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Utilization of DmbNHNH$_2$ in the synthesis of amino-substituted 4-((3,5-diamino-1*H*-pyrazol-4-yl)diazenyl)phenols

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ABSTRACT

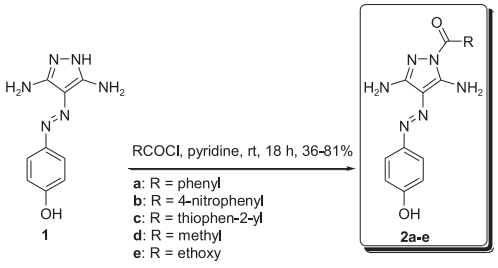
(2,4-Dimethoxybenzyl)hydrazine (DmbNHNH$_2$) was utilized in the synthesis of Dmb-protected 4-((3,5-diamino-1*H*-pyrazol-4-yl)diazenyl)phenols. This unambiguous protection of the pyrazole endocyclic nitrogen atom enabled the preparation of amino-substituted 4-((3,5-diamino-1*H*-pyrazol-4yl)diazenyl) phenols that were inaccessible through direct substitution. The Boc group could be selectively cleaved in the presence of the Dmb group.

1. Introduction

Protein kinases are the most important drug targets in the pharmaceutical industry for the treatment of proliferative disorders, such as cancer and inflammation.[1] A few years ago, derivatives of a 4-(phenyldiazenyl)-1*H*-pyrazole-3,5-diamine core were identified as ATP-competitive inhibitors of the cyclin-dependent kinases CDK2 and CDK9, which control cell proliferation and transcription, respectively.[1b,2] The X-ray structural analysis of CDK2 complexed with 4-((3,5-diamino-1*H*-pyrazol-4-yl)diazenyl)phenol **1** (CAN508, Scheme 1)[3] and the recently published structural data for CDK9 provide useful information about the structural surroundings of the enzyme active site.[2] It was believed that modification of the amino groups in **1** could provide derivatives with biological activity on the same level as previously reported.[3]

2. Results and discussion

The amino groups attached to the pyrazole ring are engaged in a relatively complex tautomeric system that complicates regioselective substitution.[4] We first attempted to carry out a benzoylation of the unprotected pyrazole, **1**, with benzoyl chloride in pyridine (Scheme 1). Unexpectedly, the benzoylation proceeded entirely on the endocyclic nitrogen atom in the pyrazole ring, affording derivative **2a**. This result led us to attempt to protect the endocyclic nitrogen atom where benzoylation occurred using a Boc group based on reports of the successful Boc protection of the endocyclic nitrogen atom in related aminopyrazole systems.[5] Several attempts to unequivocally obtain **15a**, a regioisomer of **2a**, through the benzoylation and subsequent deprotection of the Boc-protected pyrazole **1** formed a mixture of regioisomers, which



Scheme 1. Acylation of the unprotected pyrazole **1**.

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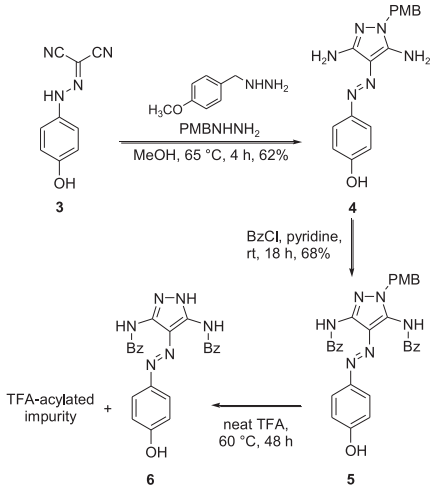
again included **2a**. The Boc protection of **1** proved to be non-regioselective.

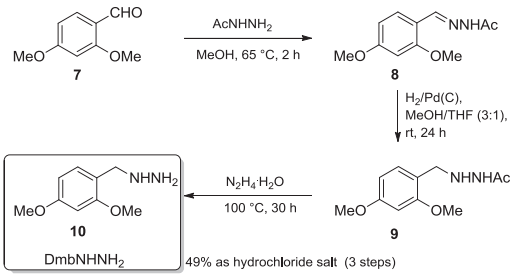
These preliminary experiences indicated that the substitutions on the 3,5-diaminopyrazole moiety were strongly influenced by the nature of the reactants and other reaction conditions. To avoid problems with regioselectivity, a different strategy was chosen. We decided to introduce the protecting group earlier in the synthesis via the cycloaddition of a hydrazine derivative, already bearing the protecting group, to hydrazone **3** (Scheme 2), which forms pyrazoles unequivocally protected at the 1 position. The choice of the protecting group was limited to those that both form a pyrazole ring during the cycloaddition reaction and cleave under acidic conditions. Because a cycloaddition reaction of *tert*-butyl hydrazinecarboxylate with a hydrazone similar to **3** has not been reported[6] and our initial attempt failed, we turned our attention to (4-methoxybenzyl)hydrazine ($PMBNHNH_2$),[7] which was more convenient for cycloaddition with **3** (Scheme 2).



Scheme 2. Cleavage study of the PMB protecting group.

A PMB-protected pyrazole derivative, **4**, was di-benzoylated to afford the amino-substituted pyrazole, **5**, which was studied by HPLC-MS to determine the cleavage conditions of the PMB group. The protecting group was almost entirely cleaved by neat TFA after 48 h at 60 °C. Although insufficient for complete deprotection, the elevated temperature and prolonged reaction time yielded not only the expected deprotected pyrazole, **6**, but also an almost equal amount of an undesired trifluoroacetylated impurity. Since the reaction led to a mixture the products were not isolated but only detected via HPLC-MS. This result indicates that another methoxy group, this time in the *ortho* position of the protective group, was needed to both promote cleavage under milder conditions and eliminate the formation of impurities.

The 2,4-dimethoxybenzyl protecting group (Dmb) is generally introduced to a hydroxy group via a reactive benzyl derivative, such as the chloride[8] or trichloroacetimidate.[9] Although Dmb-*N*-protection via both reactive benzyl derivatives[10] and a Mitsunobu reaction using 2,4-dimethoxybenzyl alcohol is also possible,[11] the predominantly used protection strategy is the reductive alkylation of 2,4-dimethoxybenzaldehyde.[12] Another common method for the regioselective introduction of Dmb is the use of 2,4-dimethoxybenzylamine for the synthesis of *N*-protected functionalities[13] or heterocyclic systems.[14] Bis(2,4-dimethoxybenzyl)amine was similarly applied during the synthesis of bis(Dmb)-*N*-protected functionalities.[15] To unequivocally prepare Dmb-protected 3,5-diaminopyrazole derivatives, we searched the literature for a synthesis of $DmbNHNH_2$, **10** (Scheme 3). To the best of our knowledge, neither a preparation procedure nor the compound itself has been reported, although some commercial companies offer it for sale.

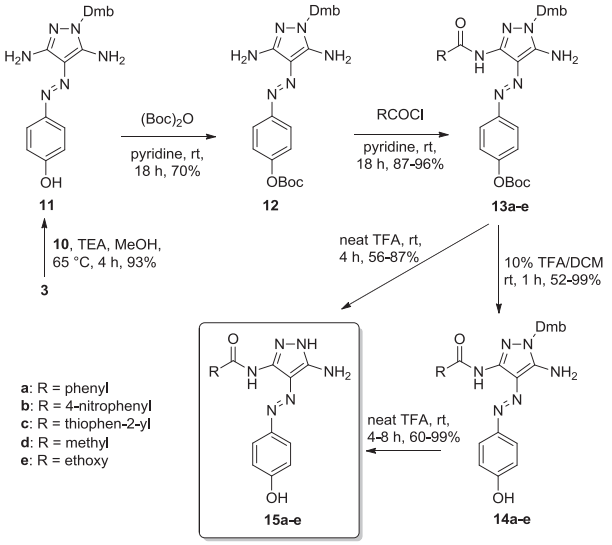


Scheme 3. Synthesis of $DmbNHNH_2$ **10**.

In this communication, we report the synthesis of both **10** and several Dmb-protected 4-((3,5-diamino-1*H*-pyrazol-4-yl)diazenyl) phenol derivatives. Furthermore, a preliminary study on the acylation reactions of both Dmb-protected and unprotected 3,5-diaminopyrazole moieties is presented and illustrates the reactivity of these heterocyclic systems.

First, it was necessary to develop a synthesis for **10**. After initial trials, an unoptimized three-step synthesis (Scheme 3) starting from 2,4-dimethoxybenzaldehyde, **7**, was found to be expedient.

It is possible to prepare **10** without first isolating the hydrazone, **8**, formed by the condensation with acetohydrazide. Subsequent catalytic hydrogenation forms a hydrazine derivative, **9**, that is directly treated with hydrazine hydrate to yield the desired product, **10**, as a free base. Because of the low stability of the free base, conversion into the corresponding hydrochloride salt is necessary for storage. Alternatively, crude **10** could be immediately used in cycloaddition reaction with **3** to form a stable pyrazole, **11**, (Scheme 4).



Scheme 4. Synthesis of the Dmb-protected pyrazole **11** and its amino-substituted derivatives.

Before the Dmb-protected pyrazole **11** can be mono-acylated with acyl chloride, it is necessary to protect the hydroxy group, which tends to acylate in pyridine along with the amino group. To this end, di-*tert*-butyl dicarbonate was used to give pyrazole **12**. Then, the 3-amino group of pyrazole **12** was acylated in pyridine with the corresponding acyl chloride to afford pyrazoles **13a**–**e** in high yield. The positions of both the acyl and protecting groups were unequivocally confirmed by the X-ray structure analysis of **13b** (Fig. 1).

The direct synthesis of the desired unprotected amino-acylated pyrazoles, **15a**–**e**, from **13a**–**e** required the use of neat TFA. Four hours at room temperature is sufficient to remove both acid-labile groups. It is also possible to selectively cleave the Boc group from

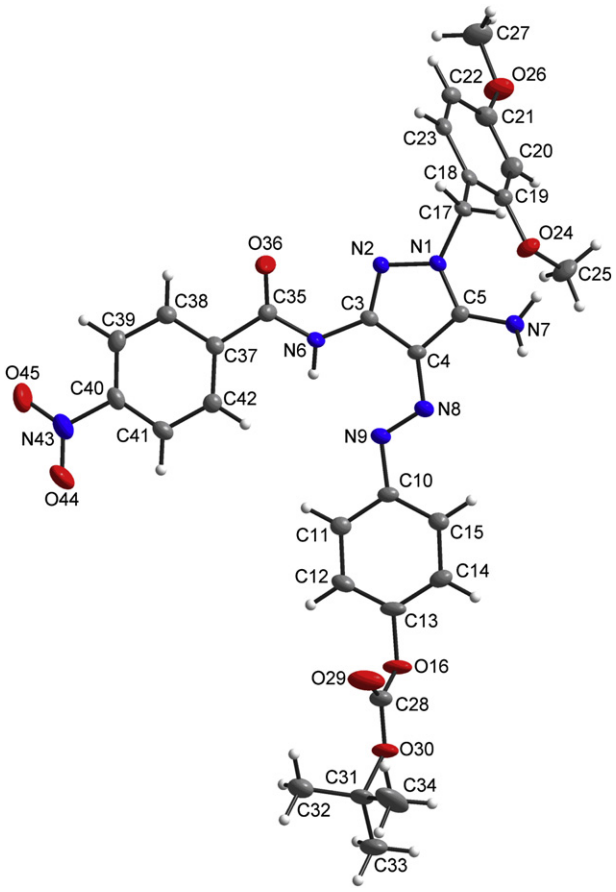


Fig. 1. X-ray structure of **13b** (CCDC 837640).

13a–**e** using dilute TFA at room temperature. After 1 h, pyrazoles **14a**–**e** were isolated and dissolved in neat TFA to yield **15a**–**e** after several hours, as expected.

Finally, several other acyl derivatives of **1** (Scheme 1) were investigated, and it was found that only the endocyclic nitrogen could be acylated, which formed the pyrazoles **2b**–**e**.

^{13}C NMR spectra of most prepared pyrazoles can evince some discrepancies. Some pyrazole quaternary carbon signals were not observed. These pyrazoles exist in tautomeric forms with slow exchange on the NMR time scale.[7,16] As a result, the signal shape is very broadened, the intensity is very low. Usually, these signals are difficult to be identified.

The biological activity of selected pyrazoles was assayed as previously described.[3] Based on the binding mode of **1** within the CDK2 active site,[3] the substitution of a key CDK-interacting motif in **2a** and **2e** substantially decreased their activity (Table 1). However, the acylation of the exocyclic amino group increased the inhibitory potency of all tested compounds. Inhibitor **15a** was the most active with a 2- and 3-fold increase in potency over **1** for CDK2 and MCF7, respectively. These results were expected from the accepted CDK pharmacophore model, which accounts for hydrophobic substituents in positions analogous to those in this study.[1b]

Table 1
Inhibitory activity on recombinant CDK2/cyclin E kinase and cytotoxicity against the MCF7 breast carcinoma cell line by selected pyrazoles

Compound	IC_{50} (μM)	
	CDK2	MCF7
1 (**CAN508**)	3.5 ± 0.7	33 ± 5
2a	23 ± 7.2	>25
2e	100 ± 16	70 ± 11
15a	1.7 ± 0.5	10.5 ± 4.2
15b	5.2 ± 1.3	>25
15c	4.3 ± 1.4	>12.5
15e	2.6 ± 0.7	13.9 ± 3.3

3. Conclusions

In conclusion, the protection of the endocyclic pyrazole nitrogen atom with Dmb was found to be crucial for obtaining the amino-acylated pyrazoles **15a**–**e**, and a novel, unambiguous, protection strategy utilizing DmbNHNH$_2$, **10**, was developed for this purpose. It was necessary to protect the hydroxy group with Boc to prevent the formation of a bis-acylated pyrazoles when the Dmb-protected pyrazole **11** was acylated. Treatment of the pyrazoles **13a**–**e** with dilute TFA selectively cleaved the Boc group in presence of the acid-labile Dmb group. Acylation of the unprotected pyrazole **1** yielded only pyrazoles **2a**–**e**. This report indicates that **10** could potentially be used to protect related heterocyclic systems and possibly even hydrazine functionalities.

4. Experimental section

4.1. General

All starting materials are commercially available. Commercial reagents were used without purification. Melting points were determined on a Boetius stage and are uncorrected. The infrared (IR) spectra were obtained on an ATI Mattson Genesis Series FT-IR spectrometer (KBr discs). Flash column chromatography was performed on silica gel (pore size 60 Å, 40–63 μm particle size). The LC/MS analyses were carried out on a UHPLC-MS system consisting of UHPLC chromatography Accela with photodiode array detector and triple quadrupole mass spectrometer TSQ Quantum Access (both Thermo Scientific, CA, USA), using Nucleodur Gravity C18 column at 30 °C and flow rate of 800 μL/min (Kinetex, Phenomenex, 2.6 μm, 2.1×50 mm, USA). Mobile phase was (A) 0.01 M ammonium acetate in water, and (B) acetonitrile, linearly programmed from 10% to 80% B over 2.5 min, kept for 1.5 min. The column was re-equilibrated with a 10% of solution B for 1 min. The APCI source operated at discharge current of 5 μA, vaporizer temperature of 400 °C, and capillary temperature of 200 °C. The HRMS analyses were carried out on HRMS—Exactive (Orbitrap) MS, Thermo, USA. The purification of compounds **13e** and **15e** was carried out on semi-preparative chromatograph (Agilent Technologies, 1200 Series) using SunFire Prep C18 OBD column 19×100 mm, 5 μm particles, gradient was formed from MeCN and water both HPLC grade, flow rate 15 mL/min. The ^{1}H and ^{13}C NMR spectra of compounds **2a**–**e**, **4**, **5**, **10**, **13a**, **13d**, **13e**, **14a**–**e**, **15a**–**e** were measured in DMSO-d_6 at 20 °C on a Bruker Avance 300 FT NMR spectrometer. The ^{1}H and ^{13}C NMR spectra of compounds **12**, **13b**, **13c** were measured in DMF-d_7 at 25 and 65 °C on a Varian 400 FT NMR spectrometer. R_f values were determined only for pyrazoles, which were purified by chromatography. A single crystal X-ray data collection of **13b** was performed on an Xcalibur™2 diffractometer (Oxford Diffraction Ltd.) with Sapphire2 CCD detector, and with Mo Kα (Monochromator Enhance, Oxford Diffraction Ltd.) and at 100 K. Additional details regarding structure determination, such as crystal data and structure refinement, selected bond lengths and angles of covalent as well as non-covalent contacts are summarized in Supplementary data.

4.1.1. General procedure for acylation of 4-((3,5-diamino-1H-pyrazol-4-yl)diazenyl)phenol. To a solution of 4-((3,5-diamino-1*H*-pyrazol-4-yl)diazenyl)phenol **1** (218 mg, 1.0 mmol) in dry pyridine (5 mL)

diluted acyl chloride (1.0 mmol in 0.5 mL of DCM) was added dropwise at 2–5 °C. The reaction mixture was allowed to stir at 2–5 °C for 30 min and then at room temperature for 18 h. After that the solvent was evaporated under reduced pressure and the residue was diluted with methanol (10 mL). The solution was added dropwise to ice water (50 mL). The precipitate was filtered-off, dried in the air to afford the acyl derivate **2a**–**e**.

*4.1.1.1. (3,5-Diamino-4-((4-hydroxyphenyl)diazenyl)-1H-pyrazol-1-yl)(phenyl) methanone (**2a**).* Yield 260 mg, 81%: yellow solid; mp 194–196 °C; IR (cm^{-1}) 3291, 3210, 3170, 3059, 1689, 1660, 1626, 1570, 1496, 1414, 1368, 1280, 1217, 840, 816, 695; ^{1}H NMR (300 MHz, DMSO-d_6) δ=9.82 (s, 1H), 8.08 (br s, 2H), 7.96 (d, J=7.0 Hz, 2H), 7.71 (d, J=8.4 Hz, 2H), 7.62–7.46 (m, 3H), 6.84 (d, J=8.4 Hz, 2H), 6.18 (br s, 2H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ=112.3, 115.4, 122.7, 127.6, 130.0, 131.6, 133.3, 145.8, 146.1, 152.5, 158.1, 169.0 ppm; HRMS (HESI, m/z) calcd for $C_{16}H_{14}N_6O_2$ (322.33) $[M+H]^+$ 323.1251, found 323.1252.

*4.1.1.2. (3,5-Diamino-4-((4-hydroxyphenyl)diazenyl)-1H-pyrazol-1-yl)(4-nitrophenyl)methanone (**2b**).* Yield 359 mg, 98%: orange solid; mp 238–240 °C; IR (cm^{-1}) 3297, 3175, 3114, 3041, 2386, 2285, 1662, 1632, 1591, 1571, 1518, 1498, 1477, 1415, 1349, 1273, 840, 813, 712; ^{1}H NMR (300 MHz, DMSO-d_6) δ=9.82 (s, 1H), 8.33 (d, J=8.8 Hz, 2H), 8.13 (d, J=8.8 Hz, 2H), 7.72 (d, J=8.8 Hz, 2H), 6.83 (d, J=8.8 Hz, 2H), 6.27 (br s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=112.3, 115.5, 122.8, 122.9, 131.0, 139.5, 146.1, 148.8, 152.9, 158.3, 167.4 ppm; HRMS (HESI, m/z) calcd for $C_{16}H_{13}N_7O_4$ (367.33) $[M+H]^+$ 368.1102, found 368.1117.

*4.1.1.3. (3,5-Diamino-4((4-hydroxyphenyl)diazenyl)-1H-pyrazol-1-yl)(thiophene-2-yl)methanone (**2c**).* The product was purified by flash column chromatography ($CHCl_3$/MeOH 40:1) to give methanone **2c** (325 mg, 99% yield of crude product; 134 mg, 41% yield of pure product): yellow solid; mp 220–222 °C; R_f=0.34; IR (cm^{-1}) 3411, 1649, 1618, 1590, 1566, 1502, 1409, 1381, 1227, 839, 812, 729, 607; ^{1}H NMR (300 MHz, DMSO-d_6) δ=9.81 (br s, 1H), 8.31 (dd, J=3.9, 1.3 Hz, 1H), 8.10 (dd, 5.0, 1.3 Hz, 1H), 8.09 (br s, 2H), 7.71 (d, J=8.9 Hz, 2H), 7.26 (dd, J=5.0, 3.9 Hz, 1H), 6.83 (d, J=8.9 Hz, 2H), 6.34 (br s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=112.3, 115.5, 122.8, 127.2, 133.0, 137.0, 137.9, 146.1, 152.5 (br s), 158.2, 160.8 ppm; HRMS (HESI, m/z) calcd for $C_{14}H_{12}N_6O_2S$ (328.35) $[M+H]^+$ 329.0815, found 329.0812.

*4.1.1.4. 1-(3,5-Diamino-4-((4-hydroxypheny)diazenyl)-1H-pyrazol-1-yl)ethanone (**2d**).* The product was purified by flash column chromatography ($CHCl_3$/MeOH 30:1) to give ethanone **2d** (146 mg, 56% yield of crude product; 938 mg, 36% yield of pure product): yellow solid; mp 228–230 °C; R_f=0.17; IR (cm^{-1}) 3423, 3291, 3208, 1678, 1598, 1576, 1499, 1422, 1266, 1220, 1158, 1137, 1099, 842, 810; ^{1}H NMR (300 MHz, DMSO-d_6) δ=9.76 (br s, 1H), 7.88 (br s, 2H), 7.67 (d, J=8.4 Hz, 2H), 6.82 (d, J=8.4 Hz, 2H), 6.15 (br s, 2H), 2.42 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=22.9, 112.4, 115.4, 122.7, 144.7 (br s), 146.0, 152.0 (br s), 158.1, 172.5 ppm; HRMS (HESI, m/z) calcd for $C_{11}H_{12}N_6O_2$ (260.26) $[M+H]^+$ 261.1095, found 261.1093.

*4.1.1.5. Ethyl 3,5-diamino-4-((4-hydroxyphenyl)diazenyl)-1H-pyrazole-1-carboxylate (**2e**).* The product was purified by flash column chromatography ($CHCl_3$/MeOH 20:1) to give ethyl carboxylate **2e** (264 mg, 91% yield of crude product; 187 g, 65% yield of pure product): yellow solid; mp 234–236 °C; R_f=0.25; IR (cm^{-1}) 3488, 3416, 3395, 3375, 3290, 1720, 1620, 1601, 1555, 1499, 1467, 1449, 1428, 1375, 1311, 1287, 1138, 841, 750, 537; ^{1}H NMR (300 MHz, DMSO-d_6) δ=9.75 (br s, 1H), 7.66 (d, J=8.6 Hz, 3H), 6.82 (d, J=8.6 Hz, 2H), 6.06 (br s, 2H), 4.33 (q, J=7.1 Hz, 2H), 1.31 (t, J=7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=14.1, 63.0, 112.2, 115.4, 122.6, 146.0, 151.3, 152.0 (br s), 158.0 ppm; HRMS (HESI, m/z) calcd for $C_{12}H_{14}N_6O_3$ (290.28) $[M+H]^+$ 291.1200, found 291.1200.

*4.1.2. 4-((3,5-Diamino-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)diazenyl)phenol (**4**).* To a suspension of (4-hydroxyphenyl)carbonohydrazonoyl dicyanide **3**[3] (508 mg, 2.73 mmol) in methanol (3 mL) a solution of (4-methoxybenzyl)hydrazine (831 g, 5.45 mmol) in methanol (3 mL) was added at room temperature. The solution was heated at reflux for 4 h. After cooling to room temperature, the solvent was evaporated under reduced pressure. The product was purified by flash column chromatography ($CHCl_3$/MeOH 20:1) to give phenol **4** (882 mg, 96% yield of crude product; 569 mg, 62% yield of pure product): yellow solid; mp=190–192 °C; R_f=0.18; IR (cm^{-1}) 3380, 3153, 2925, 1600, 1567, 1513, 1496, 1452, 1403, 1362, 1240, 1174, 1024, 836, 821, 754, 672, 535, 511; ^{1}H NMR (300 MHz, DMSO-d_6) δ=9.54 (br s, 1H), 7.55 (d, J=8.6 Hz, 2H), 7.19 (d, J=8.4 Hz, 2H), 6.89 (d, J=8.4 Hz, 2H), 6.78 (d, J=8.6 Hz, 2H), 5.55 (br s, 1H), 4.87 (s, 2H), 3.72 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=48.7, 55.1, 112.9, 113.7, 115.3, 121.9, 128.9, 129.5, 146.5, 156.9, 158.5, 161.9 ppm; HRMS (HESI, m/z) calcd for $C_{17}H_{18}N_6O_2$ (338.37) $[M+H]^+$ 339.1564, found 339.1565.

*4.1.3. N,N′-(4-((4-Hydroxyphenyl)diazenyl)-1-(4-methoxybenzyl)-1H-pyrazole-3,5-diyl)dibenzamide (**5**).* To a solution of 4-((3,5-diamino-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl)diazenyl)phenol **4** (338 mg, 1.0 mmol) in dry pyridine (3 mL) benzoyl chloride (256 μL, 2.20 mmol) was added at 2–5 °C. The reaction mixture was allowed to stir at room temperature for 18 h. After that the solvent was evaporated under reduced pressure and the residue was diluted with methanol (3 mL). The solution was added dropwise to ice water (15 mL). The precipitate was filtered-off, dried in the air to afford the crude dibenzamide **5**, which was purified by flash column chromatography ($CHCl_3$/MeOH 60:1) to give pure product (464 mg, 85% yield of crude product; 372 mg, 68% yield of pure product): yellow solid; mp 82–84 °C; R_f=0.27; IR (cm^{-1}) 3313, 2360, 2341, 1731, 1680, 1624, 1601, 1577, 1544, 1514, 1412, 1389, 1267, 1248, 1192, 1178, 1062, 707; ^{1}H NMR (300 MHz, DMSO-d_6) δ=10.53 (br s, 1H), 8.14 (d, J=7.1 Hz, 2H), 7.98 (d, J=6.6 Hz, 2H), 7.75 (d, J=6.8 Hz, 2H), 7.65–7.50 (m, 6H), 7.41 (br s, 1H), 7.36 (d, J=8.6 Hz, 2H), 7.27 (d, J=7.7 Hz, 2H), 6.94 (d, J=7.9 Hz, 2H), 6.70 (br s, 1H), 5.14 (br s, 2H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ=49.2, 55.1, 113.9, 121.7, 122.5, 127.6, 128.6, 128.7, 128.9, 129.0, 129.8, 131.8, 134.0, 134.1, 150.1, 150.8, 158.7, 164.6. HRMS (HESI, m/z) calcd for $C_{31}H_{26}N_6O_4$ (546.59) $[M+H]^+$ 547.2088, found 547.2086.

*4.1.4. (2,4-Dimethoxybenzyl)hydrazine hydrochloride (**10**).* To a solution of acetic acetohydrazide (659 mg, 8.0 mmol) in methanol (40 mL), 2,4-dimethoxy-benzaldehyde (1.33 g, 8.0 mmol) was added at room temperature. The solution was heated at reflux for 2 h. After cooling to room temperature, *N′*-(2,4-dimethoxybenzylidene)acetohydrazide **8** started to precipitate. The suspension was diluted with a mixture of methanol (20 mL) and THF (20 mL). Then to the solution 10% Pd(C) (100 mg) was added and hydrazone **8** was reduced with hydrogen under vigorous stirring at room temperature and atmospheric pressure. After 24 h the reaction mixture was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure to afford *N′*-(2,4-dimethoxybenzyl)acetohydrazide **9** as a colorless oil. To crude *N′*-(2,4-dimethoxybenzyl)acetohydrazide **9** 98% hydrazine hydrate (8 mL, 165 mmol) was added. The reaction mixture was heated at 100 °C for 30 h, cooled down to room temperature, and water (0.5 mL) was added. The aqueous hydrazine layer was extracted with ethyl ether (3×8 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford crude (2,4-dimethoxy-benzyl)hydrazine **10** as a viscous oil, that could be

directly used for the next reaction step resulting in 4-((3,5-diamino-1-(2,4-dimethoxybenzyl)-1*H*-pyrazol-4-yl)diazenyl)phenol **11**. The compound **10** was isolated as a hydrochloride salt after addition of a methanolic solution of hydrochloric acid (3 mL, concn 3.29 mol/L) to the combined organic layers. The precipitated **10**·HCl was filtered-off, washed with ethyl ether, and dried in a desiccator over phosphorus pentaoxide as a white solid (862 mg, 49% over three steps); mp 138–140 °C; IR (cm^{-1}) 3265, 3156, 2965, 2840, 2812, 2769, 2595, 2441, 1613, 1587, 1508, 1445, 1321, 1287, 1273, 1211, 1157, 1133, 1042, 925, 834; ^1H NMR (300 MHz, DMSO-d_6) δ=7.77 (br s, 2H), 7.28 (d, J=8.3 Hz, 1H), 6.58 (d, J=2.3 Hz, 1H), 6.52 (dd, J=2.3, 8.3 Hz, 1H), 3.99 (s, 2H), 3.79 (s, 3H), 3.76 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=48.5, 55.3, 55.6, 98.3, 104.7, 113.2, 131.8, 158.6, 161.0 ppm; HRMS (HESI, m/z) calcd for $C_9H_{14}N_2O_2$ (182.22) $[M+H]^+$ 183.1128, found 183.1130.

*4.1.5. 4-((3,5-Diamino-1-(2,4-dimethoxybenzyl)-1H-pyrazol-4-yl)diazenyl) phenol (**11**).* To a suspension of (4-hydroxyphenyl) carbonohydrazonoyl dicyanide **3**[3] (500 mg, 2.69 mmol) in methanol (6 mL) a solution of $DmbNHNH_2$·HCl (734 mg, 3.36 mmol) and TEA (3 mL, 21.5 mmol) in methanol (6 mL) was added dropwise at room temperature. The solution was heated at reflux for 4 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue was diluted in methanol (10 mL). The solution was added dropwise to ice water (50 mL). The precipitate was filtered-off, dried in the air to afford phenol **11** as a yellow solid (920 mg, 93%); mp 108–110 °C; IR (cm^{-1}) 3576, 3439, 3345, 3080, 2390, 2284, 1610, 1563, 1498, 1460, 1393, 1356, 1265, 1209, 1157, 1110, 840; ^1H NMR (300 MHz, DMSO-d_6) δ=9.55 (br s, 1H), 7.56 (d, J=8.6 Hz, 2H), 6.84–6.71 (m, 3H), 6.57 (d, J=2.1 Hz, 1H), 6.46 (dd, J=2.1, 8.3 Hz, 1H), 5.58 (br s, 1H), 4.81 (s, 2H), 3.81 (s, 3H), 3.73 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=44.3, 55.3, 55.5, 98.2, 104.5, 112.9, 115.3, 117.4, 121.9, 128.7, 146.5, 152.2 (br s), 156.9, 157.3, 159.9 ppm; HRMS (HESI, m/z) calcd for $C_{18}H_{20}N_6O_3$ (368.40) $[M+H]^+$ 369.1670, found 369.1666.

*4.1.6. tert-Butyl (4-((3,5-diamino-1-(2,4-dimethoxybenzyl)-1H-pyrazol-4-yl)diazenyl)phenyl) carbonate (**12**).* To a solution of compound **11** (1.00 g, 2.71 mmol) in dry pyridine (10 mL), di-*tert*-butyl dicarbonate (0.934 mL, 4.07 mmol) diluted in dry pyridine (1 mL) was added dropwise at 2–5 °C. The reaction mixture was allowed to stir at room temperature for 18 h. After that the solvent was removed under reduced pressure and the residue was purified by flash column chromatography ($CHCl_3$/MeOH 80:1) to give the carbonate **12** (1.20 g, 94% yield of crude product; 890 mg, 70% yield of pure product): yellow solid; mp 172–174 °C; R_f=0.14 (80:1); IR (cm^{-1}) 3419, 3338, 3285, 2967, 2923, 1745, 1621, 1593, 1575, 1560, 1509, 1488, 1422, 1384, 1341, 1272, 1257, 1209, 1149, 1120, 1045, 828; ^1H NMR (400 MHz, DMF-d_7) δ=7.78 (dd, J=2.0, 8.9 Hz, 2H), 7.38 (br s, 1H), 7.27 (dd, J=2.0, 8.9 Hz, 2H), 6.91 (d, J=8.4 Hz, 1H), 6.68 (br s, 1H), 6.63 (d, J=2.5 Hz, 1H), 6.52 (dd, J=2.5, 8.4 Hz, 1H), 6.04 (br s, 2H), 5.38 (br s, 2H), 4.94 (br s, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 1.55 (s, 9H) ppm; ^{13}C NMR (101 MHz, DMF-d_7) δ=27.2, 45.0, 55.2, 55.5, 83.3, 98.4, 104.7, 114.9, 117.7, 121.4, 121.9, 129.0, 139.8, 146.9, 149.0, 149.9, 152.0, 152.2, 153.9, 157.9, 160.8 ppm; ^1H NMR (400 MHz, DMF-d_7) (65 °C) δ=7.74 (d, J=8.8 Hz, 2H), 7.24 (d, J=8.8 Hz, 2H), 7.00 (d, J=8.1 Hz, 1H), 6.75 (br s, 2H), 6.64 (d, J=2.2 Hz, 1H), 6.54 (d, J=8.1 Hz, 1H), 5.52 (br s, 2H), 4.94 (br s, 2H), 3.91 (s, 3H), 3.83 (s, 3H), 1.57 (s, 9H) ppm; ^{13}C NMR (101 MHz, DMF-d_7) (65 °C) δ=27.4, 45.0, 55.4, 55.7, 83.3, 98.8, 105.2, 115.1, 117.9, 121.5, 121.7, 129.5, 143.3, 150.2, 151.5, 152.0, 152.3, 158.2, 161.0 ppm; HRMS (HESI, m/z) calcd for $C_{23}H_{28}N_6O_5$ (468.52) $[M+H]^+$ 469.2194, found 469.2188.

4.1.7. General procedure for acylation of tert-butyl (4-((3,5-diamino-1-(2,4-dimethoxybenzyl)-1H-pyrazol-4-yl)diazenyl)phenyl) carbonate. To a solution of compound **12** (300 mg, 0.640 mmol) in dry pyridine (6 mL), acyl chloride (for **13a**: benzoyl chloride (0.082 mL, 0.706 mmol) diluted with DCM (1 mL); for **13b**: 4-nitrobenzoyl chloride (131 mg, 0.708 mmol); for **13c**: thiophene-2-carbonyl chloride (0.075 mL, 0.701 mmol) diluted with DCM (0.5 mL); for **13d**: acetyl chloride (0.090 mL, 1.26 mmol) diluted with DCM (1.5 mL); for **13e**: ethyl carbonochloridate (0.067 mL, 0.704 mmol) diluted with DCM (6 mL)) was added (dropwise for **13a**, **13c**, **13d**, **13e**) at 2–5 °C. The reaction mixture was allowed to stir at room temperature for 18 h. After that the solvent was evaporated under reduced pressure and the residue was diluted with methanol (3 mL). The solution was added dropwise to ice water (15 mL). The precipitate was filtered-off, dried in the air to afford product **13a**–**e**.

*4.1.7.1. 4-((5-Amino-3-benzamido-1-(2,4-dimethoxybenyl)-1H-pyrazol-4-yl)diazenyl)phenyl tert-butyl carbonate (**13a**).* Yield 349 mg, 95%: yellow solid; mp 110–112 °C; IR (cm^{-1}) 3316, 2979, 2837, 1757, 1689, 1614, 1575, 1540, 1391, 1273, 1210, 1147, 1035, 824, 704; ^1H NMR (300 MHz, DMSO-d_6) δ=10.49 (br s, 1H), 7.96 (d, J=7.1 Hz, 2H), 7.69 (d, J=8.8 Hz, 2H), 7.63–7.50 (m, 3H), 7.28 (br s, 1H), 7.25 (d, J=8.8 Hz, 2H), 6.84 (d, J=8.3 Hz, 1H), 6.61 (d, J=2.0 Hz, 1H), 6.51 (dd, J=2.0, 8.3 Hz, 1H), 5.06 (s, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 1.49 (s, 9H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=27.2, 45.0, 55.3, 55.6, 83.3, 98.4, 104.6, 116.6, 116.8, 121.6, 121.9, 127.6, 128.5, 129.0, 129.3, 131.8, 134.0, 141.9 (br s), 150.1, 150.7, 151.1, 157.5, 160.2 ppm; HRMS (HESI, m/z) calcd for $C_{30}H_{32}N_6O_6$ (572.63) $[M+H]^+$ 573.2456, found 573.2453.

*4.1.7.2. 4-((5-Amino-1-(2,4-dimethoxybenzyl)-3-(4-nitrobenzamido)-1H-pyrazol-4-yl)diazenyl)phenyl tert-butyl carbonate (**13b**).* Yield 380 mg, 96%: orange-brown solid; mp 126–128 °C; IR (cm^{-1}) 3437, 3341, 3109, 2976, 2359, 2340, 1756, 1726, 1639, 1616, 1603, 1581, 1541, 1389, 1344, 1273, 1209, 1145, 820, 782, 711; ^1H NMR (400 MHz, DMF-d_7) δ=10.86 (br s, 1H), 8.46 (m, 2H), 8.31 (m, 2H), 8.02 (s, 1H), 7.81 (d, J=8.4 Hz, 2H), 7.40 (s, 1H), 7.31 (d, J=8.2 Hz, 2H), 6.93 (d, J=8.2 Hz, 1H), 6.66 (s, 1H), 6.54 (dd, J=2.4, 8.4 Hz, 1H), 5.16 (s, 2H), 3.90 (s, 3H), 3.81 (s, 3H), 1.54 (s, 9H) ppm; ^{13}C NMR (101 MHz, DMF-d_7) δ=27.2, 45.5, 55.3, 55.5, 83.5, 98.5, 104.8, 117.1, 122.1, 124.0, 129.1, 129.5, 131.1, 137.2, 140.6, 142.9, 149.9, 151.0, 151.4, 151.9, 158.1, 161.0, 164.2, 166.2 ppm; HRMS (HESI, m/z) calcd for $C_{30}H_{31}N_7O_8$ (617.62) $[M+H]^+$ 618.2307, found 618.2308.

*4.1.8. 4-((5-Amino-1-(2,4-dimethoxybenzyl)-3-(thiophene-2-carboxamido)-1H-pyrazol-4-yl)diazenyl)phenyl tert-butyl carbonate (**13c**).* Yield 336 mg, 91%: yellow solid; mp 110–112 °C; IR (cm^{-1}) 3315, 3222, 3098, 2978, 2936, 2836, 2354, 1757, 1673, 1615, 1574, 1542, 1509, 1422, 1390, 1371, 1273, 1209, 1147, 1034, 841, 823, 737, 573, 534; ^1H NMR (400 MHz, DMF-d_7) δ=10.62 (br s, 1H), 8.10 (d, J=3.5 Hz, 1H), 7.91 (dd, J=1.1, 5.1 Hz, 1H), 7.81 (d, J=8.6 Hz, 2H), 7.40 (br s, 1H), 7.38 (br s, 1H), 7.32 (d, J=8.8 Hz, 2H), 7.28 (m, 1H), 6.93 (d, J=8.6 Hz, 1H), 6.65 (d, J=2.5 Hz, 1H), 6.54 (dd, J=2.4, 8.5 Hz, 1H), 5.14 (s, 2H), 3.91 (s, 3H), 3.82 (s, 3H), 1.54 (s, 9H) ppm; ^{13}C NMR (101 MHz, DMF-d_7)=27.2, 44.9, 55.3, 55.6, 83.3, 98.4, 104.6, 116.5, 117.0, 121.6, 121.9, 128.2, 129.0, 129.4, 131.9, 139.3, 141.4 (br s), 142.4 (br s), 150.1, 150.7, 151.1, 157.5, 160.3 ppm; HRMS (HESI, m/z) calcd for $C_{28}H_{30}N_6O_6S$ (578.65) $[M+H]^+$ 579.2020, found 579.2047.

*4.1.9. 4-((3-Acetamido-5-amino-1-(2,4-dimethoxybenzyl)-1H-pyrazol-4-yl)diazenyl)phenyl tert-butyl carbonate (**13d**).* Yield 285 mg, 87%: yellow solid; mp 92–94 °C; IR (cm^{-1}) 3410, 3303, 2980, 2938, 2837, 1758, 1689, 1616, 1572, 1537, 1509, 1387, 1372, 1273, 1210, 1147, 1034, 842, 825, 782, 578, 535; ^1H NMR (300 MHz, DMSO-d_6) δ=9.77 (br s, 1H), 7.76 (d, J=8.6 Hz, 2H), 7.27 (d, J=8.4 Hz, 4H), 6.76 (d, J=8.4 Hz, 1H), 6.59 (d, J=2.0 Hz, 1H), 6.48 (dd, J=2.0, 8.4 Hz, 1H), 5.00 (s, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 2.05 (s, 3H), 1.50 (s, 9H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=23.2, 27.3, 44.9, 55.3, 55.6, 83.4, 98.4, 104.6, 116.2, 116.6, 121.8, 121.9, 128.8, 140.6 (br s), 143.4 (br s),

150.1, 150.8, 151.2, 157.5, 160.2, 168.6 (br s) ppm; HRMS (HESI, *m*/*z*) calcd for $C_{25}H_{30}N_6O_6$ (510.55) $[M+H]^+$ 511.2300, found 511.2298.

*4.1.10. Ethyl (5-amino-4-((4-((tert-butoxycarbonyl)oxy)phenyl)diazenyl)-1-(2,4-dimethoxybenzyl)-1H-pyrazole-3-yl)carbamate (**13e**).* The purification of carbamate **13e** was carried out on semi-preparative HPLC (319 mg, 92% yield of crude product; 128 mg, 37% yield of pure product): yellow solid; mp 86–88 °C; IR (cm^{-1}) 3566, 3413, 2980, 2949, 1756, 1618, 1558, 1273, 1209, 1146, 1044, 892, 781, 630; ^1H NMR (300 MHz, DMSO-d_6) δ=9.31 (s, 1H), 7.75 (d, *J*=8.8 Hz, 2H), 7.27 (d, *J*=8.8 Hz, 4H), 6.76 (d, *J*=8.4 Hz, 1H), 6.59 (d, *J*=1.8 Hz, 1H), 6.48 (dd, *J*=2.0, 8.4 Hz, 1H), 4.99 (s, 2H), 4.06 (q, *J*=7.0 Hz, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 1.50 (s, 9H), 1.18 (t, *J*=7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=14.5, 27.3, 44.8, 55.3, 55.6, 60.3, 83.3, 98.4, 104.6, 116.2, 116.6, 121.7, 121.9, 122.1, 128.8, 150.0, 150.8, 151.2, 153.7, 157.5, 160.0, 160.2 ppm; HRMS (HESI, *m*/*z*) calcd for $C_{26}H_{32}N_6O_7$ (540.58) $[M+H]^+$ 541.2405, found 541.2404.

4.1.11. General procedure for deprotection of Boc protective group.- Compound **13** (0.5 mmol) was dissolved in 10% TFA/DCM (15 mL). The reaction mixture was allowed to stir at room temperature. After 1 h the solvent was evaporated under reduced pressure. To the residue water (20 mL) was added and pH was adjusted with ammonia to pH 10. The suspension was allowed to stir at room temperature for 2 h. The crude product **14a**–**e** was filtered-off and dried in the air.

*4.1.11.1. N-(5-Amino-1-(2,4-dimethoxybenzyl)-4-((4-hydroxyphenyl) diazenyl)-1H-pyrazol-3-yl)benzamide (**14a**).* Yield 234 mg, 99%: orange-brown solid; mp 140–142 °C; IR (cm^{-1}) 3650, 3465, 3180, 2941, 2834, 2391, 2285, 1671, 1582, 1544, 1507, 1455, 1393, 1293, 1267, 1208, 1157, 1137, 1030, 838, 698, 536; ^1H NMR (300 MHz, DMSO-d_6) δ=10.45 (s, 1H), 9.74 (s, 1H), 7.96 (d, *J*=7.1 Hz, 2H), 7.61–7.50 (m, 5H), 7.02 (br s, 2H), 6.81 (d, *J*=8.4 Hz, 3H), 6.60 (d, *J*=2.2 Hz, 1H), 6.50 (dd, *J*=2.2, 8.4 Hz, 1H), 5.04 (s, 2H), 3.83 (s, 3H), 3.75 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=44.9, 55.3, 55.6, 98.4, 104.6, 115.5, 116.0, 116.8, 122.3, 127.5, 128.5, 128.9, 131.7, 134.1, 141.5, 142.0, 145.9, 157.5, 157.9, 160.2165.3 ppm; HRMS (HESI, *m*/*z*) calcd for $C_{25}H_{24}N_6O_4$ (472.51) $[M+H]^+$ 473.1932, found 473.1932.

*4.1.11.2. N-(5-Amino-1-(2,4-dimethoxybenzyl)-4-((4-hydroxyphenyl)diazenyl)-1H-pyrazol-3-yl)-4-nitrobenzamide (**14b**).* The crude 4-nitrobenzamide **14b** was purified by flash column chromatography ($CHCl_3$/MeOH 40:1) to give product **14b** (204 mg, 79% yield of crude product; 134 mg, 52% yield of pure product): orange solid; mp 150–152 °C; R_f=0.28; IR (cm^{-1}) 3412, 3177, 2950, 2836, 2391, 2291, 1673, 1602, 1582, 1540, 1525, 1510, 1452, 1347, 1294, 1272, 1209, 1158, 1033, 841, 831, 705, 613, 533; ^1H NMR (300 MHz, DMSO-d_6) δ=10.69 (s, 1H), 9.75 (s, 1H), 8.37 (d, *J*=8.8 Hz, 2H), 8.16 (d, *J*=8.4 Hz, 2H), 7.53 (d, *J*=8.8 Hz, 2H), 7.05 (s, 2H), 6.80 (d, *J*=8.6 Hz, 3H), 6.60 (d, *J*=1.8 Hz, 1H), 6.49 (dd, *J*=2.3, 8.3 Hz, 1H), 5.04 (s, 2H), 3.83 (s, 3H), 3.74 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=44.9, 55.3, 55.6, 98.4, 104.6, 115.5, 116.1, 116.7, 122.5, 123.7, 129.0, 129.1, 139.8, 141.1, 141.8, 145.8, 149.3, 157.5, 158.0, 160.2, 164.2 ppm; HRMS (HESI, *m*/*z*) calcd for $C_{25}H_{23}N_7O_6$ (517.51) $[M+H]^+$ 518.1783, found 518.1783.

*4.1.11.3. N-(5-Amino-1-(2,4-dimethoxybenzyl)-4-((4-hydroxyphenyl)diazenyl)-1H-pyrazol-3-yl)thiophene-2-carboxamide (**14c**).* The crude carboxamide **14c** was purified by flash column chromatography ($CHCl_3$/MeOH 40:1) to give product **14c** (233 mg, 98% yield of crude product; 134 mg, 56% yield of pure product): yellow solid; mp 132–134 °C; R_f=0.15; IR (cm^{-1}) 3549, 3469, 3413, 2409, 2279, 1637, 1618, 1578, 1543, 1508, 1422, 1397, 1293, 1268, 1209, 1157, 964, 838, 719, 622, 538, 481; ^1H NMR (300 MHz, DMSO-d_6) δ=10.39 (s, 1H), 9.73 (s, 1H), 7.94 (d, *J*=3.8 Hz, 1H), 7.84 (d, *J*=4.8 Hz, 1H), 7.54 (d, *J*=8.6 Hz, 2H), 7.22 (dd, *J*=4.8, 3.8 Hz, 1H), 7.03 (s, 2H), 6.84–6.77 (m, 3H), 6.60 (d, *J*=2.2 Hz, 1H), 6.49 (dd, *J*=2.2, 8.4 Hz, 1H), 5.03 (s, 2H), 3.83 (s, 3H), 3.75 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=44.9, 55.3, 55.6, 98.4, 104.6, 115.5, 116.3, 116.7, 122.4, 128.2, 129.0, 129.3, 131.7, 139.4, 141.0, 141.8, 145.9, 157.5, 158.0, 160.1, 160.2 ppm; HRMS (HESI, *m*/*z*) calcd for $C_{23}H_{22}N_6O_4S$ (478.53) $[M+H]^+$ 479.1496, found 479.1495.

*4.1.11.4. N-(5-Amino-1-(2,4-dimethoxybenzyl)-4-((4-hydroxyphenyl)diazenyl)-1H-pyrazol-3-yl)acetamide (**14d**).* Yield 143 mg, 69%: yellow solid; mp 136–138 °C; IR (cm^{-1}) 3420, 3205, 3024, 2934, 2838, 2408, 2283, 1680, 1613, 1573, 1537, 1508, 1454, 1395, 1294, 1267, 1237, 1209, 1157, 1119, 1035, 937, 841, 674, 538; ^1H NMR (300 MHz, DMSO-d_6) δ=9.73 (s, 1H), 7.59 (d, *J*=8.8 Hz, 2H), 7.00 (br s, 2H), 6.82 (d, *J*=8.8 Hz, 2H), 6.73 (d, *J*=8.4 Hz, 1H), 6.59 (d, *J*=2.2 Hz, 1H), 6.47 (dd, *J*=2.2, 8.4 Hz, 1H), 4.98 (s, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 2.03 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=23.1, 44.8, 55.3, 55.6, 98.4, 104.6, 115.5, 116.8, 122.5, 128.7, 140.3 (br s), 142.8, 146.0, 155.9 (br s), 157.4, 157.9, 160.1, 168.7 (br s) ppm; HRMS (HESI, *m*/*z*) calcd for $C_{20}H_{22}N_6O_4$ (410.44) $[M+H]^+$ 411.1775, found 411.1777.

*4.1.11.5. Ethyl (5-amino-1-(2,4-dimethoxybenzyl)-4-((4-hydroxyphenyl) diazenyl)-1H-pyrazol-3-yl) carbamate (**14e**).* Yield 207 mg, 94%: yellow solid; mp 118–120 °C; IR (cm^{-1}) 3430, 3337, 2933, 2836, 2360, 1727, 1614, 1568, 1507, 1465, 1399, 1294, 1267, 1209, 1157, 1041, 840, 738, 539, 438; ^1H NMR (300 MHz, DMSO-d_6) δ=9.73 (s, 1H), 9.19 (s, 1H), 7.58 (d, *J*=8.6 Hz, 2H), 6.98 (br s, 2H), 6.82 (d, *J*=8.6 Hz, 2H), 6.73 (d, *J*=8.4 Hz, 1H), 6.59 (d, *J*=2.0 Hz, 1H), 6.47 (dd, *J*=2.1, 8.3 Hz, 1H), 4.97 (s, 2H), 4.05 (q, *J*=7.1 Hz, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 1.17 (t, *J*=7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=14.5, 44.7, 55.3, 55.6, 60.3, 98.4, 104.6, 115.5, 115.5, 116.8, 122.4, 128.7, 140.5, 142.4, 146.0, 153.9, 157.4, 157.9, 160.1 ppm; HRMS (HESI, *m*/*z*) calcd for $C_{21}H_{24}N_6O_5$ (440.46) $[M+H]^+$ 441.1883, found 441.1881.

4.1.12. General procedure for deprotection of Dmb and Boc protecting groups. Compound **13** (0.5 mmol) was dissolved in neat TFA (15 mL). The reaction mixture was allowed to stir at room temperature. After 4 h the solvent was evaporated under reduced pressure. To the residue water (20 mL) was added and pH was adjusted with aqueous ammonia (25%) to pH 10. The suspension was allowed to stir at room temperature for 2 h. Then the crude product **15a**–**e** was filtered-off and dried in the air.

*4.1.12.1. N-(5-Amino-4-((4-hydroxyphenyl)diazenyl)-1H-pyrazol-3-yl)benzamide (**15a**).* The benzamide **15a** was purified by column chromatography ($CHCl_3$/MeOH 10:1) to give pure product (159 mg, 99% yield of crude product; 95.1 mg, 59% yield of pure product): yellow solid; mp 262–264 °C; R_f=0.20; IR (cm^{-1}) 3317, 3221, 3110, 2924, 2847, 1686, 1634, 1580, 1448, 1506, 1394, 1239, 1203, 1037, 833, 695, 531; ^1H NMR (300 MHz, DMSO-d_6) δ=11.79 (br s, 1H), 10.58 (br s, 1H), 9.76 (br s, 1H), 7.98 (d, *J*=7.0 Hz, 2H), 7.66–7.50 (m, 5H), 6.81 (d, *J*=8.6 Hz, 2H), 6.59 (br s, 2H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ=115.5, 115.9, 122.4, 127.6, 128.6, 131.9, 133.8, 145.8, 158.0, 165.3 ppm; HRMS (HESI, *m*/*z*) calcd for $C_{16}H_{14}N_6O_2$ (322.33) $[M+H]^+$ 323.1251, found 323.1251.

*4.1.12.2. N-(5-Amino-4-((4-hydroxyphenyl)diazenyl)-1H-pyrazol-3-yl)-4-nitrobenzamide (**15b**).* The 4-nitrobenzamide **15b** was purified by column chromatography ($CHCl_3$/MeOH 10:1) to give pure product (182 mg, 99% yield of crude product; 102 mg, 56% yield of pure product): yellow solid; mp 232–234 °C; R_f=0.20; IR (cm^{-1}) 3712, 3346, 3003, 2924, 2834, 2361, 2344, 1676, 1587, 1572, 1508,

1467, 1340, 1315, 1301, 1278, 1203, 1038, 842, 814, 704, 532; ^{1}H NMR (300 MHz, DMSO-d_6) δ=11.83 (br s, 1H), 10.76 (br s, 1H), 9.75 (s, 1H), 8.39 (d, J=8.4 Hz, 2H), 8.19 (d, J=8.4 Hz, 2H), 7.54 (d, J=8.4 Hz, 2H), 6.80 (d, J=8.8 Hz, 2H), 6.67 (br s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=116.0, 116.7, 123.03, 124.3, 124.5, 129.7, 129.9, 140.2, 146.4, 149.9, 158.6, 164.7 ppm; HRMS (HESI, m/z) calcd for $C_{16}H_{13}N_7O_4$ (367.33) $[M+H]^+$ 368.1102, found 368.1101.

*4.1.12.3. N-(5-Amino-4-((4-hydroxyphenyl)diazenyl)-1H-pyrazol-3-yl)thiophene-2-carboxamide (**15c**).* Yield 142 mg, 87%: yellow-brown solid; mp 284–286 °C; IR (cm^{-1}) 3311, 3219, 3113, 2994, 2950, 2833, 2390, 2284, 1673, 1632, 1577, 1545, 1506, 1396, 1296, 1243, 1203, 1037, 835, 726, 530; ^{1}H NMR (300 MHz, DMSO-d_6) δ=11.83 (br s, 1H), 10.48 (br s, 1H), 9.75 (br s, 1H), 7.98 (d, J=4.0 Hz, 1H), 7.87 (d, J=4.7 Hz, 1H), 7.55 (d, J=8.4 Hz, 2H), 7.24 (dd, J=4.7, 4.0 Hz, 1H), 6.81 (d, J=8.4 Hz, 2H), 6.64 (br s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=115.5, 116.3, 122.5, 128.3, 129.6, 132.0, 139.2 (br s), 145.9, 158.0, 160.1 ppm; HRMS (HESI, m/z) calcd for $C_{14}H_{12}N_6O_2S$ (328.35) $[M+H]^+$ 329.0815, found 329.0813.

*4.1.12.4. N-(5-Amino-4-((4-hydroxyphenyl)diazenyl)-1H-pyrazol-3-yl)acetamide (**15d**).* The acetamide **15d** was purified by column chromatography ($CHCl_3$/MeOH 10:1) to give product (97.3 mg, 75% yield of crude product; 51.5 mg, 40% yield of pure product): yellow-brown solid; mp 158–160 °C; R_f=0.16; IR (cm^{-1}) 3128, 2925, 2834, 2387, 2284, 1674, 1603, 1594, 1552, 1506, 1454, 1294, 1268, 1240, 1203, 1039, 841, 663, 633, 526; ^{1}H NMR (300 MHz, DMSO-d_6) δ=11.71 (br s, 1H), 10.25 (br s, 1H), 9.75 (s, 1H), 7.63 (d, J=8.8 Hz, 2H), 6.82 (d, J=8.8 Hz, 2H), 6.26 (br s, 2H), 2.12 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ=23.1, 115.4, 115.6, 122.6, 123.6, 143.3 (br s), 146.0, 158.0, 169.1 (br s) ppm; HRMS (HESI, m/z) calcd for $C_{11}H_{12}N_6O_2$ (260.26) $[M+H]^+$ 261.1095, found 261.1093.

*4.1.12.5. Ethyl (5-amino-4-((4-hydroxyphenyl)diazenyl)-1H-pyrazol-3-yl) carbamate (**15e**).* The purification of carbamate **15e** was carried out on semi-preparative HPLC (92.7 mg, 64% yield of crude product; 29.5 mg, 20% yield of pure product): yellow solid; mp 170–172 °C; IR (cm^{-1}) 3180, 3108, 2939, 2834, 2390, 2284, 1731, 1589, 1565, 1506, 1452, 1296, 1270, 1222, 1204, 1172, 1096, 1037, 837, 815, 530; ^{1}H NMR (300 MHz, DMSO-d_6) δ=11.57 (br s, 1H), 9.61 (br s, 2H), 7.59 (d, J=8.4 Hz, 2H), 6.81 (d, J=8.4 Hz, 2H), 6.51 (br s, 2H), 4.10 (q, J=7.0 Hz, 2H), 1.21 (t, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ=14.5, 60.5, 115.4, 115.5, 122.5, 142.4 (br s), 146.0, 153.8, 157.9; HRMS (HESI, m/z) calcd for $C_{12}H_{14}N_6O_3$ (290.28) $[M+H]^+$ 291.1200, found 291.1199.

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Supplementary data

Experimental details, spectroscopic data, and screening of different reaction conditions for the synthesis of **2a**–**15e**. Crystallographic data for **13b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 837640. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk). Crystal data and refinement, selected bond lengths and angles of covalent as well as non-covalent contacts are also summarized. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.03.063.

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