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The reaction of optically active α-aminocarboxylic acid hydrazides with triethyl *ortho*esters

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ABSTRACT

New derivatives of 2-(1-amino-1-phenylmethyl)-1,3,4-oxadiazole and 1,2,4-triazin-6-one were synthesised in the reactions of optically active α-aminocarboxylic acid hydrazides and triethyl *ortho*esters in xylene. The electronic and steric effects of substituents at the α position influencing the formation of five- or six-membered products are discussed.

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1. Introduction

Heterocyclic compounds containing five-membered azole or six-membered azine scaffolds have attracted the attention of many scientists in recent decades due to the fact that they exhibit a wide range of biological interactions. In addition, these scaffolds find various industrial applications. One subgroup of the azole family is 1,3,4-oxadiazole and its derivatives. Many of these have been tested and shown to have antibacterial, anticonvulsant and anticancer activities.[1–4] These heterocyclic molecules are also utilised in agriculture as pesticides,[5,6] and in electronics to produce organic light-emitting diodes (OLED), optical brighteners and laser dyes.[7–9] Generally, the most popular methods to prepare 1,3,4-oxadiazoles make use of acid hydrazides,[3,10–14] *N*,*N*′-diacylhydrazines[15–19] or conversion of other ring systems, such as 1,2,4-oxadiazoles.[20]

An interesting azine subgroup is 1,2,4-triazin-6-one and its derivatives. These are applied in medicine as potential antibacterial and antifungal agents, in the agrochemical industry as plant protecting materials, and as components of commercial dyes.[21–25] A wide range of synthetic procedures have been reported for the title 1,2,4-triazin-6-one derivatives. They are commonly prepared from acid hydrazides,[26] amides,[27] iminoesters[28,29] or from small heterocyclic azirine structures.[30]

Our earlier studies on the reactions of α-hydroxyacid hydrazides with triethyl *ortho*esters demonstrated the possibility of the synthesis of three different heterocyclic arrangements: the five-membered 4-acylamino-1,2,4-triazoles and 2-hydroxymethyl-1,3,4-oxadiazoles and the six-membered 1,3,4-oxadiazin-5-ones.[31] We showed that the formation of such heterocycles could proceed in an acidic medium as a one-step procedure or under neutral conditions as a two-step procedure through an intermediate iminoether **1** (Scheme 1). The replacement of the hydroxyl group in the α position of the hydrazide with the protected amino group and the subsequent reaction with triethyl *ortho*esters led to the formation of *N*-protected 2-aminomethyl-1,3,4-oxadiazole derivatives.[12] However, this indirect procedure for the synthesis of the free 2-aminomethyl-1,3,4-oxadiazoles required two additional reaction steps: the protection of the α-amino substrate and the cleavage of the protected heterocycle.

In contrast to the protected scaffold, the hydrazides of the free α-aminocarboxylic acids react with *ortho*esters in DMF to yield the six-membered 1,2,4-triazin-6-one derivatives exclusively.[32–34] These results contradicted our earlier studies, so we investigated the possibility of synthesizing free 2-aminomethyl-1,3,4-oxadiazoles directly from the hydrazides of α-aminocarboxylic acids.

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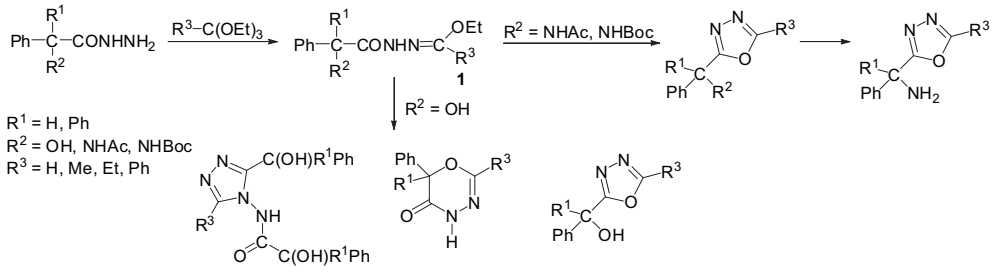
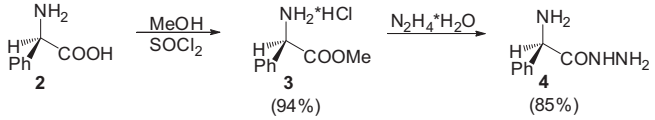


Scheme 1.

2. Results and discussion

The starting material in our reaction sequence was the optically active D-(−)-α-phenylglycine hydrazide **4**. This compound was prepared in a two-step transformation from the appropriate D-(−)-α-phenylglycine **2** by esterification with methanol and thionyl chloride followed by treatment with hydrazine hydrate (Scheme 2).



Scheme 2.

The hyrazide **4** was heated with equimolar quantities of triethyl *ortho*esters (R=H, Me, Et, Ph, Scheme 3) in nonpolar solvents, such as xylene. A catalytic amount of *p*-toluenesulphonic acid was also used in these reactions. The results showed that the six-membered 1,2,4-triazin-6-one derivatives **5a**–**d** were the main products. Generally, the reaction yields decreased with the increasing bulk of substituent R on the *ortho*ester. The highest yield was obtained in the case of the reaction conducted with triethyl *ortho*formate (**5a**, 83%, Table 1). A similar trend was observed in the reactions starting from α-hydroxy- and *N*-protected α-aminocarboxylic acids and *ortho*esters.[11,12] However, regardless of the presence or absence of *p*-toluenesulphonic acid, we did not obtain acyclic intermediates, N^2-ethoxymethylene phenylglycine hydrazides **4′**, which accompanied the latter reactions. Thus, the proposed structures **4′**, possessing a free amino group in the α position, were more reactive than their α-hydroxy or *N*-protected α-amino counterparts, undergoing cyclisation immediately after formation. In contrast to the unsubstituted or alkyl *ortho*esters, the reaction with triethyl *ortho*benzoate resulted in the simultaneous formation of the five-membered product 2-aminomethyl-1,3,4-oxadiazole **6d**.

This type of one-step procedure, where the reactive primary amino group is transferred directly from the acyclic substrate to the heterocyclic product unchanged, is rare and noteworthy. In order to generalise this method, we decided to investigate the reactions of other α-aminocarboxylic acid hydrazides with triethyl *ortho*-benzoate. These hydrazides were prepared from the appropriate α-aminocarboxylic acids **7e**–**h** according to the same procedure as described for hydrazide **4** (Scheme 4). The first trials conducted

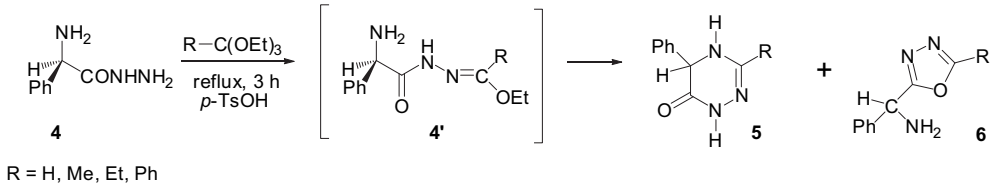
Table 1
Products of the reaction of D-(−)-α-phenylglycine hydrazide with triethyl *ortho*esters

Entry	R	Product **5**		Product **6**	
		Yield [%]	Mp °C	Yield [%]	Mp °C
a	H	83	125–127	—	—
b	Me	65	198–200	—	—
c	Et	61	136–138	—	—
d	Ph	52	241–243	45	139–141

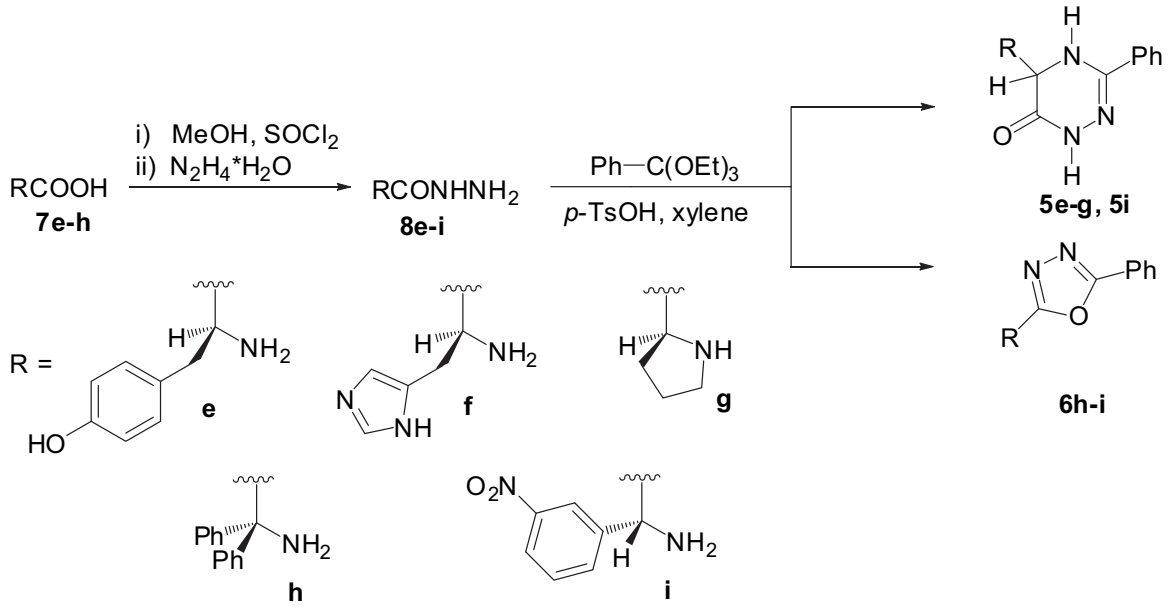
with optically active L-(−)-tyrosine **8e**, L-(+)-histidine **8f** and L-(−)-proline **8g** showed that indeed the six-membered 1,2,4-triazin-6-ones **5e**–**g** are the main reaction products (Table 2). No traces of the corresponding 1,3,4-oxadiazoles were found. However, the reaction of D-(−)-α-(*m*-nitrophenyl)glycine hydrazide **8i** resulted in the formation of both six-membered 1,2,4-triazin-6-one **5i** and five-membered 2-aminomethyl-1,3,4-oxadiazole **6i**. Meanwhile, the sterically crowded α,α-diphenylglycine hydrazide **8h** gave 2-aminomethyl-1,3,4-oxadiazole **6h** exclusively. To the best of our knowledge, experiments conducted with other acidic agents used in catalytic amounts, such as glacial acetic acid AcOH or concentrated H_2SO_4 resulted in comparative yields of 1,3,4-oxadiazoles. However, the bigger amounts of *p*-TsOH caused deactivation of the amino group and in addition, led to decomposition of 1,3,4-oxadiazole scaffold due to the fact, that this group of compound is acid-sensitive.[12,35]

The formation of free 2-aminomethyl-1,3,4-oxadiazoles was influenced by both the electronic nature and the steric hindrance of substituents adjacent to the α carbon. Electron-withdrawing substituents in α-aminocarboxylic acids (**2**, **7h**, **7i**, Table 3) decreased both the basicity and the nucleophilicity of the amino group. In this way, the amino centre, which is responsible for the formation of the six-membered ring, becomes less active than the competing carbonyl. The additional phenyl group in **7h** protected the amino group so effectively that the only product was 2-aminomethyl-1,3,4-oxadiazole **6h**. In contrast, electron-donating substituents on the acids (**7e**–**g**, Table 3) increased the basicity of the amino group considerably to form 1,2,4-triazin-6-one derivatives exclusively.

To establish the structure of the five-membered 2-aminomethyl-1,3,4-oxadiazoles **6**, X-ray crystallographic analysis was also performed. The molecular structure of 2-(1-amino-1,1-diphenylmethyl)-5-phenyl-1,3,4-oxadiazole **6h** is shown in Fig. 1.



Scheme 3.



Scheme 4.

This structure is stabilized by three intramolecular hydrogen bonds C7—H7A···O1, C15—H15A···N13 and C11—H11A ···N3 giving rise to the five-membered ring systems in all cases (Table 4). The average plane of the phenyl ring (C6—C11) linked to the 1,3,4-oxadiazole ring is almost coplanar. The dihedral angle between these planes is 1.26(5)° and the twist along C6—C5 bond is illustrated by torsion angles of −178.18(14)° (N4—C5—C6—C7) and 179.63(11) (O1—C5—C6—C11). All bond distances and angles are normal and are in good agreement with the geometry of similar derivatives of 1,3,4-oxadiazole.[12,36–38] In the crystal structure of **6h**, molecules are linked into a two-dimensional layers parallel to the *ac* plane by N13—H13A···N3^{i} (*i*=*x*+0.5, *y*, −*z*+0.5) hydrogen bond (Table 4).

The measurements of the optical rotation for all **5a**–**c**, derived from optically active D-(−)-α-phenylglycine hydrazide, showed that in the reactions with triethyl *ortho*formate, *ortho*acetate and *ortho*propionate, racemisation at the asymmetric carbon occurred although this atom was not directly involved in the formation of products. Contrary to aliphatic *ortho*esters, triethyl *ortho*benzoate reacted with partial racemisation (**5d**–**g**, **5i**, **6d**, **6i**). To our astonishment, partial racemisation occurred even in the case of bicyclic 1,2,4-triazin-6-one **5g** obtained from L-(−)-proline hydrazide. However, we believe that this phenomenon could be explained by *keto-enol* tautomerism in 1,2,4-triazin-6-one (Scheme 5). In this isomerism, the mobile hydrogen atom situated at C5 could be envisioned to migrate to the oxygen atom at C6 with simultaneous shift of the double bond and loss of optical activity. In our previous papers, concerning the reactions of α-hydroxy- and *N*-protected α-aminocarboxylic acid hydrazides, we found that racemisation took place in the acyclic intermediate, the appropriate N^2-ethoxymethylene hydrazide.[12,39]

Crystallisation of the mixture after reaction of the optically active D-(−)-α-phenylglycine hydrazide **4** with triethyl *ortho*benzoate gave only one stereoisomer of 3,5-diphenyl-1,2,4-triazin-6-one **5d**. This compound has an optical rotation $[\alpha]_D^{20}$ equal to −142.1° and a melting point of 241–243 °C, approximately 40 °C higher than that for the racemic compound.[34] Column chromatography of the oily residue resulted in the recovery of additional racemic 3,5-diphenyl-1,2,4-triazin-6-one (*rac*)-**5d** and racemic 2-aminomethyl-5-phenyl-1,3,4-oxadiazole **6d**.

The enantiomeric purity of (−)-**5d** was determined by ^{1}H NMR spectroscopy after the addition of 0.125 equiv of (+)-europium tris [3-heptafluoropropylhydroxymethylene camphorate]. The signal of the proton H—N1 connected with the ring nitrogen atom at position 1 was of special diagnostic value. In the case of the racemic compound (*rac*)-**5d**, recorded in the presence of the chiral shift reagent, the signal of H—N1 splits into two singlets at 9.48 and 9.57 ppm (Fig. 2c). The presence of only one signal at 10.14 ppm in the spectrum of (−)-**5d** (Fig. 1b) was noted, which confirmed its enantiomeric purity. However, this signal was shifted in low field and did not correspond with any of the H—N1 signals in the racemic compound. To establish, which signal came from (−)-**5d** enantiomer, we recorded the spectrum of the enriched mixture of both the racemate and the enantiomer for the ratio of (−)-**5d**:(+)-**5d**=2:1 (Fig. 2d). The spectrum revealed doubled intensity of the signal at 9.71 ppm, which thus clearly belonged to H—N1 of the enantiomeric compound (−)-**5d**.

3. Conclusions

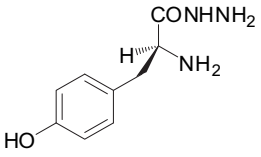
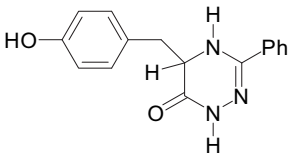
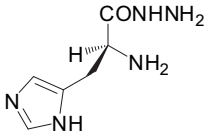
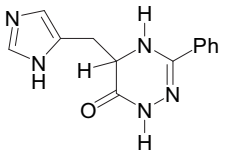
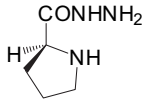
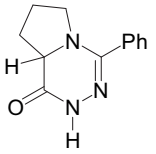
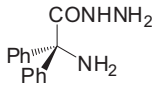
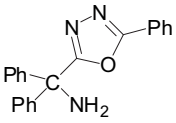
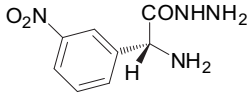
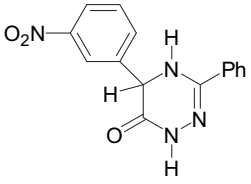
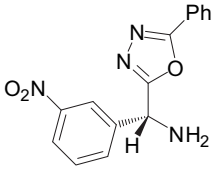
In summary, the hydrazides of free α-aminocarboxylic acids appeared to be valuable starting materials in the direct synthesis of both 1,2,4-triazin-6-ones and 1,3,4-oxadiazoles possessing a free aminomethyl group at position 2. The formation of the latter five-membered 1,3,4-oxadiazoles was the result of decreased nucleophilicity of the amino group caused by electron-withdrawing functionality and the steric hindrance of substituents adjacent to α carbon. The presented protocol can be extended to other α-amino substituted carboxylic acids. The products, 1,3,4-oxadiazoles bearing an aminomethyl group, are potentially useful building blocks for macrocyclic systems.

4. Experimental

4.1. General

Melting points were measured using a Stuart SMP3 melting point apparatus and are uncorrected. UV—vis spectra were recorded on a Shimadzu UV-2102 spectrophotometer. Elemental analyses were performed with a VarioEL analyser in PAN Zabrze. The ^{1}H and ^{13}C NMR spectra were recorded on Varian Inova 300 and Varian 600 spectrometers in DMSO, $CDCl_3$ or CD_3CN solutions using TMS as the internal standard, or in D_2O solution. Thin-layer

Table 2
Products of the reaction of optically active α-aminocarboxylic acid hydrazides with triethyl *ortho*benzoate

Entry	Carboxylic acid hydrazide	Product	Yield [%]	Mp °C
e	 **8e**	 **5e**	71	106–107
f	 **8f**	 **5f**	62	191–192
g	 **8g**	 **5g**	75	145–147
h	 **8h**	 **6h**	85	140–141
i	 **8i**	 **5i**	31	190–192
		 **6i**	45	101–103

chromatography was performed on silica gel 60 F_{254} (Merck) thin-layer chromatography plates using benzene/AcOEt (1:3 v/v) as the mobile phase. Optical rotations were measured on a Perkin–Elmer Polarimeter 141 in THF or $CHCl_3$ solutions at approximately 1% concentrations (D line of sodium light, room temperature). FT-IR spectra were recorded between 4000 and 650 cm^{-1} on an FT-IR Nicolet 6700 apparatus with a Smart iTR accessory. Mass spectra were obtained on a Waters HPLC/MS system using the EI technique (70 eV). pK_a Ionisation constants of the starting α-aminocarboxylic acids **2** and **7e**–**i** were determined by potentiometric titration in aqueous-methanol solutions (1:1 v/v) at room temperature.

4.2. Preparation of D-(−)-α-(*m*-nitrophenyl)glycine 7i

A solution of 15.1 g (100 mmol) of D-(−)-α-phenylglycine (**2**) in 15 mL of concentrated H_2SO_4 was cooled to 0 °C and a mixture of 65% HNO_3 (10 mL) and concentrated H_2SO_4 (12 mL) was added dropwise. The resulting solution was stirred for 3 h and then poured onto ice and filtered. The filtrate was neutralised with 25% NH_3 solution yielding a yellow precipitate. The precipitate was collected, rinsed with water, dried and crystallised from aqueous ethanol.

*4.2.1. D-(−)-α-(m-Nitrophenyl)glycine (**7i**).* Yellow solid, yield: 62%; mp 168–169 °C (lit.:[40] mp 160 °C); $[\alpha]_D^{20}$ −97.5 (2 M HCl, *c* 4); R_f

Table 3
pK_a Ionisation constants of α-aminocarboxylic acids **2**, **7e**–**i** in aqueous-methanol solutions

Compound		pK_a[a]		
		COOH	NH_2	Side chain
Ph-Gly	**2**	2.72±0.05	8.88±0.04	—
Tyr	**7e**	2.60±0.08	9.81±0.05	10.62±0.08
His	**7f**	2.73±0.07	9.31±0.05	6.10±0.06
Pro	**7g**	3.11±0.05	10.43±0.04	—
Ph_2-Gly	**7h**	2.78±0.06	8.72±0.05	—
m-NO_2Ph-Gly	**7i**	2.86±0.08	8.39±0.03	—

[a] Determined by potentiometric method (H_2O/MeOH, 1:1 v/v); rt.

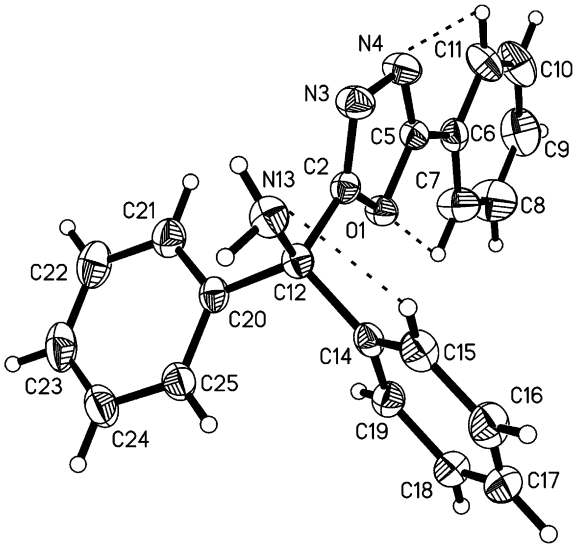


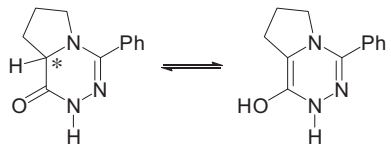
Fig. 1. The molecular structure of 2-(1-amino-1,1-diphenylmethyl)-5-phenyl-1,3,4-oxadiazole **6h** with atom labelling showing 30% displacement ellipsoids (arbitrary spheres for the H atoms). Dashed lines indicated intramolecular hydrogen bonds.

Table 4
Intra- and intermolecular interactions geometry for 2-(1-amino-1,1-diphenylmethyl)-5-phenyl-1,3,4-oxadiazole **6h**

D–H···A	d_{D-H} [Å]	$d_{H\cdots A}$ [Å]	$d_{D\cdots A}$ [Å]	<(D–H···A) [°]
N(13)–H(13A)···N(3)^{i}	0.913 (15)	2.352 (16)	3.2211 (15)	159.2 (12)
C(7)–H(7A)···O(1)	0.93	2.52	2.8383 (15)	100.1
C(15)–H(15A)···N(13)	0.93	2.40	2.7658 (18)	103.2
C(11)–H(11A)···N(4)	0.93	2.65	2.9374 (18)	98.5

Symmetry transformations used to generate equivalent atoms: (i)=x+0.5, y, −z+0.5.

(benzene/AcOEt, 1:3 v/v) 0.12; δ_H (600 MHz, D_2O) 5.21 (1H, s, H–C2), 7.57 (1H, t, *J* 8.4 Hz, Ph–C2: H5′), 7.73 (1H, d, *J* 8.4 Hz, Ph–C2: H6′), 8.17 (1H, d, *J* 8.4 Hz, Ph–C2: H4′), 8.22 (1H, s, Ph–C2: H2′); δ_C (DMSO-d_6) 55.5, 123.3, 125.1, 130.8, 133.1, 134.6, 148.2, 169.7; λ_{max} (MeOH) 262.0 nm (ε×10^{-3} 8.07 cm^{-1} M^{-1}).



Scheme 5.

4.3. General procedure for the preparation of α-aminocarboxylic acid hydrazides 4, 8e–i

A solution of the appropriate α-aminocarboxylic acid **2**, **7e**–**i** (100 mmol) in 50 mL of MeOH was cooled to 0 °C and 18 mL of thionyl chloride was added dropwise. The mixture was stirred for 6 h and then concentrated on a rotary evaporator. The white methyl ester hydrochloride was washed twice with Et_2O (2×50 mL), filtered and dried in air. Then, the crude product was dissolved in 100 mL of MeOH and 9 mL of 98% hydrazine hydrate (0.185 mol) was dropped in and stirred for 24 h. The white precipitate (N_2H_4·HCl) was removed by filtration and the filtrate was concentrated under reduced pressure. The yellow oily residue was treated with MeOH to remove the remaining N_2H_4·HCl (20 mL). The crude product was crystallised from the appropriate solvent to give pure hydrazides **4**, **8e**–**i**.

4.3.1. D-(−)-α-Phenylglycine methyl ester hydrochloride[3]. White solid, yield: 94%; mp 193–195 °C (lit.:[41] mp 194–195 °C); $[\alpha]_D^{20}$ −119.0 ($CHCl_3$, *c* 1); R_f (benzene/AcOEt/$NHEt_2$, 1:3:1 v/v/v) 0.82.

4.3.2. D-(−)-α-Phenylglycine hydrazide[4]. White solid, yield: 85%; mp 68–70 °C; $[\alpha]_D^{20}$ −55.0 ($CHCl_3$, *c* 1); R_f(benzene/AcOEt, 1:3 v/v) 0.14; [Found: C, 58.10; H, 6.68; N, 25.46. $C_8H_{11}N_3O$ requires C, 58.16; H, 6.72; N, 25.42%]; δ_H (300 MHz, DMSO-d_6, Me_4Si) 3.29 (2H, d, *J* 7.5 Hz, C1–NH–NH_2), 4.18 (2H, br s, NH_2–C2), 4.31 (1H, s, H–C2), 7.18–7.40 (5H, m, Ph), 9.25 (1H, br s, C1–NH–NH_2); δ_C (DMSO-d_6) 57.4, 126.6, 127.0, 128.0, 142.6, 172.4; λ_{max} (MeOH) 205.4 nm (ε×10^{-3} 14.39 cm^{-1} M^{-1}), 251.4 (0.34); ν_{max} (ATR) 3795, 3619, 3544, 3201, 3164, 2628, 2410, 2069, 1826, 1677, 1039, 918 cm^{-1}.

*4.3.3. L-(+)-Tyrosine hydrazide (**8e**).* White solid, yield: 85%; mp 194–196 °C (lit.:[42] mp 193–194 °C); $[\alpha]_D^{20}$ +78.6 (3 M HCl, *c* 4.2); R_f (benzene/AcOEt, 1:3 v/v) 0.12.

*4.3.4. L-(+)-Histidine hydrazide (**8f**).* White solid, yield: 72%; mp 236–247 °C (lit.:[43] mp 238–240 °C); $[\alpha]_D^{20}$ +16.0 (3 M HCl, *c* 2); R_f (benzene/AcOEt, 1:3 v/v) 0.10.

*4.3.5. L-(−)-Proline hydrazide (**8g**).* Colourless oil, yield: 78%; $[\alpha]_D^{20}$ −31.0 (3 M HCl, *c* 4.5); R_f (benzene/AcOEt, 1:3 v/v) 0.12; [Found: C, 46.40; H, 8.54; N, 32.56. $C_5H_{11}N_3O$ requires C, 46.49; H, 8.60; N, 32.52%]; δ_H (300 MHz, DMSO-d_6, Me_4Si) 1.80 (3H, m, CH_2, CH), 2.17 (1H, m, CH), 3.12 (2H, m, CH_2), 4.02 (1H, br s, NH), 4.52 (1H, t, *J* 6.9 Hz, NCH), 5.18 (2H, br s, C1–NH–NH_2), 9.08 (1H, br s, C1–NH–NH_2); δ_C (DMSO-d_6) 24.4, 30.3, 46.1, 58.4, 173.9; λ_{max} (MeOH) 202.8 nm (ε×10^{-3} 5.21 cm^{-1} M^{-1}), 262.2 (0.61); ν_{max} (ATR) 3307, 3253, 3142, 3029, 2881, 2710, 2598, 1676, 1620, 1570, 1529, 1499, 1455, 1389, 1306, 1264, 1165, 1122, 1094, 968, 938, 902, 851, 728 cm^{-1}.

*4.3.6. α,α-Diphenylglycine hydrazide (**8h**).* White solid, yield: 33%; mp 69–70 °C; R_f (benzene/AcOEt, 1:3 v/v) 0.11; [Found: C, 69.62; H, 6.25; N, 17.38. $C_{14}H_{15}N_3O$ requires C, 69.68; H, 6.28; N, 17.40%]; δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.13 (2H, br s, NH_2–C2), 3.91 (2H, br s, C1–NH–NH_2), 7.31–7.35 (10H, m, 2·Ph), 8.34 (1H, br s, C1–NH–NH_2); δ_C ($CDCl_3$) 67.5, 127.4, 127.5, 128.4, 144.5, 174.0; λ_{max} (MeOH) 206.8 nm (ε×10^{-3} 22.33 cm^{-1} M^{-1}), 252.8 (0.05); ν_{max} (ATR) 3266, 2982, 1625, 1595, 1512, 1494, 1447, 1355, 1248, 1221, 1081, 1025, 925, 787, 756, 731, 691, 663 cm^{-1}.

*4.3.7. D-(−)-α-(m-Nitrophenyl)glycine hydrazide (**8i**).* Yellow solid, yield: 62%; mp 127–128 °C; $[\alpha]_D^{20}$ −8.2 (6 M HCl, *c* 2); R_f (benzene/AcOEt, 1:3 v/v) 0.15; [Found: C, 45.75; H, 4.76; N, 26.59. $C_8H_{10}N_4O_3$ requires C, 45.71; H, 4.80; N, 26.64%]; δ_H (300 MHz, DMSO-d_6, Me_4Si) 4.20 (2H, br s, C1–NH–NH_2), 4.7 (1H, s, H–C2), 7.60 (1H, t, *J*

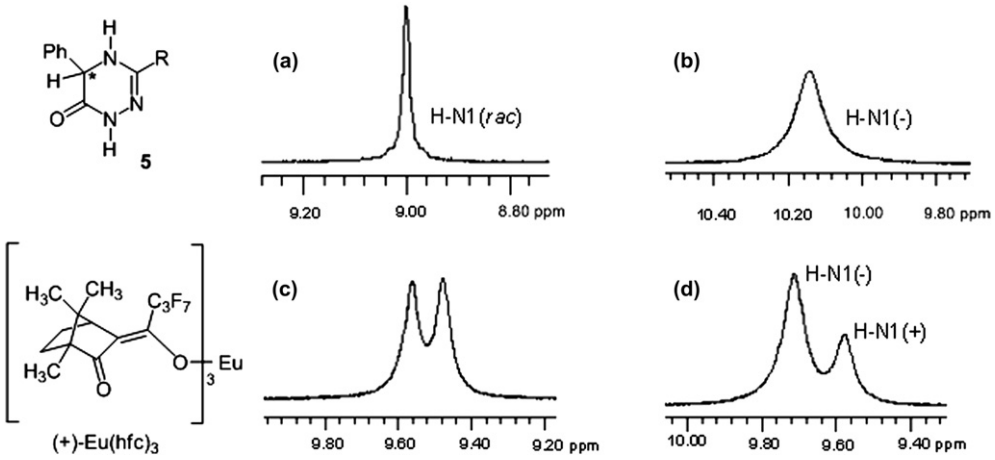


Fig. 2. Selected ^{1}H NMR signals of: (a) (*rac*)-**5d** in CD_3CN; (b) enantiomeric (−)-**5d** in CD_3CN after addition of 0.125 equiv of (+)-Eu(hfc)$_3$; (c) (*rac*)-**5d** in CD_3CN after addition of 0.125 equiv of (+)-Eu(hfc)$_3$; (d) mixture of racemic and enantiomeric **5d** in CD_3CN after addition of 0.125 equiv of (+)-Eu(hfc)$_3$, (−)-**5d**:(+)-**5d**=2:1.

8.1 Hz, Ph−C2: H5′), 7.84 (1H, d, *J* 8.1 Hz, Ph−C2: H6′), 8.09 (1H, d, *J* 8.1 Hz, Ph−C2: H4′), 8.29 (1H, s, Ph−C2: H2′), 9.35 (1H, br s, C1−NH−NH_2); δ_C (DMSO-d_6) 56.7, 121.3, 121.9, 129.5, 133.5, 145.2, 147.6, 171.6; λ_{max} (MeOH) 208.4 nm ($\varepsilon\times10^{-3}$ 11.71 cm^{-1} M^{-1}), 262.2 (6.28); ν_{max} (ATR) 3285, 3001, 1621, 1592, 1532, 1483, 1392, 1347, 1307, 1271, 1202, 1101, 1080, 1018, 919, 833, 820, 774, 734, 684 cm^{-1}.

4.4. General procedure for the synthesis of 1,2,4-triazin-6-ones 5a–g and 2-(1-amino-1-phenylmethyl)-5-phenyl-1,3,4-oxadiazoles 6d, 6h and 6i

The starting hydrazide **4**, **8e–i** (10 mmol) was added to a mixture of the appropriate triethyl *ortho*ester (10 mol) and 0.1 g *p*-TsOH in 20 mL of xylene and kept under reflux for 3 h (TLC). After cooling, the mixture was washed with water (30 mL), dried over $MgSO_4$ and then concentrated under reduced pressure. The oily residue was subjected to column chromatography (silica gel, eluent: hexane/AcOEt, 1:2 v/v) or crystallised from benzene/hexane mixture.

*4.4.1. 5-Phenyl-1,2,4-triazin-6-one (**5a**).* This compound was obtained as a white solid in 83% yield; mp 125–127 °C (lit.:[32] mp 130–131 °C); $[\alpha]_D^{20}$ 0.0 (THF, *c* 1), R_f (benzene/AcOEt, 1:3 v/v) 0.10; δ_H (300 MHz, DMSO-d_6, Me_4Si) 4.91 (1H, s, H−C5), 7.00 (1H, s, H−C3), 7.29–7.36 (5H, m, Ph−C5), 7.57 (1H, br s, H−N4), 10.27 (1H, s, H−N1); δ_H (DMSO-d_6) 56.3, 127.5, 128.5, 129.1, 137.7, 141.5, 162.0; *m*/*z* (EI) 175 (M^+, 15), 149 (16), 135 (13), 123 (17), 109 (21), 97 (29), 95 (31), 91 (16), 85 (30), 83 (41), 81 (33), 77 (30), 69 (67), 57 (91), 55 (100), 45 (81%); λ_{max} (MeOH) 206.4 nm ($\varepsilon\times10^{-3}$ 10.75 cm^{-1} M^{-1}), 277.7 (2.63); ν_{max} (ATR) 3795, 3620, 3545, 3201, 3164, 2627, 2410, 2069, 1826, 1680, 675 cm^{-1}.

*4.4.2. 3-Methyl-5-phenyl-1,2,4-triazin-6-one (**5b**).* This compound was obtained as a white solid in 65% yield; mp 198–200 °C (lit.:[32] mp 199–203 °C); $[\alpha]_D^{20}$ 0.0 (THF, *c* 1), R_f (benzene/AcOEt, 1:3 v/v) 0.14; δ_H (300 MHz, DMSO-d_6, Me_4Si) 1.86 (3H, s, CH_3), 4.85 (1H, d, *J* 1.2 Hz, H−C5), 7.27–7.39 (5H, m, Ph−C5), 7.53 (1H, br s, H−N4), 10.15 (1H, s, H−N1); δ_H (DMSO-d_6) 18.2, 56.5, 126.8, 127.8, 128.4, 141.0, 144.5, 161.0; *m*/*z* (EI) 189 (M^+, 89), 187 (14), 160 (34), 130 (11), 105 (27), 104 (54), 89 (21), 84 (100), 77 (31), 69 (18), 63 (13), 56 (31), 51 (22), 45 (20%); λ_{max} (MeOH) 205.3 nm ($\varepsilon\times10^{-3}$ 16.87 cm^{-1} M^{-1}), 282.2 (4.25); ν_{max} (ATR) 3795, 3618, 3351, 3201, 3164, 2628, 2410, 2069, 1826, 1679, 1655, 676 cm^{-1}.

*4.4.3. 3-Ethyl-5-phenyl-1,2,4-triazin-6-one (**5c**).* This compound was obtained as a white solid in 61% yield; mp 136–138 °C (lit.:[32] mp 139 °C); $[\alpha]_D^{20}$ 0.0 (THF, *c* 1); R_f (benzene/AcOEt, 1:3 v/v) 0.21; δ_H (300 MHz, DMSO-d_6, Me_4Si) 1.06 (3H, t, *J* 7.5 Hz, CH_3CH_2−C3), 2.18 (2H, q, *J* 7.5 Hz, CH_3CH_2−C3), 4.84 (1H, d, *J* 1.8 Hz, H−C5), 7.26–7.48 (5H, m, Ph−C5), 7.58 (1H, br s, H−N4), 10.19 (1H, br s, H−N1); δ_C (DMSO-d_6) 11.1, 25.2, 56.5, 126.7, 128.2, 129.5, 141.1, 148.5, 161.0; *m*/*z* (EI) 203 (M^+, 84), 174 (30), 105 (27), 104 (43), 98 (100), 91 (12), 89 (18), 77 (26), 69 (22), 57 (26), 55 (27), 45 (11%); λ_{max} (MeOH) 205.0 nm ($\varepsilon\times10^{-3}$ 16.50 cm^{-1} M^{-1}), 278.0 (4.55); ν_{max} (ATR) 3795, 3618, 3306, 3544, 3201, 3164, 2627, 2410, 2069, 1826, 1678, 1649, 1067, 675 cm^{-1}.

*4.4.4. D-(−)-3,5-Diphenyl-1,2,4-triazin-6-one (**5d**).* This compound was obtained as a white solid in 52% yield; mp 241–243 °C; $[\alpha]_D^{20}$ −142.1 (THF, *c* 1); R_f (benzene/AcOEt, 1:3 v/v) 0.34; [Found: C, 71.65; H, 5.18; N, 16.73. $C_{15}H_{13}N_3O$ requires C, 71.69; H, 5.22; N, 16.71%]; δ_H (600 MHz, CD_3CN, Me_4Si) 5.11 (1H, d, *J* 2.4 Hz, H−C5), 6.47 (1H, br s, H−N4), 7.33–7.46 (8H, m, Ph−C5, Ph−C3: H-3′, H-4′, H-5′), 7.72 (2H, d, *J* 7.8 Hz, Ph−C3: H-2′, H-6′), 10.66 (1H, s, H−N1); δ_C (CD_3CN) 58.0, 126.9, 127.7, 129.2, 129.5, 129.7, 131.1, 133.3, 141.3, 145.9, 163.0; *m*/*z* (EI) 251 (M^+, 44), 222 (32), 147 (15), 146 (100), 105 (39), 104 (72), 91 (22), 89 (27), 77 (63), 63 (13), 51 (25%); λ_{max} (MeOH) 203.9 nm ($\varepsilon\times10^{-3}$ 27.77 cm^{-1} M^{-1}), 227.30 (22.34), 302.5 (8.71); ν_{max} (ATR) 3642, 3540, 3370, 3025, 2440, 1680, 1635, 1234, 1070, 775, 670 cm^{-1}.

*4.4.5. 2-(1-Amino-1-phenylmethyl)-5-phenyl-1,3,4-oxadiazole (**6d**).* This compound was obtained as a white solid in 45% yield; mp 139–141 °C; $[\alpha]_D^{20}$ −1.8 (THF, *c* 1); R_f (benzene/AcOEt, 1:3 v/v) 0.17; [Found: C, 71.62; H, 5.20; N, 16.68. $C_{15}H_{13}N_3O$ requires C, 71.69; H, 5.22; N, 16.71%]; δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.21 (2H, br s, NH_2), 5.47 (1H, s, C−H), 7.26–7.53 (8H, m, Ph, Ph−C5: H-3′, H-4′, H-5′), 8.00 (2H, d, *J* 7.8 Hz, Ph−C5: H-2′, H-6′); δ_C ($CDCl_3$) 52.6, 123.6, 126.8, 128.4, 128.9, 129.0, 129.1, 131.7, 139.4, 165.2, 168.2; *m*/*z* (EI) 251 (M^+, 27), 174 (16), 147 (30), 146 (12), 118 (29), 106 (55), 105 (100), 104 (56), 91 (18), 79 (29), 77 (58), 51 (30%); λ_{max} (MeOH) 207.2 nm ($\varepsilon\times10^{-3}$ 33.33 cm^{-1} M^{-1}), 252.3 (27.69). ν_{max} (ATR) 3795, 3640, 3542, 3035, 2448, 1635, 1236, 1084, 775, 670 cm^{-1}.

*4.4.6. 5-(p-Hydroxybenzyl)-3-phenyl-1,2,4-triazin-6-one (**5e**).* This compound was obtained as a yellow solid in 71% yield; mp 106–107 °C; $[\alpha]_D^{20}$ −2.0 (MeOH, *c* 5); R_f (benzene/AcOEt, 1:3 v/v) 0.36; [Found: C, 68.25; H, 5.32; N, 14.87. $C_{16}H_{15}N_3O_2$ requires C, 68.31; H, 5.38; N, 14.93%]; δ_H (300 MHz, DMSO-d_6, Me_4Si) 2.78 (1H, t, *J* 8.1 Hz, CH−C5), 2.83 (1H, t, *J* 8.1 Hz, CH−C5), 4.14 (1H, m, CH−C5), 6.58 (2H, d, *J* 8.1 Hz, Ar−C5: H-3″, H-5″), 6.95 (2H, d, *J*

8.1 Hz, $ArCH_2$–C5: H-2″, H-6″), 7.29 (1H, s, H–N4), 7.35–7.40 (3H, m, Ph–C3: H-3′, H-4′, H-5′), 7.62 (2H, d, *J* 6.9 Hz, Ph–C3: H-2′, H-6′), 9.14 (1H, s, OH), 10.28 (1H, s, H–N1); δ_C (DMSO-d_6) 38.3, 54.9, 115.5, 126.6, 127.2, 128.8, 130.2, 131.5, 133.4, 144.8, 156.6, 163.1; *m*/*z* (EI) 281 (M^+, 14), 206 (22), 77 (53), 72 (26), 63 (15), 59 (32), 55 (18), 44 (100), 43 (17%); λ_{max} (MeOH) 204.4 nm ($\varepsilon\times10^{-3}$ 7.67 cm^{-1} M^{-1}), 226.0 (18.28), 286.2 (5.59), 303.6 (5.62); ν_{max} (ATR) 3224, 1652, 1612, 1574, 1514, 1435, 1402, 1319, 1235, 1172, 1103, 1067, 1048, 1016, 866, 815, 772, 722, 693 cm^{-1}.

*4.4.7. 5-(5-Imidazoylmethyl)-3-phenyl-1,2,4-triazin-6-one (**5f**).* This compound was obtained as a yellow solid in 62% yield; mp 191–192 °C; $[\alpha]_D^{20}$ −2.5 (MeOH, *c* 5); R_f (benzene/AcOEt, 1:3 v/v) 0.34; [Found: C, 61.09; H, 5.12; N, 27.37. $C_{13}H_{13}N_5O$ requires C, 61.16; H, 5.14; N, 27.42%]; δ_H (300 MHz, DMSO-d_6, Me_4Si) 2.84 (2H, m, CH_2–C5), 4.04 (1H, m, CH–C5), 6.68–6.80 (3H, m, Ph–C3: H-3′, H-4′, H-5′), 6.96 (1H, s, H-N4), 7.52 (2H, d, *J* 6.9 Hz, Ph–C3: H-2′, H-6′), 8.47 (1H, s, $ArCH_2$–C5: H-4″), 8.53 (1H, s, $ArCH_2$–C5: H-2″), 10.05 (1H, s, H–N1); δ_C (DMSO-d_6) 37.5, 53.1, 119.2, 127.5, 129.6, 129.6, 131.4, 135.5, 143.5, 152.4, 163.3; *m*/*z* (EI) 255 (M^+, 12), 229 (31), 215 (13), 150 (45), 77 (68), 72 (37), 63 (13), 44 (100). λ_{max} (MeOH): 208.4 nm ($\varepsilon\times10^{-3}$ 11.35 cm^{-1} M^{-1}), 213.4 (12.57), 244.2 (29.55%); ν_{max} (ATR) 3184, 3020, 1656, 1610, 1552, 1413, 1175, 1104, 1068, 1044, 945, 859, 817, 772, 694 cm^{-1}.

*4.4.8. 4-Phenyl-6,7,8,8a-tetrahydropyrrolo[1,2-d][1,2,4]triazin-1(2H)-one (**5g**).* This compound was obtained as a yellow solid in 75% yield; mp 145–147 °C; $[\alpha]_D^{20}$ +1.8 (MeOH, *c* 5); R_f (benzene/AcOEt, 1:3 v/v) 0.38; [Found: C, 66.88; H, 6.05; N, 19.47. $C_{12}H_{13}N_3O$ requires C, 66.95; H, 6.10; N, 19.51%]; δ_H (300 MHz, DMSO-d_6, Me_4Si) 1.60 (1H, m, H–C7), 1.80 (1H, m, H–C7), 2.19 (2H, m, H–C8), 3.21 (1H, m, H–C6), 3.51 (1H, m, H–C6), 3.93 (1H, t, *J* 6.9 Hz, H–C8a), 7.40–7.44 (3H, m, Ph–C4: H-3′, H-4′, H-5′), 7.58 (2H, d, *J* 6.9 Hz, Ph–C4: H-2′, H-6′), 10.57 (1H, s, H–N2); δ_C (DMSO-d_6) 23.6, 28.6, 50.89, 55.8, 128.2, 128.3, 129.8, 133.5, 147.7, 163.3; *m*/*z* (EI) 215 (M^+, 91), 186 (25), 159 (23), 158 (100), 145 (12), 118 (8), 104 (21), 91 (9), 77 (13), 68 (14), 51 (5), 41 (10%); λ_{max} (MeOH) 204.4 nm ($\varepsilon\times10^{-3}$ 21.78 cm^{-1} M^{-1}), 228.6 (14.98), 302.6 (5.82); ν_{max} (ATR) 3167, 3050, 2885, 1658, 1608, 1463, 1421, 1328, 1285, 1223, 1178, 1156, 1108, 1066, 1050, 1025, 927, 892, 819, 772, 728, 699, 688 cm^{-1}.

*4.4.9. 2-(1-Amino-1,1-diphenylmethyl)-5-phenyl-1,3,4-oxadiazole (**6h**).* This compound was obtained as a white solid in 85% yield; mp 140–141 °C; R_f (benzene/AcOEt, 1:3 v/v) 0.34; [Found: C, 76.98; H, 5.20; N, 12.80. $C_{21}H_{17}N_3O$ requires C, 77.04; H, 5.24; N, 12.83%]; δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.62 (2H, br s, NH_2), 7.30–7.51 (13H, m, $(Ph)_2$–C–C2, Ph–C5: H-3′, H-4′, H-5′), 7.99 (2H, d, *J* 8.1 Hz, Ph–C5: H-2′, H-6′); δ_C ($CDCl_3$) 62.9, 126.9, 127.2, 127.9, 128.3, 128.4, 128.9, 131.7, 143.5, 165.6, 170.7; *m*/*z* (EI) 327 (M^+, 26), 194 (100), 180 (25), 165 (10), 118 (85), 103 (11), 91 (13), 77 (42), 51 (14), 44 (17%); λ_{max} (MeOH) 206.0 nm ($\varepsilon\times10^{-3}$ 41.23 cm^{-1} M^{-1}), 253.2 (25.56); ν_{max} (ATR) 3369, 3293, 1604, 1558, 1546, 1490, 1449, 1361, 1196, 1184, 1168, 1098, 1086, 1067, 1028, 1013, 961, 949, 928, 862, 776, 755, 730, 701, 685 cm^{-1}.

*4.4.10. 5-(m-Nitrophenyl)-3-phenyl-1,2,4-triazin-6-one (**5i**).* This compound was obtained as a yellow solid in 45% yield; mp 190–192 °C; $[\alpha]_D^{20}$ −3.0 (MeOH, *c* 1); R_f (benzene/AcOEt, 1:3 v/v) 0.45; [Found: C, 60.75; H, 4.11; N, 18.83. $C_{15}H_{12}N_4O_3$ requires C, 60.80; H, 4.09; N, 18.90%]; δ_H (300 MHz, DMSO-d_6, Me_4Si) 5.31 (1H, d, *J* 2.1 Hz, H–C5), 7.43–7.46 (3H, m, Ph–C3: H-3′, H-4′, H-5′), 7.69 (1H, t, *J* 7.8 Hz, Ph–C5: H-5″), 7.78–7.83 (3H, m, Ph–C5: H-6″, Ph–C3: H-2′, H-6′), 8.17–8.20 (3H, m, Ph–C5: H-2″, H-4″, H–N4), 10.80 (1H, s, H–N1); δ_C (DMSO-d_6) 56.2, 122.0, 123.6, 126.7, 129.2, 130.7, 131.0, 132.7, 133.9, 143.1, 145.0, 148.5, 161.4; *m*/*z* (EI) 296 (M^+, 12), 281 (38), 221 (100), 207 (54), 161 (36), 159 (52), 146 (24), 77 (45), 73 (64), 44 (35%); λ_{max} (MeOH) 204.4 nm ($\varepsilon\times10^{-3}$ 28.77 cm^{-1} M^{-1}), 222.8 (18.62), 290.0 (8.27), 296.8 (8.08); ν_{max} (ATR) 3212, 3065, 1659, 1575, 1525, 1488, 1393, 1347, 1247, 1179, 1069, 1044, 1002, 925, 827, 803, 773, 724, 691 cm^{-1}.

*4.4.11. 2-(1-Amino-1-(m-nitrophenyl)methyl)-5-phenyl-1,3,4-oxadiazole (**6i**).* This compound was obtained as a yellow solid in 31% yield; mp 97–99 °C; $[\alpha]_D^{20}$ −1.5 (MeOH, *c* 1); R_f (benzene/AcOEt, 1:3 v/v) 0.13; [Found: C, 60.72; H, 4.07; N, 18.93. $C_{15}H_{12}N_4O_3$ requires C, 60.80; H, 4.09; N, 18.90%]; δ_H (300 MHz, DMSO-d_6, Me_4Si) 2.06 (2H, br s, NH_2), 6.24 (1H, s, C–H), 7.36–7.53 (3H, m, Ph–C5: H-3′, H-4′, H-5′), 7.92 (1H, t, *J* 7.8 Hz, Ph: H-5″), 8.08 (2H, d, *J* 7.8 Hz, Ph–C5: H-2′, H-6′), 8.22 (2H, d, *J* 7.8 Hz, Ph: H-4″, H-6″), 8.36 (1H, s, Ph: H-2″); δ_C (DMSO-d_6) 48.5, 122.6, 127.5, 128.7, 128.9, 129.2, 129.4, 129.9, 137.2, 143.3, 154.1, 164.1, 168.0; *m*/*z* (EI) 296 (M^+, 25), 206 (46), 146 (35), 105 (26), 104 (25), 103 (31), 91 (23), 77 (100), 44 (58%); λ_{max} (MeOH) 204.6 nm ($\varepsilon\times10^{-3}$ 34.89 cm^{-1} M^{-1}), 250.0 (18.90); ν_{max} (ATR) 2924, 1678, 1605, 1528, 1471, 1446, 1405, 1348, 1177, 1073, 1028, 922, 804, 771, 692 cm^{-1}.

4.5. X-ray crystal structure analysis for 6h

The single crystal of 2-(1-amino-1,1-diphenylmethyl)-5-phenyl-1,3,4-oxadiazole **6h** were used for data collection at 293 (2)K on a four-circle Oxford Diffraction Xcalibur diffractometer equipped with a two-dimensional CCD detector with graphite monochromatised Mo Kα radiation (λ=0.71073 Å) and the ω-scan technique. Integration of the intensities and correction for Lorenz and polarisation effects were performed using CrysAlis RED software.[44] Crystal structures were solved by direct methods and refined by a full-matrix least-squares method on F^2 using the program SHELXL-97.[45]

Empirical formula $C_{21}H_{17}N_3O$, formula weight 327.38, crystal size 0.16×0.17×0.20 mm, crystal system orthorhombic, space group Pbca (No. 61), unit cell dimensions: *a*=9.3893(2) Å, *b*=14.7810(3) Å, *c*=24.8854(4) Å, *V*=3453.68(12) $Å^3$, *Z*=8, calculated density 1.259 Mg/m^3, absorption coefficient 0.080 mm^{-1}, *F*(000)=1376, θ range for data collection: 3.05–25.00°, limiting indices: $-11\le h\le10$, $-17\le k\le17$, $-29\le l\le29$, reflections collected/unique: 20345/3035 [R_{int}=0.0236], data/parameters: 3035/233, goodness-of-fit on F^2 1.067, final *R* indices [$I>2\sigma(I)$]: R_1=0.0314, wR_2=0.0865, *R* indices (all data): R_1=0.0389, wR_2=0.0895, largest diff. peak and hole: 0.150 and −0.127 $eÅ^{-3}$. The H atoms were positioned geometrically and treated as riding on their parent atoms, with C–H distances of 0.930 Å (aromatic). The amino H-atoms coordinate parameters are refined only.

Complete crystallographic details for **6h** are available as Supplementary data (CCDC 827086) and have been deposited at the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge, CB21EZ, UK; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk. Any request to the CCDC for this material should quote the full literature citation.

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