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# Study of the nucleophilic behaviour of *N*-phenylbenzamidine towards 1,2-diaza-1,3-dienes: domino reactions for imidazole scaffolds

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ABSTRACT

Depending on the nature of the solvent, alcohol or DMF, *N*-phenylbenzamidine shows different nucleophilic behaviour towards the conjugated azo–ene system of 1,2-diaza-1,3-dienes. In alcohol it reacts as a nucleophile through the *N*-phenyl imino nitrogen affording spiro pyrroloimidazoles and 1,3-diphenyl-1*H*-imidazoles. In DMF, by contrast, it behaves as nucleophile mainly by means of the imino amidino nitrogen providing 2-phenylimidazole derivatives by loss of the aniline molecule.



## 1. Introduction

The development of new methods for the synthesis of azaheterocycles[1] is of particular interest in organic chemistry since they occur in a wide variety of natural products.[2] This is especially true for nitrogen-containing five-membered ring, such as imidazoles,[3] which are core components of a large number of substances that possess a wide range of interesting biological activities.[4] In particular, 2-arylimidazoles represent an important class of structures because of their reported antifungal,[5] NPY5 receptor antagonism[6] and macromolecular ligand[7] properties. Due to their importance, many methods have been developed for assembling the imidazole ring.[8] In connection with our ongoing interest to employ 1,2-diaza-1,3-dienes (DDs) as building blocks for heterocyclic skeletons,[9] recently we reported the Michael addition of arylamidines to azo–ene system for the synthesis of 2-arylimidazole derivatives and spirocyclic compounds including the imidazole framework.[10] Starting from these results, we envisaged the opportunity to investigate the nucleophilic behaviour of *N*-phenylbenzamidine (PBA)[11] towards DDs in order to enlarge our approach for the synthesis of imidazole-containing compounds. Even if two tautomeric forms can be expected for PBA (Fig. 1), previously reported IR spectra[12] and $^{15}$N NMR studies[13] show that the predominant tautomer of PBA has the C=N double bond conjugated with the phenyl group (Fig. 1, amino form B). Since each tautomeric form possesses potential nucleophilic sites, we hypothesized that, depending on the reaction solvent (alcohol or DMF), the nucleophilic behaviour of such a bidentate molecule could change and thus influence the results of the reaction with DDs.

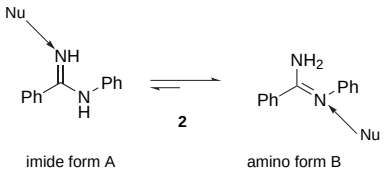


**Figure 1.** Tautomeric equilibrium of *N*-phenylbenzamidine with potential nucleophilic centres.

## 2. Results and discussion

On the basis of our previous results,[10] in which arylamidines reacted with DDs **1** in 1:2 ratios to afford spiro pyrroloimidazoles, we planned to perform a one-pot reaction of DDs **1a**–**d** (2 equiv) and PBA **2** (1 equiv) in MeOH or EtOH, firstly at room temperature until the disappearance of the reagents and then under reflux to promote the conversion of the intermediates (Scheme 1). By

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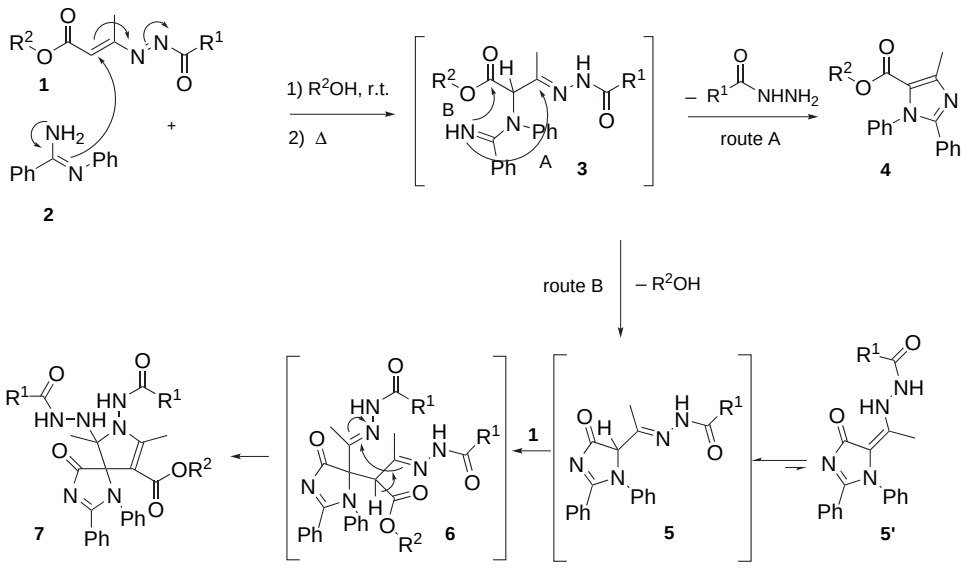



**Scheme 1.** Reaction pathway between **1** (2 equiv) and **2** (1 equiv) in MeOH or EtOH.

column chromatography of the crude reaction mixture, we found two main products: **4** and **7** (Table 1). As shown in Scheme 1, the reaction pathway proceeds via nucleophilic attack of PBA **2** through the imino *N*-phenyl nitrogen at the terminal carbon atom of the conjugated azo–ene system of **1** to give hydrazone intermediate **3** by Michael-type addition. At this point two different internal cyclization routes are possible for the intermediate **3**: one (route A) in which the imino amidino function provides a nucleophilic attack at the hydrazono moiety affording 1,2-diphenyl-1*H*-imidazole derivative **4** by loss of a hydrazinecarboxylic ester residue, the other (route B), in which the same function attacks the ester group at C4 producing 4*H*-imidazol-5-one derivative **5** by loss of an alcohol molecule, According to our previous results,[10] the carbanion formation from **5**, catalyzed by the amidine itself, gives rise to nucleophilic 1,4-addition to another molecule of **1** furnishing the intermediate **6**. Finally, the two hydrazone side chains of **5** cooperate in the pyrroline ring closure producing spiro pyrroloimidazole derivative **7** as a diastereomeric mixture (ranging from 52 to 65%, see Table 1).

**Table 1**
Results of the reactions of DDs **1** and PBA **2** in MeOH or EtOH

| Entry | DD **1** | | | 1,3-Diphenyl-1*H*-imidazole **4** | | | Spiro Pyrroloimidazole **7** | | | 4*H*-Imidazol-5-one **5**/**5′** | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $R^1$ | $R^2$ | | $R^2$ | Yield[b] (%) | | Yield[a] (%) C4(*S*/*R*),C6(*S*/*R*) | Yield[a] (%) C4(*S*/*R*),C6(*R*/*S*) | | $R^1$ |
| 1 | **1a** | OMe | Me | **4a** | Me | 15 | **7a** | 20 | 32 | **5′a** | OMe |
| 2 | **1b** | OMe | Et | **4b** | Et | 16 | **7b** | 26 | 29 | | |
| 3 | **1c** | O$^t$Bu | Me | **4a** | Me | 8 | **7c** | 30 | 35 | | |
| 4 | **1d** | O$^t$Bu | Et | **4b** | Et | 10 | **7d** | 32 | 33 | | |

[a] Yield of pure isolated diastereomer based on **2**.
[b] Yield of pure isolated product based on **2**.

Confirmation of this reaction pathway is given by means of the occasional isolation of the hydrazino tautomeric form **5′a** and by the X-ray structure determination of the diastereomer 4*S*/*R*,6*S*/*R* of **7a** (Table 1) (Fig. 2).[14]

The structure of imidazole **4**, arising from the loss of the hydrazide residue, was deduced by comparison of **4a** with its regioisomer, which appeared in the literature.[15] Since the ester function at C4 of **1** played a key role in route B, we thought that its replacement with an amide residue could allow the regioselective ring closure according to route A and the unambiguous assignment of the structure **4**. In fact, the reaction in EtOH between **1e** and **2** in equimolar ratio (Scheme 2), afforded **4e** (70%).

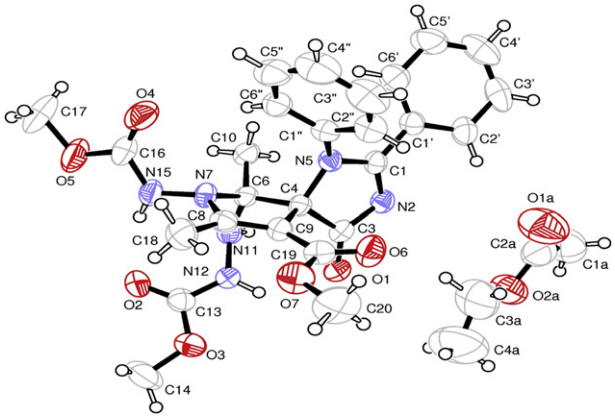
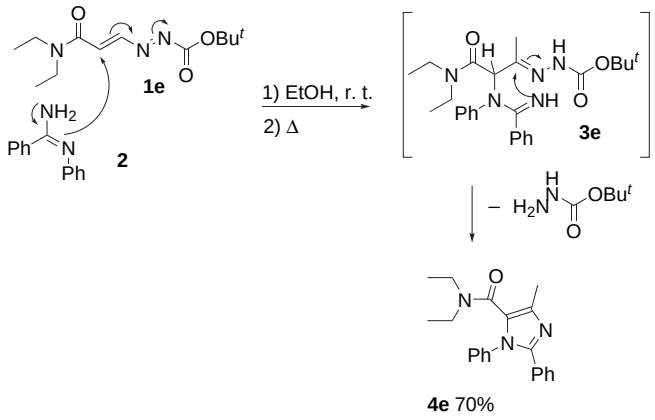


**Figure 2.** X-ray molecular structure of **7a** with EtOAc molecule enclosed.

The X-ray study of **4e** (Fig. 3)[16] confirmed the hypothesized structure obtained from intermediate **3** through route A. Both derivatives **4** and **7** establish, thus, the involvement of the *N*-phenyl nitrogen of PBA **2** in the nucleophilic addition on DDs in alcoholic medium.




**Scheme 2.**

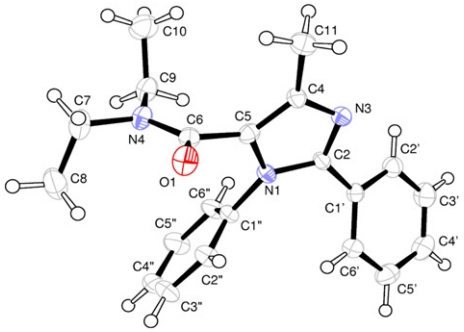
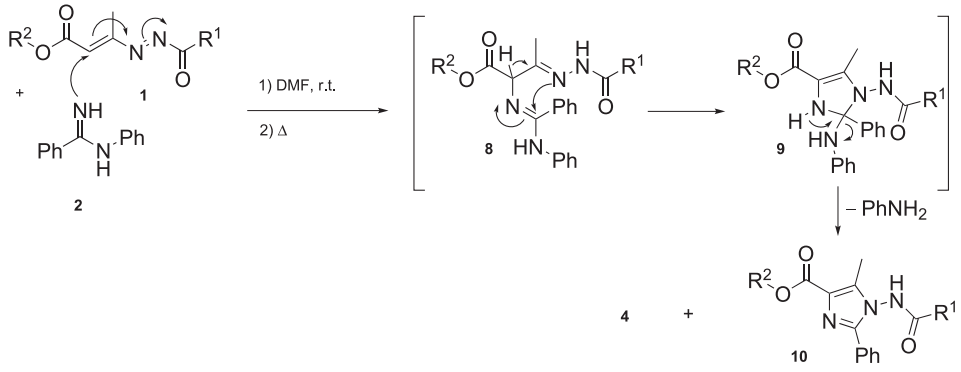



**Figure 3.** Crystal structure of **4e**.

Next, based on NMR studies carried out by Clement,[13] we decided to investigate the reactions between DDs **1a**–**h** (2 equiv) and PBA **2** (1 equiv) in DMF under the same conditions: at room temperature, until the disappearance of the reagents and then under reflux. After the removal of DMF and chromatographic purification of the crude products, imidazole derivatives **4a**–**d** (14–38%) and new alkyl 1-[(alkoxycarbonyl)amino]-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylate derivatives **10a**–**h** (57–70%) were obtained (see Scheme 3 and Table 2). The prevalent formation of these last compounds requires the nucleophilic attack by the unsubstituted nitrogen of **2** at the azo–ene system resulting in the Michael adduct **8**. The subsequent intramolecular nucleophilic attack of the $sp^2$ hydrazone nitrogen at the imino function of the amidine residue, affords intermediate **9** that in turn provides 2-phenylimidazole derivative **10** by extrusion of an aniline molecule. In DMF, therefore, both the imino nitrogen of PBA **2** (Fig. 1) are operative in the nucleophilic addition.

Both reaction pathways, in protic and non protic polar medium, implicate the role of the amidine derivative as nucleophile as well as base in a domino heterocyclization process. Besides, the different imidazole derivatives obtained allows us to assert that PBA **2** acts as a nucleophile by the *N*-substituted imino group of the amino form in alcohol; on the contrary, the nucleophilic attack through the *N*-unsubstituted imino function of the imide form is favoured in DMF.

In order to extend the scope for the cascade spiro annulation process, the reaction of DDs **1** with *N*,*N*′-diphenylguanidine (DPG) **11**,[11] under the optimized stoichiometric conditions, was then examined. All the reactions carried out in alcohol were exothermic and **11**, being a stronger base with respect to PBA **2**, worked so well to rapidly produce spiroheterocycles **15** that these were often obtained by precipitation (**15c**,**d**) from the reaction medium at room temperature (Scheme 4, Table 3). In some cases, 2-anilino-1-phenylimidazol-4-one derivative intermediate **13** (Table 3) was separated by chromatography. The formation of **15** can be

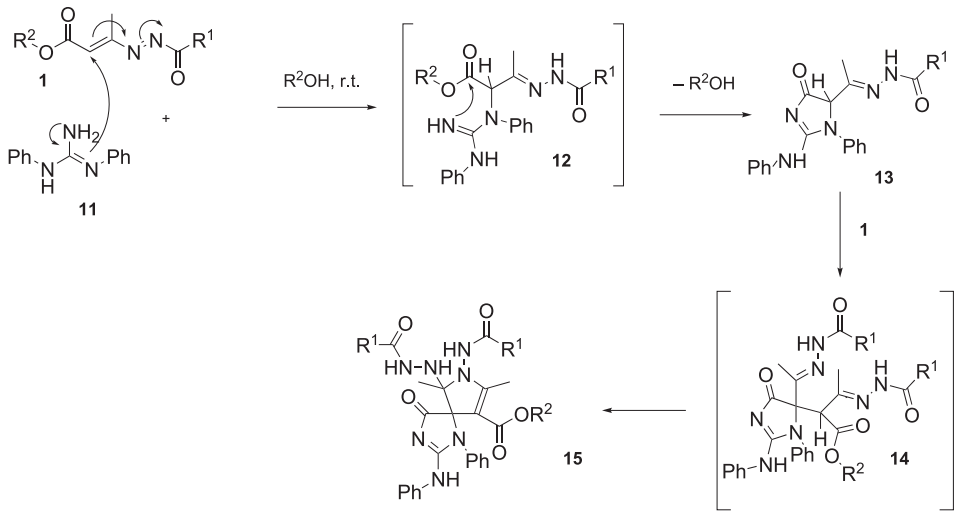



**Scheme 3.** Reaction pathway between DDs **1** and PBA **2** in DMF.

**Table 2**
Results of the reactions between DDs **1** and PBA **2** in DMF

| Entry | DD **1** | | | 1,2-Diphenyl-1*H*-imidazole **4** | | | Alkyl 1-[(alkoxycarbonyl)amino]-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylate **10** | |
|---|---|---|---|---|---|---|---|---|
| | | $R^1$ | $R^2$ | | $R^2$ | Yield[a] (%) | | Yield[a] (%) |
| 1 | **1a** | OMe | Me | **4a** | Me | 14 | **10a** | 58 |
| 2 | **1b** | OMe | Et | **4b** | Et | 17 | **10b** | 70 |
| 3 | **1c** | O$^t$Bu | Me | **4a** | Me | 26 | **10c** | 59 |
| 4 | **1d** | O$^t$Bu | Et | **4b** | Et | 25 | **10d** | 60 |
| 5 | **1e** | OEt | Et | **4b** | Et | 21 | **10e** | 63 |
| 6 | **1f** | O$^t$Bu | *i*-Pr | **4c** | *i*-Pr | 38 | **10f** | 58 |
| 7 | **1g** | OBn | Me | **4a** | Me | 29 | **10g** | 66 |
| 8 | **1h** | OMe | Allyl | **4d** | Allyl | 20 | **10h** | 57 |

[a] Yield of pure isolated product based on **2**.




**Scheme 4.** Reaction pathway between **1** (2 equiv) and **11** (1 equiv) in MeOH or EtOH.

**Table 3**
Results of the reactions of DDs **1** and DPG **11** in MeOH or EtOH

| Entry | DD **1** | | | 2-Anilino-1-phenylimidazol-4-one **13** | | | Spiro pyrroloimidazole **15** | | |
|---|---|---|---|---|---|---|---|---|---|
| | | R1 | R2 | | R1 | | | Yield[a] (%) C4(*S*/*R*),C6(*R*/*S*) | Yield[a] (%) C4(*S*/*R*),C6(*S*/*R*) |
| 1 | **1a** | OMe | Me | **13a** | OMe | 40 | **15a** | 36 | |
| 2 | **1b** | OMe | Et | **13a** | OMe | 38 | **15b** | 41 | |
| 3 | **1c** | O$^t$Bu | Me | | | | **15c** | 47 | 23 |
| 4 | **1d** | O$^t$Bu | Et | | | | **15d** | 49 | 24 |
| 5 | **1e** | OEt | Et | **13b** | OEt | 37 | **15e** | 49 | |

[a] Yield of pure isolated product based on **11**.

explained by the attack of *N*-phenyl imino group of DPG **11** at the terminal carbon of the conjugated azo–ene system of DDs **1** to give hydrazone derivative **12** that in turn, by formal [3+2] cyclization, affords **13** by loss of an alcohol molecule. This last one, by DPG-promoted carbanion formation, adds to another DD molecule in a Michael fashion providing the intermediate **14**. Subsequent intramolecular cyclization between the two hydrazone side chains finally produces spiro pyrroloimidazole derivative **15**.

The X-ray diffraction study of **15a** confirmed the structure hypothesized by spectroscopic data (Fig. 4)[17] and allowed us to establish the stereochemical assignement of the two stereogenic carbons of the major diastereomer.

Conversely, complicated reaction mixtures were obtained when DPG **11** was tested to react with DDs in DMF.

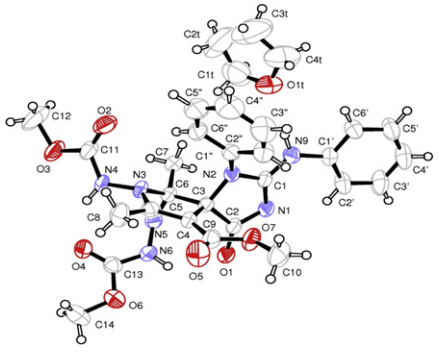


**Figure 4.** X-ray molecular structure of **15a**.

## 3. Conclusions

In summary, based on the products, which resulted from the study of the reactivity of PBA **2** with DDs **1** in different polar solvents, we can conclude that **2** behaves as a nucleophile with the *N*-phenyl imino group in alcoholic solvents, whereas the imino amidino nitrogen prevailes as the nucleophile in DMF. The choice of solvent is, therefore, strategic in influencing the nucleophilic behaviour of PBA, allowing the acquisition of structurally different imidazole scaffolds. In both routes, moreover, PBA plays a critical role in the success of the reaction by serving as base for the intramolecular ring closure and for the spirocyclization process. Similarly, DPG **11** realizes carbon/nitrogen bond formation with DDs **1** by nucleophilic attack of the substituted imino nitrogen in alcoholic solvents, and acts as base for the construction of complex spiro azaheterocycles through a domino process.

## 4. Experimental

### 4.1. General experimental section

*N*-Phenylbenzamidine and *N*,*N*′-diphenylguanidine were commercial materials and were used without further purification. 1,2-Diaza-1,3-dienes were prepared as reported[9] and solvents were used without further purification. Melting points were determined in open capillary tubes and are uncorrected. FTIR spectra were obtained as Nujol mulls. Mass spectra (MS) were carried out by electron impact (EI) at an ionizing voltage of 70 eV. $^1$H (400 MHz) and $^{13}$C (100 MHz) spectra were recorded in $CDCl_3$ or in DMSO-$d_6$, as specified below. Chemical shifts ($\delta_H$) are reported in parts per

million (ppm), relative to TMS as internal standard. All coupling constant (*J* values) are given in hertz (Hz). The abbreviations for the multiplicity are used as follows: s, singlet; d, doublet; dd, double-doublet; t, triplet; q, quartet; sept, septet; m, multiplet; br, broad; ArH, aromatic hydrogen. All the NH exchanged with $D_2O$. Chemical shifts ($\delta_C$) are reported in parts per million (ppm), relative to the central peak of $CDCl_3$ or DMSO-$d_6$ as internal standard. Precoated silica gel plates 0.25 mm were employed for analytical thin layer chromatography and silica gel 35–70 μm for column chromatography. All new compounds showed satisfactory elemental analysis (C+0.35; H+0.30; N+0.30). The nomenclature was generated using ACD/IUPACName (version 3.50, 5 Apr. 1998), Advanced Chemistry Development Inc., Toronto, ON (Canada).

### 4.2. General procedure for the reactions of PBA in alcohol

In a 25-mL flask, PBA **2** (1 mmol) was dissolved in MeOH or EtOH (2 mL) and a solution of DD **1a**–**d** (2 mmol) in the same solvent (4 mL) was added dropwise quickly. The reaction mixture was stirred at room temperature until the disappearance of DD was confirmed by TLC (0.3–1.0 h). Upon completion, the reaction mixture was heated under reflux (1–4 h) until its colour turned purple and the intermediates evolved in two major spots (by TLC). After removal of the solvent in vacuo, the residue was purified by chromatography (silica gel, DCM/EtOAc) to give **4a**,**b** and **7a**–**d**.

*4.2.1. Methyl 4-methyl-1,2-diphenyl-1H-imidazole-5-carboxylate (**4a**).* Yield: 43.8 mg (15%). White powder, mp: 144–147 °C (from EtOAc). IR (Nujol) $\nu_{max}$ 1713, 1600, 1538, 1499 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 2.63 (3H, s, $CH_3$), 3.71 (3H, s, $OCH_3$), 7.19–7.22 (5H, m, ArH), 7.31–7.33 (2H, m, ArH), 7.39–7.41 (3H, m, ArH). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 16.1, 51.6, 122.0, 128.5, 128.6, 129.2, 129.3, 129.4, 129.9, 138.3, 148.2, 150.3, 161.4. MS (EI): *m*/*z* (%)=292 ($M^+$, 100), 261 (18), 233 (8), 130 (35). Anal. Calcd for $C_{18}H_{16}N_2O_2$ (292.33): C, 73.95; H, 5.52; N, 9.58. Found: C, 74.30; H, 5.48; N, 9.72.

*4.2.2. Ethyl 4-methyl-1,2-diphenyl-1H-imidazole-5-carboxylate (**4b**).* Yield: 52.1 mg (52%). White powder, mp: 111–114 °C (from DCM/*n*-pentane). IR (Nujol) $\nu_{max}$ 1699, 1681, 1597, 1562, 1500 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$: 0.98 (3H, t, *J*=7.2 Hz, $OCH_2CH_3$), 2.48 (3H, s, $CH_3$), 4.00 (2H, q, *J*=7.2 Hz, $OCH_2CH_3$), 7.20–7.30 (7H, m, ArH), 7.38–7.43 (3H, m, ArH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$: 13.7, 15.3, 59.7, 121.5, 128.1, 128.3, 128.7, 128.8, 128.9, 129.0, 129.5, 137.7, 146.6, 148.9, 159.6. MS (EI): *m*/*z* (%)=306 ($M^+$, 100), 277 (24), 261 (17), 234 (29), 130 (33). Anal. Calcd for $C_{19}H_{18}N_2O_2$ (306.35): C, 74.49; H, 5.92; N, 9.14. Found: C, 74.56; H, 6.02; N, 9.10.

*4.2.3. Methyl 2-[1-(5-oxo-2,3-diphenyl-3,5-dihydro-4H-imidazol-4-ylidene)ethyl]hydrazinecarboxylate (**5′a**).* Yield: 35 mg (10%). Beige solid, mp: 217–218 °C (from MeOH). IR (Nujol) $\nu_{max}$ 3220, 3085, 1746, 1714, 1605, 1534 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.97 (3H, s, $CH_3$), 3.72 (3H, s, $OCH_3$), 7.14–7.27 (5H, m, Ph), 7.36 (2H, t, *J*=8 Hz, ArH), 7.47 (1H, t, *J*=8 Hz, ArH), 7.54 (2H, d, *J*=8 Hz, ArH), 10.23 (1H, s, NH), 11.41 (1H, br s, NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$: 13.6, 52.0, 94.1, 128.0, 128.5, 128.6, 129.2, 130.0, 132.3, 138.1, 148.7, 155.0, 160.2, 178.1, 186.94. Anal. Calcd for $C_{19}H_{18}N_4O_3$ (350.37): C, 65.13; H, 5.18; N, 15.99. Found: C, 64.89; H, 5.30; N, 16.06.

*4.2.4. Methyl 7-[(methoxycarbonyl)amino]-6-[2-(methoxycarbonyl) hydrazino]-6,8-dimethyl-4-oxo-1,2-diphenyl-1,3,7-triazaspiro[4.4] nona-2,8-diene-9-carboxylate (**7a**): 4S/R,6S/R isomer.* Yield: 107.3 mg (20%). Colourless crystals, mp: 212–213 °C dec (from EtOAc). IR (Nujol) $\nu_{max}$ 3434, 3209, 3089, 1752, 1732, 1722, 1683, 1610, 1588, 1550 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.51 (3H, s, $CH_3$), 1.85 (3H, s, $CH_3$), 3.39 (3H, s, $OCH_3$), 3.59 (3H, s, $OCH_3$), 3.78 (3H, s, $OCH_3$), 6.38 (1H, s, NH), 7.20 (5H, br s, Ph), 7.42 (2H, t, *J*=8.4 Hz, ArH), 7.55 (1H, t, *J*=8.4 Hz, ArH), 7.64 (2H, d, *J*=8.4 Hz, ArH), 7.99 (1H, s, NH), 8.92 (1H, s, NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$: 11.0, 15.7, 50.4, 52.5, 52.8, 81.7, 89.6, 93.4, 127.7, 128.4, 128.7, 129.0, 130.2, 132.9, 137.5, 156.8, 162.9, 167.6, 179.8, 189.7. MS (EI): *m*/*z* (%)=536 ($M^+$, 1), 447 (100), 415 (6), 340 (5), 312 (4), 284 (5). Anal. Calcd for $C_{26}H_{28}N_6O_7$ (536.53): C, 58.20; H, 5.26; N, 15.66. Found: C, 58.42; H, 5.23; N, 15.48.

4*S*/*R*,6*R*/*S* isomer: Yield: 171.7 mg (32%). Beige solid, mp: 123–125 °C dec (from THF/*n*-pentane). IR (Nujol) $\nu_{max}$ 3349, 3331, 3290, 1740, 1735, 1720, 1600 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.28 (3H, s, $CH_3$), 1.83 (3H, s, $CH_3$), 3.56 (3H, s, $OCH_3$), 3.69 (3H, s, $OCH_3$), 3.75 (3H, s, $OCH_3$), 5.61 (1H, br s, NH), 7.14 (5H, br s, Ph), 7.35 (2H, t, *J*=7.6 Hz, ArH), 7.46 (1H, t, *J*=7.6 Hz, ArH), 7.65 (2H, d, *J*=7.6 Hz, ArH), 9.68 (1H, br s, NH), 10.39 (1H, br s, NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$: 11.6, 17.1, 50.3, 51.6, 52.6, 79.2, 88.7, 95.1, 127.1, 127.9, 128.0, 129.6, 130.2, 130.7, 132.2, 138.7, 154.4, 157.2, 163.9, 165.0, 180.1, 187. 7. MS (EI): *m*/*z* (%)=536 ($M^+$, 1), 447 (100), 415 (7), 340 (6), 312 (5), 284 (5). Anal. Calcd for $C_{26}H_{28}N_6O_7$ (536.53): C, 58.20; H, 5.26; N, 15.66. Found: C, 58.32; H, 5.33; N, 15.48.

*4.2.5. Ethyl 7-[(methoxycarbonyl)amino]-6-[2-(methoxycarbonyl) hydrazino]-6,8-dimethyl-4-oxo-1,2-diphenyl-1,3,7-triazaspiro[4.4] nona-2,8-diene-9-carboxylate (**7b**): 4S/R,6S/R isomer.* Yield: 143.1 mg (26%). White solid, mp: 219–220 °C dec (from MeOH). IR (Nujol) $\nu_{max}$ 3302, 3236, 3190, 1743, 1721, 1687, 1601, 1553 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 1.17 (3H, t, *J*=7.2 Hz, $OCH_2CH_3$), 1.73 (3H, s, $CH_3$), 1.97 (3H, s, $CH_3$), 3.63 (3H, s, $OCH_3$), 3.85 (3H, s, $OCH_3$), 3.88–4.01 (2H, m, $OCH_2CH_3$), 4.69 (1H, br s, NH), 7.18 (5H, br s, Ph), 7.28 (2H, t, *J*=8.4 Hz, ArH), 7.43 (1H, t, *J*=8.4 Hz, ArH), 7.69 (2H, d, *J*=8.4 Hz, ArH), 7.94 (1H, s, NH), 8.99 (1H, s, NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$: 11.7, 14.6, 16.6, 53.1, 53.4, 60.0, 82.8, 90.5, 95.0, 128.3, 128.9, 129.3, 129.6, 131.2, 133.1, 138.2, 158.1, 158.3, 163.8, 169.1, 180.7, 190.3. MS (EI): *m*/*z* (%)=550 ($M^+$, 1), 461 (27), 279 (30), 252 (100). Anal. Calcd for $C_{27}H_{30}N_6O_7$ (550.56): C, 58.90; H, 5.49; N, 15.26. Found: C, 58.76; H, 5.52; N, 15.43.

4*S*/*R*,6*R*/*S* isomer: yield: 159.7 mg (29%). Beige solid, mp: 119–122 °C dec (from $Et_2O$/light petroleum ether). IR (Nujol) $\nu_{max}$ 3536, 3276, 3220, 1738, 1725, 1703, 1608 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.09 (3H, t, *J*=6.8 Hz, $OCH_2CH_3$), 1.30 (3H, s, $CH_3$), 1.81 (3H, s, $CH_3$), 3.66–3.85 (8H, m, $2CH_3$ and $OCH_2CH_3$), 5.62 (1H, br s, NH), 7.14 (5H, br s, Ph), 7.35 (2H, t, *J*=7.6 Hz, ArH), 7.46 (1H, t, *J*=7.6 Hz, ArH), 7.63 (2H, d, *J*=7.6 Hz, ArH), 8.18 (1H, br s, NH), 9.66 (1H, br s, NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$: 11.5, 14.0, 17.08, 51.6, 52.7, 58.9, 79.3, 88.8, 95.4, 127.2, 128.1, 128.9, 129.7, 130.6, 132.3, 138.6, 157.3, 163.5, 165.0, 180.1, 187.8. Anal. Calcd for $C_{27}H_{30}N_6O_7$ (550.56): C, 58.90; H, 5.49; N, 15.26. Found: C, 58.69; H, 5.53; N, 15.34.

*4.2.6. Methyl 7-[(tert-butoxycarbonyl)amino]-6-[2-(tert-butoxycarbonyl)hydrazino]-6,8-dimethyl-4-oxo-1,2-diphenyl-1,3,7-triazaspiro[4.4]nona-2,8-diene-9-carboxylate (**7c**): 4S/R,6S/R isomer.* Yield: 186.2 mg (30%). White solid, mp: 222–223 °C dec (from MeOH). IR (Nujol) $\nu_{max}$ 3347, 3227, 3075, 1747, 1729, 1711, 1690, 1609, 1598 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.37 (9H, s, $O^tBu$), 1.49 (3H, s, $CH_3$), 1.52 (9H, s, $O^tBu$), 1.85 (3H, s, $CH_3$), 3.38 (3H, s, $OCH_3$), 6.19 (1H, s, NH), 7.19 (5H, br s, Ph), 7.41 (2H, t, *J*=7.6 Hz, ArH), 7.54 (1H, t, *J*=7.6 Hz, ArH), 7.65 (2H, d, *J*=7.6 Hz, ArH), 7.78 (1H, s, NH), 8.77 (1H, s, NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$: 11.2, 15.8, 27.9, 28.0, 50.4, 79.9, 80.8, 81.9, 89.7, 92.9, 127.6, 128.4, 128.7, 129.1, 130.2, 132.9, 137.6, 155.6, 155.7, 163.1, 167.6, 179.8, 189.8. MS (EI): *m*/*z* (%)=489 ([M−NHNHBoc]$^+$, 55), 433 (100), 389 (6), 340 (5). Anal. Calcd for $C_{32}H_{40}N_6O_7$ (620.69): C, 61.92; H, 6.50; N, 13.54. Found: C, 61.84; H, 6.61; N, 13.63.

4*S*/*R*,6*R*/*S* isomer: yield: 217.2 (35%). Beige solid, mp: 189–191 °C dec (from EtOAc/*n*-pentane). IR (Nujol) $\nu_{max}$ 3360, 3330, 3206, 1752, 1680, 1599 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.24 (9H, s, $O^tBu$),

1.40 (9H, s, O$^t$Bu), 1.77 (3H, s, $CH_3$), 1.85 (3H, s, $CH_3$), 3.36 (3H, s, $OCH_3$), 5.63 (1H, br s, NH), 7.13 (5H, br s, Ph), 7.34 (2H, t, $J$=7.6 Hz, ArH), 7.45 (1H, t, $J$=7.6 Hz, ArH), 7.73 (2H, d, $J$=7.6 Hz, ArH), 8.96 (1H, br s, NH), 9.41 (1H, br s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 11.5, 16.9, 27.8, 28.1, 50.3, 79.8, 80.8, 81.7, 88.7, 94.8, 127.2, 128.1, 128.9, 129.7, 130.7, 132.3, 138.6, 155.1, 156.0, 163.8, 165.3, 179.9, 187.3. MS (EI): $m/z$ (%)=489 ([M−NHNHBoc]$^+$, 74), 433 (100), 389 (7), 340 (5). Anal. Calcd for $C_{32}H_{40}N_6O_7$ (620.69): C, 61.92; H, 6.50; N, 13.54. Found: C, 61.88; H, 6.64; N, 13.66.

*4.2.7. Ethyl 7-[(tert-butoxycarbonyl)amino]-6-[2-(tert-butoxycarbonyl)hydrazino]-6,8-dimethyl-4-oxo-1,2-diphenyl-1,3,7-triazaspiro[4.4]nona-2,8-diene-9-carboxylate (**7d**): 4S/R,6S/R isomer.* Yield: 203.1 mg (32%). White solid, mp: 214–215 °C dec (from EtOH). IR (Nujol) $\nu_{max}$ 3337, 3220, 3079, 1736, 1718, 1687, 1613, 1563 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 1.16 (3H, t, $J$=7.2 Hz, $OCH_2CH_3$), 1.40 (9H, s, O$^t$Bu), 1.54 (9H, s, O$^t$Bu), 1.66 (3H, s, $CH_3$), 1.97 (3H, s, $CH_3$), 3.86–4.00 (2H, m, $OCH_2CH_3$), 4.38 (1H, br s, NH), 7.12–7.17 (5H, br s, Ph), 7.29 (2H, t, $J$=7.6 Hz, ArH), 7.43 (1H, t, $J$=7.6 Hz, ArH), 7.69 (2H, d, $J$=7.6 Hz, ArH), 7.71 (1H, s, NH), 8.70 (1H, s, NH). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 11.8, 14.6, 16.6, 28.7, 28.8, 59.8, 81.2, 81.5, 83.0, 90.2, 94.0, 128.1, 128.9, 129.2, 131.3, 133.3, 138.2, 156.6, 156.8, 163.90, 180.5, 190.0. MS (EI): $m/z$ (%)=503 ([M−NHNHBoc]$^+$, 75), 447 (100), 403 (5), 375 (3), 340 (6). Anal. Calcd for $C_{33}H_{42}N_6O_7$ (634.72): C, 62.45; H, 6.67; N, 13.24. Found: C, 62.58; H, 6.75; N, 13.50.

4*S*/*R*,6*R*/*S* isomer: yield: 209.5 mg (33%). White solid, mp: 184–185 °C dec (from $Et_2O$/light petroleum ether). IR (Nujol) $\nu_{max}$ 3277, 3181, 3067, 1753, 1725, 1703, 1657, 1607 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.05 (3H, t, $J$=6.8 Hz, $OCH_2CH_3$), 1.24 (9H, s, O$^t$Bu), 1.28 (3H, s, $CH_3$), 1.41 (9H, s, O$^t$Bu), 1.77 (3H, s, $CH_3$), 3.74–3.86 (2H, m, $OCH_2CH_3$), 5.64 (1H, br s, NH), 7.13 (5H, br s, Ph), 7.34 (2H, t, $J$=7.6 Hz, Ar), 7.47 (1H, t, $J$=7.6 Hz, Ar), 7.72 (2H, d, $J$=7.6 Hz, Ar), 8.40 (1H, br s, NH), 9.40 (1H, br s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 11.5, 14.0, 16.9, 58.7, 78.7, 79.4, 80.5, 89.0, 93.8, 127.1, 127.7, 127.9, 129.6, 130.8, 132.1, 138.4, 154.9, 156.0, 163.3, 165.1, 180.0, 187.5. MS (EI): $m/z$ (%)=503 ([M−NHNHBoc]$^+$, 70), 447 (100), 403 (6), 375 (4), 340 (7). Anal. Calcd for $C_{33}H_{42}N_6O_7$ (634.72): C, 62.45; H, 6.67; N, 13.24. Found: C, 62.61; H, 6.59; N, 13.36.

### 4.3. General procedure for the synthesis of *N*5,*N*5-diethyl-4-methyl-1,2-diphenyl-1*H*-5-imidazolecarboxamide (7e)

In a 25-mL flask, PBA **2** (1 mmol) was dissolved in EtOH (2 mL) and a solution of DD **1e** (1 mmol) in the same solvent (4 mL) was added dropwise quickly. The reaction mixture was stirred at room temperature until the disappearance of **1e** was confirmed by TLC (6.0 h). Upon completion, the reaction mixture was heated under reflux (8 h) until the polar intermediates evolved into a major non polar spot (by TLC). After removal of the solvent in vacuo, the residue was purified by chromatography (silica gel, DCM/EtOAc mixtures) to obtain **4e**.

*4.3.1. N5,N5-Diethyl-4-methyl-1,2-diphenyl-1H-5-imidazolecarboxamide (**4e**).* Yield: 233.4 mg (70%). Colourless crystals, mp: 140–141 °C (from EtOAc/light petroleum ether). IR (Nujol), $\nu_{max}$ 1655, 1637, 1595, 1498 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 0.82 (3H, br s, $NCH_2CH_3$), 0.92 (3H, br s, $NCH_2CH_3$), 2.18 (3H, s, $CH_3$), 3.19 (4H, br s, 2 $NCH_2CH_3$), 7.22–7.29 (7H, m, ArH), 7.40–7.43 (3H, m, ArH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 12.1, 12.9, 13.9, 37.7, 42.2, 126.4, 127.2, 128.1, 128.3, 128.6, 129.2, 129.9, 134.4, 136.6, 145.4, 161.2. MS (EI): $m/z$ (%)=333 (M$^+$, 88), 261 (100), 234 (95), 193 (22), 130 (51). Anal. Calcd for $C_{21}H_{23}N_3O$ (333.43): C, 75.65; H, 6.95; N, 12.60. Found: C, 75.50; H, 6.71; N, 12.58.

### 4.4. General procedure for the reactions of PBA in DMF

In a 5-mL flask, PBA **2** (1 mmol) was dissolved in DMF (1 mL) and a solution of DD **1a**–**h** (2 mmol) in DMF (2 mL) was then added at room temperature with stirring. After the disappearance of DD (0.2–0.5 h), monitored by TLC, the crude reaction mixture was heated (0.5 h) until its colour turned brown (0.5–1 h). After partial evaporation of DMF in vacuo, the crude was dissolved in EtOAc (20 mL) and washed with $H_2O$ (5×5 mL). The organic layer was dried ($Na_2SO_4$), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, cyclohexane/EtOAc) to separate **4a**–**d** from **10a**–**h**.

*4.4.1. Isopropyl 4-methyl-1,2-diphenyl-1H-imidazole-5-carboxylate (**4c**).* Yield: 121.7 mg (38%). White powder, mp: 113–115 °C (from $Et_2O$/*n*-pentane). IR (Nujol) $\nu_{max}$ 1700, 1600, 1559, 1495 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 0.97 (6H, d, $J$=6.0 Hz, $CH_3CHCH_3$), 2.48 (3H, s, $CH_3$) 4.84 (1H, sept, $J$=6.0 Hz, $CH_3CHCH_3$), 7.22–7.31 (7H, m, ArH), 7.40–7.44 (3H, m, ArH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 15.2, 21.3, 67.1, 121.5, 128.7, 128.0, 128.3, 128.6, 128.7, 128.8, 128.9, 129.5, 137.8, 146.5, 148.7, 159.0. MS (EI): $m/z$ (%)=320 (M$^+$, 75), 278 (71), 233 (13), 130 (30), 125 (60), 111(100). Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.38): C, 74.98; H, 6.29; N, 8.74. Found: C, 74.87; H, 6.35; N, 8.81.

*4.4.2. Allyl 4-methyl-1,2-diphenyl-1H-imidazole-5-carboxylate (**4d**).* Yield: 63.7 mg (20%). White powder, mp: 70–78 °C (from DCM/light petroleum ether). IR (Nujol) $\nu_{max}$ 1718, 1670, 1651, 1599, 1546, 1502 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 2.64 (3H, s, $CH_3$), 4.59–4.61 (2H, m, $OCH_2$), 5.15–5.23 (2H, m, $CH_2$=CH), 5.75–5.85 (1H, m, $CH_2$=CH), 7.17–7.26 (5H, m, ArH), 7.32–7.36 (2H, m, ArH), 7.38–7.42 (3H, m, ArH). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 16.2, 65.2, 118.5, 122.0, 128.5, 128.6, 129.2, 129.3, 129.4, 130.0, 132.4, 138.4, 148.5, 150.3, 160.5. MS (EI): $m/z$ (%)=318 (M$^+$, 100), 277 (26), 234 (64), 219 (3), 193 (29). Anal. Calcd for $C_{20}H_{18}N_2O_2$ (318.36): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.30; H, 5.78; N, 8.64.

*4.4.3. Methyl 1-[(methoxycarbonyl)amino]-5-methyl-2-phenyl-1H-imidazole-4-carboxylate (**10a**).* Yield: 167.8 mg (58%). Beige powder, mp: 188–191 °C (from $Et_2O$/light petroleum ether). IR (Nujol) $\nu_{max}$ 3475, 1740, 1720, 1580, 1550 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 2.38 (3H, s, $CH_3$), 3.70 (3H, s, $OCH_3$), 3.79 (3H, s, $OCH_3$), 7.48 (3H, t, $J$=7.0 Hz, ArH), 7.72 (2H, d, $J$=7.0 Hz, ArH), 11.21 (1H, s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 9.1, 51.1, 53.2, 125.7, 127.5, 128.5, 128.6, 129.4, 129.9, 138.2, 145.4, 155.3, 163.2. MS (EI): $m/z$ (%)=289 (M$^+$, 100), 257 (82), 229 (39), 155 (77), 104 (56). Anal. Calcd for $C_{14}H_{15}N_3O_4$ (289.29): C, 58.13; H, 5.23; N, 14.53. Found: C, 58.42; H, 5.12; N, 14.72.

*4.4.4. Ethyl 1-[(methoxycarbonyl)amino]-5-methyl-2-phenyl-1H-imidazole-4-carboxylate (**10b**).* Yield: 212.3 mg (70%). Beige powder, mp: 169–171 °C dec(from EtOAc/*n*-pentane). IR (Nujol) $\nu_{max}$ 3390, 1755, 1708, 1590, 1560 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.30 (3H, t, $J$=7.2 Hz, $OCH_2CH_3$), 2.38 (3H, s, $CH_3$), 3.70 (3H, s, $OCH_3$), 4.27 (2H, q, $J$=7.2 Hz, $OCH_2CH_3$), 7.48 (3H, t, $J$=8.0 Hz, ArH), 7.73 (2H, d, $J$=8.0 Hz, ArH), 11.19 (1H, s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 9.9, 15.0, 53.9, 60.4, 126.5, 128.2, 129.2, 129.3, 130.1, 138.8, 146.1, 156.0, 163.5. MS (EI): $m/z$ (%)=303 (M$^+$, 79), 257 (64), 229 (36), 155 (52), 125 (57), 111 (100). Anal. Calcd for $C_{15}H_{17}N_3O_4$ (303.31): C, 59.40; H, 5.65; N, 13.85. Found: C, 59.61; H, 5.69; N, 13.68.

*4.4.5. Methyl 1-[(tert-butoxycarbonyl)amino]-5-methyl-2-phenyl-1H-imidazole-4-carboxylate (**10c**).* Yield: 195.5 (59%). Beige powder, mp: 177–179 °C dec (from THF/*n*-pentane). IR (Nujol) $\nu_{max}$ 3342, 1745, 1710, 1595, 1550 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$:

1.41 (9H, s, O$^t$Bu), 2.36 (3H, s, $CH_3$), 3.79 (3H, s, $OCH_3$), 7.47 (3H, t, $J$=7.2 Hz, ArH), 7.72 (2H, d, $J$=7.2 Hz, ArH), 10.83 (1H, s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 9.1, 27.7, 50.9, 81.6, 125.5, 127.4, 128.5, 128.6, 129.2, 138.1, 145.4, 153.8, 163.2. MS (EI): $m/z$ (%)=331 ($M^+$, 28), 275 (100), 243 (92), 215 (35), 155 (40), 111 (34), 104 (56). Anal. Calcd for $C_{17}H_{21}N_3O_4$ (331.36): C, 61.62; H, 6.39; N, 12.68. Found: C, 61.55; H, 6.49; N, 12.79.

*4.4.6. Ethyl 1-[(tert-butoxycarbonyl)amino]-5-methyl-2-phenyl-1H-imidazole-4-carboxylate (**10d**).* Yield: 207.2 mg (60%). Pink powder, mp: 143–145 °C dec (from DCM/light petroleum ether). IR (Nujol) $\nu_{max}$ 3330, 1735, 1715, 1600, 1560 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.30 (3H, t, $J$=7.2 Hz, $OCH_2CH_3$), 1.41 (9H, s, O$^t$Bu), 2.36 (3H, s, $CH_3$), 4.26 (2H, q, $J$=7.2 Hz, $OCH_2CH_3$), 7.47 (3H, t, $J$=7.2 Hz, ArH), 7.71 (2H, d, $J$=7.2 Hz, ArH), 10.81 (1H, s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 9.1, 14.3, 27.7, 59.5, 81.5, 125.7, 127.4, 128.4, 128.7, 129.2, 137.9, 145.4, 153.8, 163.7. MS (EI): $m/z$ (%)=345 (12), 289 (40), 243 (33), 199 (22), 125 (60), 111 (100). Anal. Calcd for $C_{18}H_{23}N_3O_4$ (345.39): C, 62.59; H, 6.71; N, 12.17. Found: C, 62.80; H, 6.58; N, 12.29.

*4.4.7. Ethyl 1-[(ethoxycarbonyl)amino]-5-methyl-2-phenyl-1H-imidazole-4-carboxylate (**10e**).* Yield: 199.9 mg (63%). White powder, mp: 148–150 °C dec (from EtOAc/*n*-pentane). IR (Nujol) $\nu_{max}$ 3345, 1735, 1710, 1595, 1570 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.20 (3H, t, $J$=6.8 Hz, $OCH_2CH_3$), 1.30 (3H, t, $J$=6.8 Hz, $OCH_2CH_3$), 2.38 (3H, s, $CH_3$), 4.17 (2H, q, $J$=6.8 Hz, $OCH_2CH_3$), 4.27 (2H, q, $J$=6.8 Hz, $OCH_2CH_3$), 7.48 (3H, t, $J$=6.8 Hz, ArH), 7.71 (2H, d, $J$=6.8 Hz, ArH), 11.12 (1H, s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 9.9, 15.0, 60.3, 62.7, 126.6, 128.2, 129.3, 130.0, 138.7, 146.1, 155.6, 163.5. MS (EI): $m/z$ (%)=317 ($M^+$, 100), 271 (62), 245 (50), 172 (34), 155 (51), 111 (38), 105 (69). Anal. Calcd for $C_{16}H_{19}N_3O_4$ (317.33): C, 60.56; H, 6.03; N, 13.24. Found: C, 60.61; H, 6.12; N, 13.48.

*4.4.8. Isopropyl 1-[(tert-butoxycarbonyl)amino]-5-methyl-2-phenyl-1H-imidazole-4-carboxylate (**10f**).* Yield: 208.5 mg (58%). Beige powder, mp: 154–156 °C dec (from EtOAc/*n*-pentane). IR (Nujol) $\nu_{max}$ 3290, 1740, 1710, 1590, 1560 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.30 (6H, t, $J$=6.4 Hz, 2 $CH_3$), 1.41 (9H, s, O$^t$Bu), 2.36 (3H, s, $CH_3$), 5.11 (1H, sept, $J$=6.4 Hz, OCH), 7.47 (3H, t, $J$=7.2 Hz, ArH), 7.70 (2H, d, $J$=7.2 Hz, ArH), 10.83 (1H, s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 9.2, 21.8, 27.7, 66.8, 81.5, 126.0, 127.4, 128.4, 128.7, 129.2, 137.7, 145.4, 153.8, 162.2. MS (EI): $m/z$ (%)=359 ($M^+$, 34), 303 (74), 243 (55), 199 (41), 155 (29), 125 (61), 111 (100). Anal. Calcd for $C_{19}H_{25}N_3O_4$ (359.41): C, 63.49; H, 7.01; N, 11.69. Found: C, 63.54; H, 6.95; N, 11.75.

*4.4.9. Methyl 1-{[(benzyloxy)carbonyl]amino}-5-methyl-2-phenyl-1H-imidazole-4-carboxylate (**10g**).* Yield: 241.2 mg (66%). White powder, mp: 135–138 °C (from EtOAc/*n*-pentane). IR (Nujol) $\nu_{max}$ 3350, 1730, 1708, 1595, 1560 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 2.63 (3H, s, $CH_3$), 3.79 (3H, s, $OCH_3$), 5.19 (2H, q, $J$=12.4 Hz, $OCH_2Ph$), 7.32–7.46 (8H, m, ArH), 7.68 (2H, d, $J$=7.6 Hz, ArH), 11.32 (1H, s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 9.1, 67.1, 125.7, 127.5, 127.8, 128.3, 128.4, 128.5, 128.6, 129.4, 135.9, 138.1, 145.4, 154.8, 163.2. MS (EI): $m/z$ (%)=365 ($M^+$, 13), 288 (19), 274 (8), 230 (14), 216 (29), 149 (69), 125 (55), 111 (100). Anal. Calcd for $C_{20}H_{19}N_3O_4$ (365.38): C, 65.74; H, 5.24; N, 11.50. Found: C, 65.63; H, 5.31; N, 11.32.

*4.4.10. Allyl 1-[(methoxycarbonyl)amino]-5-methyl-2-phenyl-1H-imidazole-4-carboxylate (**10h**).* Yield: 179.7 mg (57%). White powder, mp: 138–140 °C (from DCM/light petroleum ether). IR (Nujol) $\nu_{max}$ 3306, 1748, 1710, 1660, 1605 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 2.38 (3H, s, $CH_3$), 3.70 (3H, s, $OCH_3$), 4.76 (2H, d, $J$=5.6 Hz, $OCH_2$), 5.26 (1H, dd, $^2J$=1.6 Hz, $^3J$=10.4 Hz, $CH_2$=CH), 5.38 (1H, dd, $^2J$=1.6 Hz, $^3J$=17.2 Hz, $CH_2$=CH), 5.99–6.09 (1H, m, $CH_2$=CH), 7.48 (3H, t, $J$=7.6 Hz, ArH), 7.72 (2H, d, $J$=7.6 Hz, ArH), 11.21 (1H, s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 9.2, 53.1, 64.1, 117.9, 125.5, 127.4, 128.4, 128.6, 129.4, 132.9, 138.3, 145.4, 155.3, 162.3. MS (EI): $m/z$ (%)=315 ($M^+$, 7), 274 (3), 258 (4), 125 (54), 111 (100). Anal. Calcd for $C_{16}H_{17}N_3O_4$ (315.32): C, 60.94; H, 5.43; N, 13.33. Found: C, 60.96; H, 5.28; N, 13.41.

### 4.5. General procedure for the reactions of DPG in alcohol

In a 25-mL flask, DPG **11** (1 mmol) was dissolved in MeOH or EtOH (2 mL) and a solution of DD **1a**–**e** (2 mmol) in the same solvent (4 mL) was added dropwise quickly under magnetic stirring at room temperature. The reaction mixture became warm and the disappearance of DD (by TLC) was fast (0.1–03 h). After removal of the solvent in vacuo, the residue was purified by chromatography (silica gel, DCM/EtOAc) to give **13a**,**b** and **15a**–**e**.

*4.5.1. Methyl 2-[1-(2-anilino-4-oxo-1-phenyl-4,5-dihydro-1H-imidazol-5-yl)ethylidene]hydrazinecarboxylate (**13a**).* Yield: 146.1 mg (40%). White powder, mp: 138–142 °C dec (from EtOAc/$Et_2O$). IR (Nujol) $\nu_{max}$ 3243, 3197, 3152, 1734, 1718, 1700, 1610, 1570, 1560 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.70 (3H, s, $CH_3$), 3.64 (3H, s, $OCH_3$), 4.92 (1H, s, CH), 7.12 (1H, t, $J$=7.6 Hz, ArH), 7.30–7.47 (7H, m, ArH), 7.57 (2H, d, $J$=8.0 Hz, ArH), 9.47 (1H, s, NH), 10.10 (1H, s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 12.1, 51.8, 73.2, 122.6, 126.9, 127.6, 128.2, 129.7, 136.3, 138.0, 146.5, 154.3, 167.8, 182.9. MS (EI): $m/z$ (%)=365 ($M^+$, 100), 333 (35), 291 (90), 276 (49), 273 (84), 251 (30), 241 (18). Anal. Calcd for $C_{19}H_{19}N_5O_3$ (365.39): C, 62.46; H, 5.24; N, 19.17. Found: C, 62.59; H, 5.50; N, 19.34.

*4.5.2. Ethyl 2-[1-(2-anilino-4-oxo-1-phenyl-4,5-dihydro-1H-imidazol-5-yl)ethylidene]hydrazinecarboxylate (**13b**).* Yield: 140.3 mg (37%). White powder, mp: 164–167 °C dec (from $Et_2O$/light petroleum ether). IR (Nujol) $\nu_{max}$ 3259, 3203, 3154, 3112, 1733, 1717, 1617, 1570, 1559 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.20 (3H, t, $J$=7.2 Hz, $OCH_2CH_3$), 1.70 (3H, s, $CH_3$), 4.10 (2H, q, $J$=7.2 Hz, $OCH_2CH_3$), 4.92 (1H, s, CH), 7.12 (1H, t, br s, ArH), 7.30–7.55 (9H, m, ArH), 9.47 (1H, s, NH), 10.05 (1H, s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 12.1, 14.5, 60.4, 73.1, 122.5, 124.3, 126.9, 127.6, 128.3, 129.6, 136.4, 138.0, 146.4, 153.8, 167.8, 182.9. MS (EI): $m/z$ (%)=379 ($M^+$, 100), 333 (44), 291 (77), 287 (67), 276 (56), 251 (45). Anal. Calcd for $C_{20}H_{21}N_5O_3$ (379.16): C, 63.31; H, 5.58; N, 18.46. Found: C, 63.51; H, 5.39; N, 18.56.

*4.5.3. Methyl 2-anilino-7-[(methoxycarbonyl)amino]-6-[2-(methoxycarbonyl)hydrazino]-6,8-dimethyl-4-oxo-1-phenyl-1,3,7-triazaspiro[4,4]nona-2,8-diene-9-carboxylate (**15a**).* 4*S*/*R*,6*S*/*R* isomer: yield: 198.6 mg (36%). White powder, mp: 178–179 °C dec (from THF/*n*-pentane). IR (Nujol) $\nu_{max}$ 3293, 3252, 3230, 1748, 1730, 1717, 1702, 1617, 1606, 1559 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.40 (3H, s, $CH_3$), 1.82 (3H, s, $CH_3$), 3.37 (3H, s, $OCH_3$), 3.55 (3H, s, $OCH_3$), 3.76 (3H, s, $OCH_3$), 6.14 (1H, s, NH), 7.11 (1H, t, $J$=6.8 Hz, ArH), 7.23–7.35 (7H, m, ArH), 7.58 (2H, br s, ArH), 8.39 (1H, s, NH), 8.86 (1H, s, NH), 10.00 (1H, br s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 10.9, 15.8, 50.2, 52.2, 52.6, 80.4, 80.8, 94.3, 121.6, 124.1, 126.3, 126.8, 128.5, 136.9, 138.0, 156.8, 163.2, 167.1, 168.1, 186.3. MS (EI): $m/z$ (%)=551 ($M^+$, 3), 462 (100), 430 (26), 387 (23), 355 (23). Anal. Calcd for $C_{26}H_{29}N_7O_7$ (551.55): C, 56.62; H, 5.30; N, 17.78. Found: C, 56.48; H, 5.36; N, 17.82.

*4.5.4. Ethyl 2-anilino-7-[(methoxycarbonyl)amino]-6-[2-(methoxycarbonyl)hydrazino]-6,8-dimethyl-4-oxo-1-phenyl-1,3,7-triazaspiro[4,4]nona-2,8-diene-9-carboxylate (**15b**).* 4*S*/*R*,6*S*/*R* isomer: yield: 231.9 mg (41%). White powder, mp: 167–168 °C dec (from $Et_2O$). IR (Nujol) $\nu_{max}$ 3307, 3227, 3186, 3067, 1734, 1718, 1697, 1668, 1605, 1559 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.07 (3H, t, $J$=7.2 Hz,

$OCH_2CH_3$), 1.40 (3H, s, $CH_3$), 1.82 (3H, s, $CH_3$), 3.56 (3H, s, $OCH_3$), 3.76 (3H, s, $OCH_3$), 3.77–3.89 (2H, m, $OCH_2CH_3$), 6.13 (1H, s, NH), 7.11 (1H, br s, ArH), 7.25–7.33 (7H, m, ArH), 7.59 (2H, br s, ArH), 8.41 (1H, s, NH), 8.86 (1H, s, NH), 10.01 (1H, br s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 10.8, 13.9, 15.8, 52.3, 58.6, 80.4, 88.4, 94.4, 121.5, 124.1, 126.2, 126.8, 128.5, 136.8, 138.1, 156.8, 162.8, 167.0, 168.1, 186.4. Anal. Calcd for $C_{27}H_{31}N_7O_7$ (565.58): C, 57.34; H, 5.52; N, 17.34. Found: C, 57.48; H, 5.62; N, 17.29.

*4.5.5. Methyl 2-anilino-7-[(tert-butoxycarbonyl)amino]-6-[2-(tert-butoxycarbonyl)hydrazino]-6,8-dimethyl-4-oxo-1-phenyl-1,3,7-triazaspiro[4,4]nona-2,8-diene-9-carboxylate (**15c**).* 4*S*/*R*,6*S*/*R* isomer: yield: 298.8 mg (47%). White powder, mp: 200–202 °C dec (from MeOH). IR (Nujol) $\nu_{max}$ 3372, 3263, 3208, 3154, 1732, 1716, 1706, 1706, 1610, 1571 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.35 (9H, s, O$^t$Bu), 1.38 (3H, s, $CH_3$), 1.50 (9H, s, O$^t$Bu), 1.82 (3H, s, $CH_3$), 3.36 (3H, s, $OCH_3$), 5.94 (1H, s, NH), 7.11 (1H, t, *J*=7.2 Hz, ArH), 7.24–7.33 (7H, m, ArH), 7.58 (2H, br s, ArH), 8.12 (1H, s, NH), 8.70 (1H, s, NH), 9.94 (1H, br s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 11.1, 15.9, 27.9, 28.0, 50.0, 79.5, 80.5, 88.9, 93.7, 121.7, 124.1, 126.4, 126.8, 128.4, 128.5, 137.0, 138.0, 155.6, 163.3, 166.9, 168.2, 186.3. MS (EI): *m*/*z* (%)=635 ($M^+$, 1), 504 (88), 472 (8), 448 (100), 416 (17), 405 (40), 387 (28), 355 (34). Anal. Calcd for $C_{32}H_{41}N_7O_7$ (635.71): C, 60.46; H, 6.50; N, 15.42. Found: C, 60.54; H, 6.36; N, 15.64.

4*S*/*R*,6*R*/*S*, isomer: yield: 146.2 mg (23%). White solid, mp: 161–162 °C dec (from EtOAc/$Et_2O$). IR (Nujol) $\nu_{max}$ 3434, 3369, 3268, 3238, 1745, 1717, 1701, 1636, 1610, 1570 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.30 (3H, s, $CH_3$), 1.41 (9H, s, O$^t$Bu), 1.50 (9H, s, O$^t$Bu), 1.80 (3H, s, $CH_3$), 3.31 (3H, s, $OCH_3$), 5.25 (1H, br s, NH), 7.05–7.19 (1H, m, ArH), 7.21–7.47 (7H, m, ArH), 7.56–7.63 (2H, m, ArH), 8.34 (1H, br s, NH), 8.62 (1H, br s, NH), 9.27 (1H, br s, NH), 9.43 (1H, s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 11.6, 17.0, 27.8, 27.9, 49.5, 77.9, 80.2, 86.8, 91.9, 120.8, 123.5, 126.1, 126.5, 128.0, 137.4, 137.7, 154.4, 164.0, 166.7, 168.3, 186.4. MS (EI): *m*/*z* (%)=635 ($M^+$, 1), 504 (94), 389 (7), 472 (14), 448 (100), 416 (35), 405 (93), 388 (44), 355 (51). Anal. Calcd for $C_{32}H_{41}N_7O_7$ (635.71): C, 60.46; H, 6.50; N, 15.42. Found: C, 60.57; H, 6.39; N, 15.38.

*4.5.6. Ethyl 2-anilino-7-[(tert-butoxycarbonyl)amino]-6-[2-(tert-butoxycarbonyl)hydrazino]-6,8-dimethyl-4-oxo-1-phenyl-1,3,7-triazaspiro[4,4]nona-2,8-diene-9-carboxylate (**15d**).* 4*S*/*R*,6*S*/*R* isomer: yield: 318.4 mg (49%). White powder, mp: 203–204 °C dec (from EtOH). IR (Nujol) $\nu_{max}$ 3371, 3260, 3233, 3152, 1731, 1715, 1706, 1690, 1611, 1570, 1509 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.04–1.07 (3H, m, $OCH_2CH_3$), 1.35 (9H, s, O$^t$Bu), 1.37 (9H, s, O$^t$Bu), (3H, s, $CH_3$), 1.56 (3H, s, $CH_3$), 1.82 (3H, s, $CH_3$), 3.78–3.86 (2H, m, $OCH_2CH_3$), 5.93 (1H, s, NH), 7.11 (1H, t, *J*=7.4 Hz, ArH), 7.22–7.35 (7H, m, ArH), 7.58 (2H, br s, ArH), 8.16 (1H, s, NH), 8.70 (1H, s, NH), 9.93 (1H, br s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 11.0, 13.9, 15.9, 27.9, 28.0, 58.5, 79.5, 80.4, 88.9, 93.8, 121.5, 124.1, 126.4, 126.7, 128.5, 137.0, 138.1, 155.6, 162.9, 166.9, 168.1, 186.8. Anal. Calcd for $C_{33}H_{43}N_7O_7$ (649.74): C, 61.00; H, 6.67; N, 15.09. Found: C, 61.13; H, 6.58; N, 15.29.

4*S*/*R*,6*R*/*S* isomer: yield: 155.9 mg (24%). White solid, mp: 182–185 °C dec (from EtOAc/light petroleum ether). IR (Nujol) $\nu_{max}$ 3343, 3241, 3201, 3149, 1729, 1715, 1697, 1676, 1617, 1568, 1508 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.04 (3H, t, *J*=7.4 Hz, $OCH_2CH_3$), 1.30 (3H, s, $CH_3$), 1.41 (9H, s, O$^t$Bu), 1.50 (9H, s, O$^t$Bu), 1.80 (3H, s, $CH_3$), 3.72–3.85 (2H, m, $OCH_2CH_3$), 5.23 (1H, br s, NH), 7.07 (1H, br s, ArH), 7.28–7.56 (9H, m, ArH), 8.29 (1H, br s, NH), 8.60 (1H, br s, NH), 9.43 (1H, br s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 11.4, 14.0, 17.0, 28.0, 28.1, 58.1, 78.8, 79.4, 86.8, 91.7, 121.0, 121.2, 122.6, 126.5, 127.0, 128.3, 129.7, 137.7, 138.4, 156.0, 163.6, 164.5, 168.5, 184.1. Anal. Calcd for $C_{33}H_{43}N_7O_7$ (649.74): C, 61.00; H, 6.67; N, 15.09. Found: C, 60.92; H, 6.85; N, 15.23.

*4.5.7. Ethyl 2-anilino-7-[(ethoxycarbonyl)amino]-6-[2-(ethoxycarbonyl)hydrazino]-6,8-dimethyl-4-oxo-1-phenyl-1,3,7-triazaspiro[4,4]nona-2,8-diene-9-carboxylate (**15e**).* Yield: 290.9 mg (49%). White powder, mp: 183–184 °C dec (from EtOAc). IR (Nujol) $\nu_{max}$ 3362, 3282, 3238, 3191, 1742, 1706, 1660, 1614, 1569 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 1.07 (3H, t, *J*=7.2 Hz, $OCH_2CH_3$), 1.12 (3H, t, *J*=7.2 Hz, $OCH_2CH_3$), 1.27 (3H, t, *J*=7.2 Hz, $OCH_2CH_3$), 1.40 (3H, s, $CH_3$), 1.82 (3H, s, $CH_3$), 3.76–3.88 (2H, m, $OCH_2CH_3$), 3.98–4.05 (2H, m, $OCH_2CH_3$), 4.18–4.23 (2H, m, $OCH_2CH_3$), 6.09 (1H, s, NH), 7.11 (1H, t, *J*=8.0 Hz, ArH), 7.25–7.34 (7H, m, ArH), 7.58 (2H, br s, ArH), 8.37 (1H, s, NH), 8.85 (1H, s, NH), 9.98 (1H, br s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 10.9, 13.2, 13.9, 14.5, 15.8, 58.6, 60.7, 61.4, 80.5, 88.9, 94.4, 121.5, 124.1, 126.8, 127.8, 128.5, 136.8, 138.1, 156.4, 162.8, 166.9, 168.1, 186.4. MS (EI): *m*/*z* (%)=489 ([M−NHNHCO$_2$Et]$^+$, 100), 401 (75), 355 (79). Anal. Calcd for $C_{29}H_{35}N_7O_7$ (593.63): C, 58.67; H, 5.94; N, 16.52. Found: C, 58.39; H, 6.08; N, 16.58.

### 4.6. X-ray crystallography

Single crystals of **7a**×EtOAc, **15a**×THF and **4e** were submitted to X-ray data collections. A Siemens P4 four-circle (for **7a**×EtOAc and **15a**×THF) and a Bruker–Nonius FR591 rotating anode diffractometers (for **7e**) with graphite monochromated Mo-K$\alpha$ radiation ($\lambda$=0.71073 Å) were used for data collections. The structures were solved by direct methods implemented in the SHELXS-97 program.[18] The refinements were carried out by full-matrix anisotropic least-squares on $F^2$ for all reflections for non-H atoms by using the SHELXL-97 program.[19]

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