of **1o** as pink-violet solid, which was further purified by recrystallization from EtOAc: mp 205−206 °C; IR (neat) ν 1741 (C═O), 1699 (C═O), 1500, 1261, and 1202 (C−O) cm^{-1}. Anal. Calcd for $C_{34}H_{29}N_4O_5$: C, 71.19; H, 5.10; N, 9.77. Found: C, 71.15; H, 4.79; N, 9.72.

*1-(4-Benzyloxyphenyl)-5-(4-benzamidophenyl)-3-phenyl-6-oxoverdazyl (**1q**).* A suspension of PtO_2 (25 mg, 0.1 mmol) in EtOH (150 mL) was hydrogenated in a hydrogenator for 15 min at 50 psi after being purged from oxygen three times. A solution of crude **1d** (522 mg, 1.1 mmol) in THF (35 mL) was added and hydrogenated with H_2 for 2 h until starting material disappeared. The reaction was then exposed to air. A color change from colorless to dark purple was observed indicating *leuco* to verdazyl transformation. The mixture was passed through Celite, and solvents were evaporated to give 400 mg (82% yield) of dark blue-purple crude product partially oxidized to radical **1p** and partially in a form of *leuco* **8**: HRMS-TOF, calcd for $C_{27}H_{22}N_5O_2$ $[M + H]^+$ *m*/*z* 448.1768, found *m*/*z* 448.1770.

To a crude mixture of **8** and **1p** (470 mg, 1.0 mmol) in CH_2Cl_2 (15 mL) was added benzoyl chloride (1.0 mmol) and Et_3N (01.2 mmol), and a mixture was stirred for 2 h at rt. The mixture was washed with 5% HCl and extracted (CH_2Cl_2), organic layers were dried (Na_2SO_4), and solvent was evaporated. A crude product was oxidized (Method A) and purified by column chromatography (SiO_2, CH_2Cl_2) to give 400 mg (67% yield) of amide **1q**. Black purple crystals: mp 233−234 °C dec (EtOH then MeCN); HRMS, calcd for $C_{34}H_{27}N_5O_3$ $[M + H]^+$ *m*/*z* 553.2108, found *m*/*z* 553.2101. Anal. Calcd for $C_{34}H_{26}N_5O_3$: C, 73.90; H, 4.74; N, 12.67. Found: C, 73.15; H, 4.77; N, 12.45.

*1-(4-Benzoyloxyphenyl)-5-(4-benzamidophenyl)-3-phenyl-6-oxoverdazyl (**1s**).* To a solution of 10% Pd/C (29 mg) in 10 mL of EtOH was added a solution of **1q** (103 mg. 0.19 mmol) in 7.5 mL of THF in hydrogenator flask. The mixture was purged from oxygen three times and was then hydrogenated with H_2 at 50 psi for 24 h. An equal portion of 10% Pd/C was then added to the mixture, which was subsequently repurged three times, and hydrogenation was continued for another 24 h. The mixture was oxidized with air, solvents were evaporated, and the residue was passed through silica gel (CH_2Cl_2/EtOAc, 10:1) to give phenol **1r** (58 mg, 57% yield) as a deep purple solid: mp 104 °C, dec; HRMS-TOF, calcd for $C_{27}H_{24}N_5O_3$ $[M + H]^+$ *m*/*z* 466.1874, found *m*/*z* 466.1884.

To a crude mixture of **1r** (75 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) was added benzoyl chloride (0.13 mmol) and Et_3N (0.15 mmol), and a mixture was stirred for 2 h at rt. The mixture was washed with 5% HCl and extracted (CH_2Cl_2), organic layers were dried (Na_2SO_4), solvent was evaporated, and the crude product was purified by column chromatography (SiO_2, CH_2Cl_2) to give 60 mg (74% of yield) of ester **1s** as dark purple crystals, which were recrystallized from MeCN, followed by EtOAc: mp 265 °C (dec). Anal. Calcd for $C_{34}H_{24}N_5O_4$: C, 72.07; H, 4.27; N, 12.36. Found: C, 71.78; H, 4.41; N, 12.47.

*4-Benzoyloxyphenylhydrazine hydrochloride (**2c·HCl**).* 4-Benzoyloxyaniline[25] (**7b**, 12.50 g, 58.6 mmol) was suspended in H_2O (30 mL), and conc. hydrochloric acid (30 mL) was added. The mixture was cooled to −5 °C, and a solution of $NaNO_2$ (4.10 g, 59.4 mmol) in H_2O (8 mL) was added dropwise. The mixture was stirred at −5 °C for 1 h, $SnCl_2·2H_2O$ (35.0 g, 0.155 mol) in conc. hydrochloric acid (90 mL) was slowly added, and the resulting mixture was stirred for 3 h. The resulting precipitate was filtered, washed with diluted hydrochloric acid, dried, and recrystallized from hot aqueous ethanol to give analytically pure **2c·HCl** (8.70 g, 56% yield) as colorless crystals: mp 215−218 °C (EtOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.08 (d, *J* = 8.9 Hz, 2H), 7.23 (d, *J* = 8.9 Hz, 2H), 7.59−7.65 (m, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 8.13 (d, *J* = 7.1 Hz, 2H), 8.33 (br s, 1H), 10.25 (br s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 115.5 (CH), 122.3 (CH), 128.9 (CH), 129.0, 129.7 (CH), 133.9 (CH), 143.4, 145.0, 164.8 (C═O); IR (KBr) ν 3450−3220 (N−H), 1735 (C═O), 1284 (C−O) cm^{-1}. Anal. Calcd for $C_{13}H_{13}ClN_2O_2$: C, 58.99; H, 4.95; N, 10.58. Found: C, 58.79; H, 5.07; N, 10.45.

*Benzaldehyde 4-benzyloxyphenylhydrazone (**3b**).* To hydrazine **2b·HCl** (5.15 g, 20.5 mmol) suspended in EtOH (70 mL), freshly distilled benzaldehyde (2.19 g, 20.6 mmol) was added in one portion at 0 °C, and the mixture was stirred at rt overnight. The mixture was placed in the fridge for 24 h, and the resulting precipitate was filtered, washed with several portions of cooled water, and air-dried to give crude **3b** (4.59 g, 74% yield) as red crystals, which were used in the next step without further purification: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.04 (s, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 7.04−7.07 (br, 2H), 7.27−7.40 (m, 7H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.66 (br s, 1H).

*Benzaldehyde 4-benzoyloxyphenylhydrazone (**3c**).* In analogy to the procedure described for the preparation of **3b**, hydrochloride **2c·HCl** (5.0 g, 18.8 mmol) in EtOH (90 mL) was reacted with benzaldehyde (1.99 g, 18.8 mmol) to give crude hydrazone **3c** (5.68 g, 95% yield) as a gray solid: mp 183−185 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (s, 4H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.36−7.39 (m, 2H), 7.50−7.53 (m, 2H), 7.61−7.70 (m, 5H), 8.22 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 113.3 (CH), 122.3 (CH), 126.2 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 129.8, 130.1 (CH), 133.4 (CH), 135.3, 137.6 (CH), 142.7, 144.2, 165.7 (C═O).

Carbamoyl Chlorides 4. General Procedure. To a solution of hydrazone **3** (1 mmol) in dry CH_2Cl_2 (5 mL), pyridine (1.2 mmol) followed by triphosgene (297 mg, 1 mmol) were added under Ar. The mixture was stirred at rt for 3 h, diluted HCl (2%) was added, organic products were extracted (CH_2Cl_2), extracts were dried (Na_2SO_4), and solvent was evaporated. The crude product was purified by a short column chromatography (SiO_2, hexane/CH_2Cl_2, 1:1) to give chlorides **4**, which were recrystallized from EtOH.

*Benzaldehyde α-chloroformyl-4-nitrophenylhydrazone (**4a**).*[23] Yield 93% from hydrazone **3a**.[38] Yellow solid: mp 168−170 °C [lit.[23] mp 168 °C] (EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.47 (m, 4H), 7.53 (d, *J* = 8.9 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 8.45 (d, *J* = 8.9 Hz, 2H).

*Benzaldehyde α-chloroformyl-4-benzyloxyphenylhydrazone (**4b**).* Yield 90%. Colorless solid: mp 167−169 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.14 (s, 2H), 7.14−7.19 (m, 4H), 7.36−7.47 (m, 9H), 7.65−7.67 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 70.5, 116.6, 127.6, 127.9, 128.3, 128.6, 128.7, 128.8, 130.7, 130.1, 133.4, 136.2, 159.9; IR (KBr) ν 1735 (C═O), 1250 and 1238 (C−O) cm^{-1}; ESI-MS, *m*/*z* 328.6 (100, $[M\text{-}Cl]^+$); HRMS, calcd. for $C_{21}H_{17}ClN_2O_2$ $[M]^+$ *m*/*z* 364.0980, found *m*/*z* 364.0982. Anal. Calcd for $C_{21}H_{17}ClN_2O_2$: C, 69.14; H, 4.70; N, 7.68. Found: C, 69.17; H, 4.85; N, 7.49.

*Benzaldehyde α-chloroformyl-4-benzoyloxyphenylhydrazone (**4c**).* Data: mp 156−157 °C (MeOH); ^{1}H NMR (600 MHz,

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$CDCl_3$) δ 7.35 (d, J = 8.7 Hz, 2H), 7.38−7.42 (m, 3H), 7.46−7.50 (m, 3H), 7.53−7.58 (m, 2H), 7.67−7.71 (m, 3H), 8.24 (d, J_1 = 8.3 Hz, J_2 = 1.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 123.9, 127.9, 128.7, 128.8, 129.0, 130.1, 130.2, 130.8, 133.2, 133.5, 134.0, 152.0, 164.6; IR (KBr) ν 1725 (C═O), 1262, 1202 (C−O) cm^{-1}. Anal. Calcd for $C_{21}H_{15}ClN_2O_3$: C, 66.58; H, 3.99; N, 7.40. Found: C, 66.47; H, 4.03; N, 7.33.

Tetrahydro-1,2,4,5-tetrazin-3(2*H*)-ones 5a−5e. General Procedure. To a solution of carbamoyl chloride **4** (1.0 mmol) in EtOH (15 mL), arylhydrazine hydrochloride **2·HCl** or 4-hydrazinobenzoic acid (**2e**, 1.2 mmol) followed by Et_3N (2.4 mmol) were added. The resulting mixture was heated at 50 °C for 2−4 h and cooled to rt. For tetrazines **5a**−**5c**, colorless precipitate was separated and washed with cold EtOH. For tetrazines **5d** and **5e**, the cooled reaction mixture was poured into ice, and the resulting precipitation was filtered. For tetrazines **5f** and **5g**, the cooled reaction mixture was poured into 2% HCl and ice, and the product was filtered.

*2,6-bis(4-Benzyloxyphenyl)-4-phenyltetrahydro-1,2,4,5-tetrazin-3(2H)-one (**5a**).* Crude tetrazine obtained in 77% yield was partially purified by flash chromatography (SiO_2 washed with 1% Et_3N in hexanes, hexanes/CH_2Cl_2 20:1) and used in the next step. Analytical sample of **5a** was obtained by recrystallization from EtOAc at −5 °C: mp 208−211 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.74 (d, J = 10.6 Hz, 2H), 5.06 (s, 4H), 5.47 (t, J = 10.6 Hz, 1H), 6.96 (d, J = 9.0 Hz, 4H), 7.32 (t, J = 7.3 Hz, 2H), 7.36−7.44 (m, 11H), 7.54 (d, J = 9.0 Hz, 4H), 7.58 (br d, J = 6.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 70.4, 72.3, 114.8, 124.1, 126.4, 127.4, 127.9, 128.5, 128.6, 128.8, 129.0, 130.1, 135.8, 137.1, 156.1; IR (KBr) ν 3238 (N−H), 1629 (C═O), 1504, 1237 (C−O) cm^{-1}; EI-HRMS, calcd. for $C_{34}H_{30}N_4O_3$ [M]$^+$ m/z 542.2318, found m/z 542.2314. Anal. Calcd for $C_{34}H_{30}N_4O_3$: C, 75.26; H, 5.57; N, 10.33. Found: C, 75.29; H, 5.64; N, 10.15.

*2,6-bis(4-Benzoyloxyphenyl)-4-phenyltetrahydro-1,2,4,5-tetrazin-3(2H)-one (**5b**).* The crude tetrazine was obtained in 81% yield as colorless solid. An analytically pure sample was prepared by recrystallization from EtOH: mp 219−220 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.87 (d, J = 10.1 Hz, 2H), 5.45 (t, J = 10.1 Hz, 1H), 7.20 (d, J = 9.0 Hz, 4H), 7.37−7.43 (m, 3H), 7.49−7.52 (m, 4H), 7.59 (d, J = 7.2 Hz, 2H), 7.63 (t, J = 7.4 Hz, 2H), 7.74 (d, J = 9.0 Hz, 4H), 8.19 (d, J = 7.2 Hz, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 72.7 (CH_2), 121.5 (CH), 122.8 (CH), 126.5 (CH), 128.5 (CH), 128.9 (CH), 129.1, 129.6 (CH), 130.2 (CH), 133.5 (CH), 135.5, 139.7, 147.4, 155.3 (C═O), 165.3 (C═O); IR (KBr) ν 3240 (N−H), 1737, 1625 (C═O), 1500, 1268, and 1200 (C−O) cm^{-1}; EI-HRMS, calcd. for $C_{34}H_{26}N_4O_5$ [M]$^+$ m/z 570.1903, found m/z 570.1896. Anal. Calcd for $C_{34}H_{26}N_4O_5$: C, 71.57; H, 4.59; N, 9.82. Found: C, 71.39; H, 4.62; N, 9.87.

*2-(4-Benzoyloxyphenyl)-6-(4-benzyloxyphenyl)-4-phenyltetrahydro-1,2,4,5-tetrazin-3(2H)-one (**5c**).* Crude tetrazine was obtained from chloride **4b** in 75% yield as a white solid (mp 211−213 °C). Analytical sample of **5c** was obtained by recrystallization from EtOAc: mp 213-214 °C; ^{1}H NMR (200 MHz, $CDCl_3$) 4.77 (d, J = 10.4 Hz, 1H), 4.83 (d, J = 10.4 Hz, 1H), 5.07 (s, 2H), 5.49 (t, J = 10.4 Hz, 1H), 6.96−7.00 (m, 2H), 7.18−7.23 (m, 2H), 7.34−7.64 (m, 15H), 7.77 (m, 2H), 8.21 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 70.4, 72.5, 114.9, 121.4, 122.7, 124.2, 126.4, 127.4, 127.9, 128.5, 128.6, 128.9, 129.1, 129.7, 130.1, 130.2, 133.5, 135.5, 137.1, 139.9, 147.3, 155.1, 156.2, 165.2; IR (KBr) ν 3213 (N−H), 1736 (C═O), 1625 (C═O), 1505, 1265, 1246 (C−O), 1203 (C−O) cm^{-1}; EI-HRMS calcd for $C_{34}H_{28}N_4O_4$ [M]$^+$ 556.2111, found 556.2108.

*2-(4-Benzyloxyphenyl)-6-(4-nitrophenyl)-4-phenyltetrahydro-1,2,4,5-tetrazin-3(2H)-one (**5d**).* Crude tetrazine was obtained in 72% yield and was partially purified by flash chromatography (SiO_2 washed with 1% Et_3N in hexanes, hexanes/CH_2Cl_2 1:1) and used in the next step. Analytical sample of **5d** was obtained by recrystallization from EtOH: mp 78−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (d, J = 9.9 Hz, 1H), 4.87 (d, J = 10.2 Hz, 1H), 5.08 (s, 2H), 5.54 (t, J = 9.9 Hz, 1H), 7.00 (d, J = 9.1 Hz, 2H), 7.30−7.46 (m, 8H), 7.51 (d, J = 9.1 Hz, 2H), 7.52−7.59 (m, 2H), 7.95 (d, J = 9.4 Hz, 2H), 8.20 (d, J = 9.4 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 70.2, 72.8, 114.9, 119.7, 124.1, 124.3, 126.3, 127.4, 128.0, 128.6, 129.0, 129.3, 134.4, 135.0, 136.7, 143.0, 147.7, 155.2, 156.5. Anal. Calcd for $C_{27}H_{23}N_5O_4$: C, 67.35; H, 4.81; N, 14.54. Found: C, 67.49; H, 4.84; N, 14.26.

*2-(4-Iodophenyl)-6-(4-nitrophenyl)-4-phenyltetrahydro-1,2,4,5-tetrazin-3(2H)-one (**5e**).* Obtained in 90% yield as yellow solid using carbamoyl chloride **4a**, 4-iodophenylhydrazine free base (**2d**) and 1 equiv of Et_3N. Crude product was washed with warm EtOAc and recrystallized from EtOH: mp 197−200 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 5.59 (t, J = 9.0 Hz, 1H), 6.09 (d, J = 9.1 Hz, 1H), 6.13 (d, J = 8.8 Hz, 1H), 7.22−7.32 (m, 3H), 7.47 (d, J = 8.9 Hz, 2H), 7.50−7.56 (m, 2H), 7.60 (d, J = 8.9 Hz, 2H), 7.89 (d, J = 9.4 Hz, 2H), 8.12 (d, J = 9.4 Hz, 2H); ^{13}C NMR (400 MHz, acetone-d_6) δ 74.2, 118.9, 122.7, 123.9, 126.8, 128.4, 128.5, 137.0, 137.6, 142.3, 142.4, 148.5. Anal. Calcd for $C_{20}H_{16}IN_5O_3$: C, 47.92; H, 3.22; N, 13.97. Found: C, 47.75; H, 3.24; N, 13.70.

*2-(4-Carboxyphenyl)-6-(4-nitrophenyl)-4-phenyltetrahydro-1,2,4,5-tetrazin-3(2H)-one (**5f**).* Obtained in 30% yield. Crude tetrazine was purified by washing with hot EtOAc: ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.47 (t, J = 8.9 Hz, 1H), 6.62 (d, J = 8.9 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 7.30−7.40 (m, 3H), 7.49 (d, J = 6.5 Hz, 2H), 7.76 (d, J = 8.9 Hz, 2H), 7.84 (d, J = 9.4 Hz, 2H), 7.92 (d, J = 8.9 Hz, 2H), 8.24 (d, J = 9.4 Hz, 2H). Anal. Calcd for $C_{21}H_{17}N_5O_5$: C, 60.14; H, 4.09; N, 16.70. Found: C, 59.88; H, 4.18; N, 16.74.

*2-(4-Benzyloxyphenyl)-6-(4-carboxyphenyl)-4-phenyltetrahydro-1,2,4,5-tetrazin-3(2H)-one (**5g**).* Obtained in 33% yield as a colorless solid after washing with hot toluene: mp 248−249 °C (EtOAc); ^{1}H NMR (600 MHz, DMSO-d_6) δ 5.11 (s, 2H), 5.39 (t, J = 9.0 Hz, 1H), 6.41 (d, J = 9.1 Hz, 1H), 6.43 (d, J = 8.9 Hz, 1H), 7.00 (d, J = 9.1 Hz, 2H), 7.32−7.37 (m, 4H), 7.38−7.41 (m, 2H), 7.45−7.48 (m, 4H), 7.53 (d, J = 7.1 Hz, 2H), 7.76 (d, J = 8.9 Hz, 2H), 7.89 (d, J = 8.9 Hz, 2H), 12.6 (br s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 69.4, 72.7, 114.3, 119.2, 123.6, 124.4, 126.9, 127.6, 127.7, 128.1, 128.3, 128.4, 129.5, 135.8, 137.2, 137.5, 146.8, 155.0, 156.6, 167.0; IR (KBr) ν 3241 (N−H), 1684, 1632 (C═O), 1506, 1293, 1247 (C−O) cm^{-1}; EI-HRMS, calcd. for $C_{28}H_{24}N_4O_4$ [M]$^+$ m/z 480.1798, found m/z 480.1796. Anal. Calcd for $C_{28}H_{24}N_4O_4$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.87; H, 5.23; N, 11.68.

*2-(4-Benzyloxyphenyl)-6-(4-(3,5-dimethylphenyloxycarbonyl)-phenyl)-4-phenyltetrahydro-1,2,4,5-tetrazin-3(2H)-one (**5t**).* The mixture of tetrazine **5g** (250 mg, 0.52 mmol) and 3,5-dimethylphenol (254 mg, 2.08 mmol) in dry DMF (2.5 mL) was added at 0 °C DCC (118 mg, 0.57 mmol) followed by DMAP (13 mg, 20% mol with respect to tetrazine). After 30 min the cooling bath was removed, and the mixture was stirred at rt for 3 days. Then H_2O (30 mL) was added, and the mixture was extracted with EtOAc (3 × 25 mL). Combined organics were dried ($MgSO_4$), and solvents were removed to dryness. Resulting violet oil was filtered through a silica gel pad (CH_2Cl_2, SiO_2 washed with 1% Et_3N in CH_2Cl_2 before usage) to give the fraction (386 mg) containing desired material contaminated with unconsumed phenol (ca. 1:3.5 mixture, respectively). Additional flash chromatography (SiO_2 washed with 1% Et_3N in CH_2Cl_2; CH_2Cl_2/EtOAc, 20:1) furnished analytically pure ester **5t** (171 mg, 56% yield) as colorless solid: mp 210−212 °C (MeCN); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.33 (s, 6H), 4.75 (d, J = 9.9 Hz, 1H), 4.82 (d, J = 10.3 Hz, 1H), 5.05 (s, 2H), 5.45 (t, J = 10.1 Hz, 1H), 6.82 (s, 2H), 6.89 (s, 1H), 6.97 (d, J = 9.0 Hz, 2H), 7.31−7.34 (m, 1H), 7.37−7.44 (m, 7H), 7.51 (d, J = 9.0 Hz, 2H), 7.54−7.56 (m, 2H), 7.87 (d, J = 8.9 Hz, 2H), 8.13 (d, J = 8.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 70.3, 72.9, 114.9, 119.3, 119.9, 124.0, 124.5, 126.4, 127.4, 127.5, 128.0, 128.6, 128.9, 129.1, 130.7, 134.9, 135.5, 136.9, 139.3, 146.8, 150.9, 155.5, 156.4, 165.0; IR (KBr) ν 3235 (N−H), 1737 (C═O), 1629 (C═O), 1258 (C−O) cm^{-1}; EI-HRMS, calcd. for $C_{36}H_{32}N_4O_4$ [M]$^+$ m/z 584.2424, found m/z 584.2431. Anal. Calcd for $C_{36}H_{32}N_4O_4$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.67; H, 5.76; N, 9.42.

*4-Benzoyloxyaniline (**7b**).*[25] 4-Nitrophenyl benzoate[25,39] (**6b**, 37.4 g, 0.153 mol) was dissolved in *i*-propanol (400 mL) at 60 °C, followed by addition of $SnCl_2·2H_2O$ (178 g, 0.740 mol). The resulting mixture was heated at this temperature for 4 h and then stirred overnight at rt and quenched with excess saturated aqueous Na_2CO_3 solution. After the evolution of CO_2 was stopped, the resulting precipitate was filtered, and the filtrate was extracted with three portions of EtOAc.

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Combined organics were dried, solvents were removed in vacuo, and the resulting crude product was washed with aqueous EtOH (50%) to give aniline **7b** (26.4 g, 81% yield) as colorless crystals: mp 156−159 °C [lit.[25] mp 153−154 °C]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.66 (br s, 2H), 6.71 (d, J = 8.9, 2H), 7.00 (d, J = 8.9, 2H), 7.45−7.55 (m 2H), 7.57−7.67 (m, 1H), 8.15−8.23 (m, 2H).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

1D ^{1}H and ^{13}C NMR spectra for **3b**, **3c**, **4b**, **4c**, **5a**−**5g**, and **5t**, partial output from TD-DFT calculations, archive of calculated equilibrium geometries for **1v**−**1z**, EPR experimental, simulated, and the difference spectra for **1a**, **1c**, **1d**, and **1t**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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