Chemistry of Polyhalogenated Nitrobutadienes, 6: A New Ring-Closure Approach to Perfunctionalized 5-Nitropyrimidines

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Abstract: The recently reported capability of pentachloro-2-nitrobutadiene and some closely related derivatives to allow the synthesis of highly substituted acyclic as well as five-membered (hetero)cyclic compounds is herein extended to pyrimidines with an exceptional substitution pattern. Our novel approach starts from a 1,1-diamino-3,4,4-trichloro-2-nitrobuta-1,3-diene and an appropriate amidine. Some of the resulting perfunctionalized pyrimidines were subjected to further transformations to give promising candidates with respect to biological, especially pharmacological, activity.

Key words: nitro compounds, halides, pyrimidines, ring closure, nucleophilic substitution

The electronically remarkable pentachloro-2-nitrobuta-1,3-diene and similar polysubstituted butadienes are versatile starting materials for a series of synthetic applications. Among these, we have previously synthesized thiophenes, developed an unprecedented C_4-to-C_3 cleavage of such a butadiene, and taken advantage of the dienophilic properties of these electron-deficient molecules. In addition, we have obtained imidazolidines, oxazolidines, and related five-membered 1,3-heterocycles from the corresponding thiolated butadiene derivatives.[1]

Further efforts are underway to explore the entire synthetic potential of this type of compound. In this paper, we give the first account of the reaction of 1,1-bis(1*H*-benzotriazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-diene (**1**) or the 1-amino-1-(benzotriazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-dienes **2**–**5** with acetamidine or benzamidine hydrochlorides. The latter nitrobutadienes were prepared from the bis(benzotriazole) derivative **1** in up to 95% yield in accordance with the procedure of Zapol'skii and Kaberdin.[2] Thus, applying sodium hydride or lithium hydride, aqueous sodium hydroxide, or other bases in tetrahydrofuran or dimethyl sulfoxide to **2**–**5** we obtained the pyrimidines **6**–**10** in up to 85% yield (Table 1).

The optimized procedure includes the application of three equivalents of the amidine with a fourfold excess of sodium hydride in tetrahydrofuran and requires the reaction mixture to be initially maintained at –10 °C and then at room temperature. The proposed mechanism of this novel ring formation is depicted in Scheme 1.

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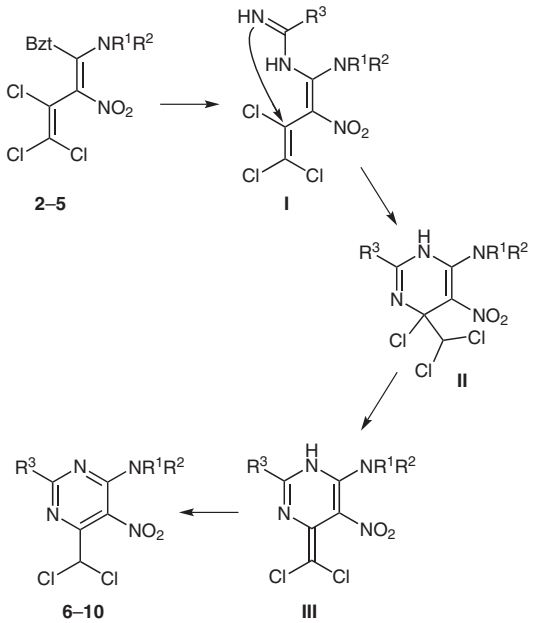
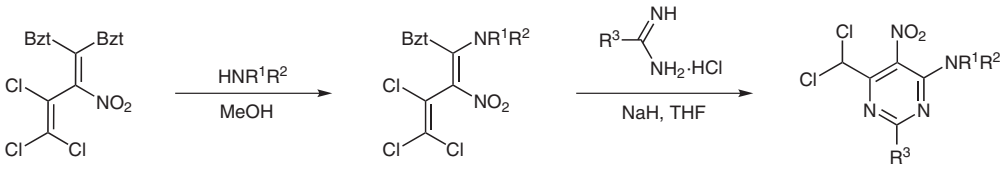
The free amidine is initially generated by the added base. The ring-closing reaction starts with vinylic nucleophilic substitution at C1, whereupon the amino group of the amidine acts as the nucleophile and, expectedly, the benzotriazolyl substituent plays the role of leaving group. Then, as the key step, the imino nitrogen within the amidine moiety of **I** forms the six-membered heteroring **II** in an intramolecular cyclization reaction. Subsequently, hydrochloric acid is eliminated from **II** by additional base, giving the exomethylene compound **III**. Finally, aromatization occurs that leads to the persubstituted pyrimidines **6**–**10**. As an example, the structure of **7** was confirmed by X-ray crystallography (Figure 1).[3,4]

Evidence for the mechanism proposed in Scheme 1 was obtained by isolating the initial substitution product **11** from the bis(benzotriazole) derivative **1** and benzamidine and then cyclizing it to the pyrimidine derivative **12** with base. In conclusion, **1** afforded **11** in 79% yield employing benzamidine hydrochloride and sodium hydrogen carbonate in acetonitrile. The subsequent ring closure was accomplished using potassium carbonate in tetrahydrofuran to give pyrimidine **12** (43%). In contrast, direct conversion of **1**, i.e. without isolation of the intermediate **11**, re-

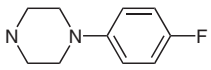
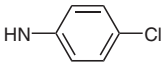


Scheme 1 Proposed mechanism of pyrimidine formation

Table 1 Synthesis of 4-Amino-6-(dichloromethyl)-5-nitropyrimidines



1 2–5 6–10

Entry	NR^1R^2	2–5	Yield (%)	Base	Solvent	Product	Yield (%)
1		**2**	88	NaH	THF	**6**, R^3 = Ph	73
2				NaOH	DMSO		61
3		**2**	88	NaH	DMSO	**7**, R^3 = Me	56
4				NaH	THF		54
5				LiH	THF		22
6				Cs_2CO_3	DMSO		21
7		**3**	95	NaH	THF	**8**, R^3 = Ph	76
8				NaOH	DMSO		40
9		**4**	95	NaH	THF	**9**, R^3 = Me	35
10				NaOH	DMSO		32
11		**5**	57	NaH	THF	**10**, R^3 = Me	85
12				NaOH	DMSO		30

sulted in the same product, but with lower yield (Scheme 2).

It is worthwhile to note that syntheses of 5-nitropyrimidines are rare in literature. One method, published in 1977, employs the condensation of sodium nitromalonaldehyde with amidines.[5] The same salt is part of a three-component ring-closure reaction in combination with 2-methylisothiourea sulfate and morpholine.[6] An alternative access uses the reaction of 5-nitro-1*H*-pyrimidine-2,4-dione with phosphoryl chloride to obtain 2,4-dichloro-5-nitropyrimidine.[7] Another synthesis starts from a mixture of 3-nitrobut-3-en-2-ones, 2-methylisourea, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to afford 2-methoxy-5-nitropyrimidine.[8] In addition, 5-nitropyrimidines have been obtained by ring opening of a 3-nitrochromen-4-one.[9]

Aside from the viewpoint of an organic chemist, such 5-nitropyrimidines are interesting due to their structural similarity to natural compounds, such as bases in nucleosides and nucleotides, and their corresponding physiological activity. Various bioactivities of pyrimidines and other heterocycles are highlighted in a review.[10]

Among numerous applications, some examples are noteworthy: antitumor activity is documented[11a–c] as well as the potential to inactivate human DNA repair.[11d] The broad variety can be illustrated, for example by the activity against chronic obstructive pulmonary disease,[11e] applicability against herpes simplex,[11f] and other viral

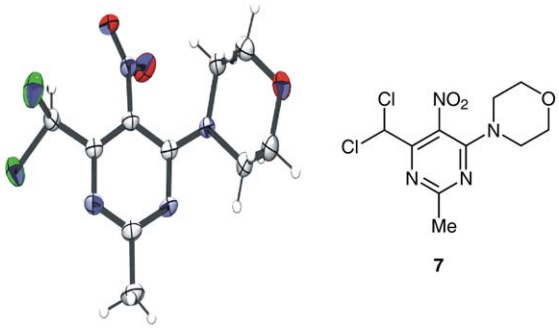
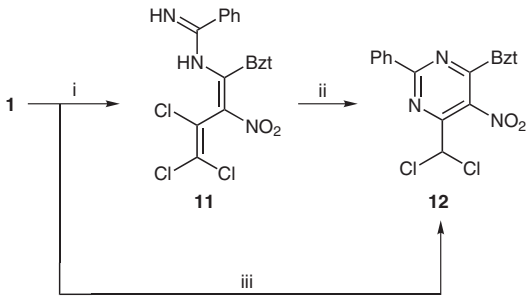
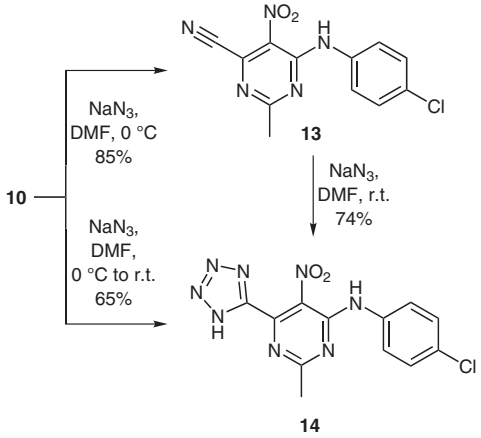


Figure 1 X-ray crystal structure of pyrimidine **7**[3,4]



i: benzamidine hydrochloride, $NaHCO_3$, MeCN, 79%
ii: K_2CO_3, THF, 43%
iii: i, 23%

Scheme 2



Scheme 3

diseases.[11g] Furthermore, one field of application of 5-nitropyrimidines uses their positive modulating effect of the GABAB receptor.[11h,i]

During the course of our synthetic efforts, we obtained interesting derivatives of some of the aforementioned persubstituted pyrimidines **6**–**10**. Thus, in analogy to a recently found reaction,[12] the cyanopyrimidine **13** was obtained in 85% yield by applying sodium azide at 0 °C, whereas the same reagent afforded the tetrazole **14** (74%) at room temperature. Alternatively, **14** is obtained from **10** using an excess of sodium azide at room temperature (Scheme 3).

Moreover, the phenyl group in **6** was selectively nitrated at the *meta*-position using fuming nitric acid at 0 °C, to give **15** (Scheme 4).

Furthermore, treatment of **6** with tin(II) chloride in acetone converted the nitro into an amino group, but also resulted in an unexpected reduction of the dichloromethyl to a methyl group. Thus, the methylated aminopyrimidine **16** was isolated in 75% yield (Scheme 4), whereupon the assumed intermediate, i.e. the 5-amino-6-(dichloromethyl) derivative, was not observed.

To the best of our knowledge, the reduction of a dichloromethyl group attached to a carbo- or hetero-cyclic ring to a methyl group with tin(II) chloride is unprecedented. Only a few reactions, somewhat similar to our conversion, have been previously published.

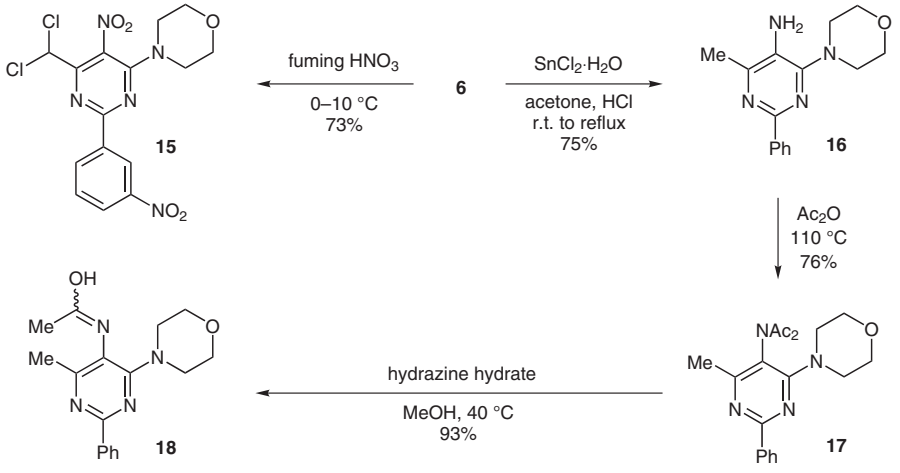
Among these, the complete reduction of a dichloroacetyl substitutent by zinc in acetic acid,[13a] the reductive elimination of two chloro atoms during an indium(I) bromide mediated coupling of α,α-dichloro ketones to 1-arylbutane-1,4-diones,[13b] and the conversion of a dichloroacetyl into an acetyl group upon the influence of tributyltin hydride,[13c] are worthy of note.

Interestingly, such 5-aminopyrimidine derivatives exhibit pharmacological activities, e.g. against anoxia.[14]

In the course of our own investigations, the exhaustive acetylation of the amino group in **16** afforded **17** as expected (76% yield), but in the subsequent reaction with hydrazine hydrate no triazole was obtained, but one of the *N*-acetyl groups was removed reductively. The second acetyl substituent, in principle remained unaffected, but tautomerized to a mixture of the *Z*- and *E*-isomers (3:1) of acetimidic acid **18**, as evidenced by H NMR spectroscopy. Obviously, the exclusive presence of these enol tautomers is caused by the stabilizing conjugation of the enol double bond with the pyrimidine ring (Scheme 4).

In conclusion, we have found a novel synthesis of persubstituted 5-nitropyrimidines starting from the easily accessible 1,1-bis(1*H*-benzotriazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-diene (**1**) and an appropriate amidine. Furthermore, we investigated some subsequent conversions. Especially from a chemical point of view, the latter syntheses gave some remarkable results, but in addition, some products should offer interesting biological, in particular pharmacological properties. Therefore, corresponding tests of these promising compounds are presently underway.

Melting points were determined with a Büchi apparatus 520 and are uncorrected. NMR spectra were referenced to the residual solvent peak: $CDCl_3$, δ = 7.26 (^{1}H), δ = 77.0 (^{13}C); DMSO-d_6, δ = 2.50



Scheme 4

(^{1}H), 39.7 (^{13}C); acetone-d_6, δ = 2.09 (^{1}H), 29.8 (^{13}C). IR spectral data were obtained on a Bruker Vector 22 FT-IR. Mass spectra were obtained on a Hewlett Packard MS 5989B spectrometer, usually in direct mode with EI (70 eV). In the case of chlorinated compounds, all peak values of molecular ions as well as fragments *m*/*z* refer to the isotope ^{35}Cl. HRMS-ESI were measured with a Bruker APEX IV 7 Tesla FT ion cyclotron resonance mass spectrometer. TLC was done on Merck TLC plates (aluminum backed) silica gel 60 F 254. Column chromatography was carried out on silica gel 60 (Merck).

Benzotriazole derivative **1** was prepared in 72% yield from pentachloro-2-nitrobuta-1,3-diene in Et_2O according to Kaberdin et al.[15] Pentachloro-2-nitrobuta-1,3-diene was prepared in 53% yield (bp 69–71 °C).[16]

1,1-Bis(1*H*-benzotriazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-diene (1)

Mp 138–139 °C.

IR (KBr): 3099, 3080, 1798, 1650, 1574, 1536 (NO_2), 1459, 1426, 1317 (NO_2), 1295, 1209, 1173, 1019, 902, 862, 824, 792, 742, 652, 635, 615, 563, 432 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.13–8.26 (m, 2 H), 7.37–7.55 (m, 4 H), 6.71–6.83 (m, 1 H), 6.50–6.57 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 146.2 ($C_{q,Bzt}$), 146.1 ($C_{q,Bzt}$), 134.1 (CNO_2), 132.4 (C1), 131.4 ($C_{q,Bzt}$), 131.3 ($C_{q,Bzt}$), 130.9 (CH), 130.8 (CH), 130.7 (C3), 126.5 (CH), 126.4 (CH), 121.6 (CH), 121.5 (CH), 119.6 (C4), 109.6 (CH), 109.3 (CH).

MS: *m*/*z* (%) = 435 [M$^+$] (1), 316 [M$^+$ – benzotriazole] (2), 198 [M$^+$ – 2 benzotriazole] (4), 51 (100).

1-(1*H*-Benzotriazol-1-yl)-3,4,4-trichloro-1-(morpholin-4-yl)-2-nitrobuta-1,3-diene (2); Typical Procedure

To a suspension of bisbenzotriazole derivative **1** (5.00 g, 11.45 mmol) in MeOH (70 mL) at 5 °C was added a soln of morpholine (1.13 g, 13.0 mmol) in MeOH (5 mL) over 3 min. The resulting mixture was stirred at 10–15 °C for 2 h and at r.t. for 3 h. The precipitate was filtered off, washed with H_2O (2 × 50 mL) and cold MeOH (20 mL), and dried in vacuo to give **2**; yield: 4.07 g (88%); mp 164–166 °C (MeOH–acetone, 2:1) (Lit.[17] mp 163–164 °C).

IR (KBr): 2986, 1599, 1558 (NO_2), 1467, 1345, 1283 (NO_2), 1230, 1110, 1012, 903, 875, 808, 768, 745, 713, 650, 573, 503 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.16 (d, *J* = 8.3 Hz, 1 H), 7.44–7.83 (m, 3 H), 3.84–4.19 (m, 4 H, OCH_2), 3.17–3.62 (m, 4 H, NCH_2).

^{1}H NMR (acetone-d_6): δ = 8.24 (d, *J* = 8.3 Hz, 1 H), 7.53–8.02 (m, 3 H), 3.88–4.17 (m, 4 H, OCH_2), 3.31–3.80 (m, 4 H, NCH_2).

^{13}C NMR ($CDCl_3$): δ = 147.6, 146.3, 132.4, 130.7 (CH), 126.1 (CH), 126.3 and 124.3 ($CCl{=}CCl_2$), 120.7 (CNO_2), 121.1 (CH), 110.3 (CH), 66.4 (2 C, OCH_2), 50.4 (2 C, NCH_2).

^{13}C NMR (acetone-d_6): δ = 148.8, 147.2, 133.5, 131.2 (CH), 126.7 (CH), 125.9 and 125.2 ($CCl{=}CCl_2$), 124.3 (CNO_2), 121.4 (CH), 111.6 (CH), 67.0 (2 C, OCH_2), 51.1 (2 C, NCH_2).

MS: *m*/*z* (%) = 403 [M$^+$] (1), 368 [M$^+$ – Cl] (1), 93 (100).

1-(1*H*-Benzotriazol-1-yl)-3,4,4-trichloro-2-nitro-1-(piperidin-1-yl)buta-1,3-diene (3)

Following the typical procedure for **2** using piperidine and recrystallization (MeOH–acetone, 2:1); yield: 95%; mp 133–134 °C (Lit.[3] mp 132–133 °C).

IR (KBr): 2946, 1600, 1560 (NO_2), 1498, 1453, 1285 (NO_2), 1251, 1160, 1025, 931, 918, 895, 803, 765, 751, 708, 665, 573, 461 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.11 (d, *J* = 8.3 Hz, 1 H), 7.40–7.74 (m, 3 H), 3.00–3.67 (m, 4 H, NCH_2), 1.59–2.02 (m, 6 H, CH_2).

^{13}C NMR ($CDCl_3$): δ = 148.2, 146.2, 132.4, 130.3 (CH), 125.8 (CH), 125.0 and 124.5 ($CCl{=}CCl_2$), 120.8 (CH), 115.0 (CNO_2), 110.4 (CH), 51.8 (2 C, NCH_2), 25.8 (2 C, NCH_2CH_2), 23.4 (CH_2CCH_2).

MS: *m*/*z* (%) = 401 [M$^+$] (1), 93 (100).

1-(1*H*-Benzotriazol-1-yl)-3,4,4-trichloro-1-[4-(4-fluorophenyl)piperazin-1-yl]-2-nitrobuta-1,3-diene (4)

Following the typical procedure for **2** using 4-(4-fluorophenyl)piperazine and recrystallization (MeOH–acetone, 2:1); yield: 95%; mp 177–179 °C.

IR (KBr): 3050, 1601, 1562 (NO_2), 1504, 1452, 1301 (NO_2), 1005, 904, 812, 773, 704, 542 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.17 (d, *J* = 8.1 Hz, 1 H), 7.40–7.75 (m, 3 H), 6.87–7.05 (m, 4 H), 3.26–3.65 (m, 8 H, NCH_2).

^{13}C NMR ($CDCl_3$): δ = 158.1 (CF, $^1J_{C\text{-}F}$ = 244 Hz), 147.7, 146.7, 146.4, 132.4, 130.7 (CH), 126.3 (CCl), 126.0 (CH), 124.5 (CCl_2), 121.1 (CH), 119.3 (2 C, CH, $^3J_{C\text{-}F}$ = 8 Hz), 116.0 (2 C, CH, $^2J_{C\text{-}F}$ = 22 Hz), 111.8 (CNO_2), 110.3 (CH), 50.7 (2 C, NCH_2), 50.5 (2 C, NCH_2).

MS: *m*/*z* (%) = 496 [M$^+$] (3), 479 [M$^+$ – OH] (1), 123 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{17}Cl_3FN_6O_2$: 497.04571; found: 497.04565.

1-(1*H*-Benzotriazol-1-yl)-3,4,4-trichloro-1-(4-chlorophenylamino)-2-nitrobuta-1,3-diene (5)

Following the typical procedure for **2** using 4-chloroaniline and recrystallization (MeOH–acetone, 2:1); yield: 57%; mp 112–113 °C.

IR (KBr): 3263, 1620, 1578 (NO_2), 1488, 1461, 1375 (NO_2), 1342, 1188, 1045, 874, 830, 812, 744, 710, 636, 587 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 11.55 (br s, 1 H, NH), 8.05 (d, *J* = 8.4 Hz, 1 H, Bzt-H), 7.48 (dd, *J* = 7.8, 7.6 Hz, 1 H, Bzt-H), 7.40 (dd, *J* = 8.4, 7.6 Hz, 1 H, Bzt-H), 7.36 (d, *J* = 7.8 Hz, 1 H, Bzt-H), 7.04 (d, *J* = 8.6 Hz, 2 H, C*H*=CCl), 6.72 (d, *J* = 8.6 Hz, 2 H, C*H*=CNH).

^{13}C NMR ($CDCl_3$): δ = 146.0, 145.3, 133.6, 133.3, 131.8, 129.9 (CH), 129.8 (2 C, *C*HCCl), 125.6 (CH), 124.1 (2 C, *C*HCNH), 120.9 (CH), 120.2 (CNO_2), 109.6 (CH). The carbon atoms within the trichlorovinyl group were not detected.

MS: *m*/*z* (%) = 443 [M$^+$] (1), 368 [M$^+$ – Cl] (1), 93 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{10}Cl_4N_5O_2$: 443.95831; found: 443.95845.

4-(Dichloromethyl)-6-(morpholin-4-yl)-5-nitro-2-phenylpyrimidine (6); Typical Procedures

Method I (using aq NaOH, DMSO): To a suspension of **2** (1.00 g, 2.47 mmol) in DMSO (20 mL) at 0 °C was added over 3 min a mixture of benzamidine hydrochloride (1.16 g, 7.41 mmol), 30% aq NaOH (1.32 g, 9.88 mmol), and DMSO (10 mL). The combined slurry was stirred at 0–5 °C for 1 h and at r.t. for 3 h. Subsequently, the mixture was poured into a soln of concd HCl (10 mL) in cold H_2O (100 mL). After 10 min with stirring, the precipitate was filtered off, washed with H_2O (2 × 20 mL) and MeOH (2 × 10 mL), and dried in vacuo to give pyrimidine **6**; yield: 0.56 g (61%); mp 167–169 °C (MeOH–$CHCl_3$, 2:1).

IR (KBr): 3055, 2865, 1590, 1569 (NO_2), 1458, 1395, 1345 (NO_2), 1221, 1112, 1022, 999, 927, 865, 836, 811, 752, 699, 542 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.40–8.50 (m, 2 H, Ph), 7.40–7.55 (m, 3 H, Ph), 7.11 (s, 1 H, $CHCl_2$), 3.78–3.86 (m, 4 H, OCH_2), 3.63–3.72 (m, 4 H, NCH_2).

^{13}C NMR ($CDCl_3$): δ = 162.9 (C2), 156.8, 154.6, 135.0 ($C_{q,Ph}$), 131.5 (C_{Ph}), 128.6 (2 C, C_{Ph}), 127.9 (2 C, C_{Ph}), 125.5 (CNO_2), 65.7 (2 C, OCH_2), 65.3 ($CHCl_2$), 46.3 (2 C, NCH_2).

MS: *m/z* (%) = 368 [M^+] (30), 351 [M^+ – OH] (17), 333 [M^+ – Cl] (31), 322 [M^+ – NO_2] (12), 295 (68), 105 (100).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{15}Cl_2N_4O_3$: 369.05157; found: 369.05178.

Method II (with NaH in THF): To a suspension of NaH [0.071 g, 2.964 mmol; 0.118 g of 60% NaH in mineral oil washed with anhyd pentane (2 ×)] in anhyd THF (10 mL) was added benzamidine hydrochloride (0.348 g, 2.222 mmol). After cooling this slurry to –10 °C, a soln of **2** (0.300 g, 0.741 mmol) in THF (3 mL) was added dropwise. The resulting mixture was stirred at –10 °C for 1 h then at r.t. overnight. Subsequently, the mixture was poured into a soln of concd HCl (3 mL) in cold H_2O (30 mL). The mixture was stirred for 10 min and the crude product was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were washed with H_2O (2 × 20 mL) and dried in vacuo. Column chromatography (silica gel, petroleum ether–EtOAc, 4:1) gave pyrimidine **6**; yield: 0.199 g (73%).

4-(Dichloromethyl)-2-methyl-6-(morpholin-4-yl)-5-nitropyrimidine (7)

Following the typical procedure for **6**, Method II using **2** (0.300 g, 0.741 mmol), acetamidine hydrochloride (0.210 g, 2.221 mmol), and NaH (0.071 g, 2.964 mmol) with purification by column chromatography (petroleum ether–EtOAc, 1:1). Subsequent crystallization was induced by adding cold MeOH (5 mL) and drying the resultant precipitate in vacuo to give **7**; yield: 0.123 g (54%); mp 95–96 °C (MeOH–$CHCl_3$, 2: 1).

IR (KBr): 3031, 2861, 1576 (NO_2), 1510, 1405, 1339 (NO_2), 1209, 1114, 1064, 995, 874, 838, 826, 778, 741, 672, 532 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.98 (s, 1 H, $CHCl_2$), 3.72–3.78 (m, 4 H, OCH_2), 3.54–3.60 (m, 4 H, NCH_2), 2.62 (s, 3 H, Me).

^{13}C NMR ($CDCl_3$): δ = 168.7 (C2), 156.7, 154.5, 126.0 (CNO_2), 66.2 (2 C, OCH_2), 65.2 ($CHCl_2$), 46.6 (2 C, NCH_2), 26.1 (Me).

MS: *m/z* (%) = 306 [M^+] (32), 271 [M^+ – Cl] (25), 233 (70), 58 (100).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{10}H_{13}Cl_2N_4O_3$: 307.03592; found: 307.03593.

For comparison (see Table 1): NaH in DMSO or LiH in THF gave **7** in 56% and 22% yield, respectively. In addition, using Cs_2CO_3 in DMSO gave **7** in only 21% yield.

4-(Dichloromethyl)-5-nitro-2-phenyl-6-(piperidin-1-yl)pyrimidine (8)

Following the typical procedure for **6**, Method II gave **8** in 76% yield, whereas using Method I gave only 40% yield; mp 128–129 °C (MeOH–$CHCl_3$, 2:1).

IR (KBr): 3061, 2934, 2852, 1589, 1570 (NO_2), 1528, 1395, 1342 (NO_2), 1215, 1060, 1028, 921, 832, 771, 746, 705, 663 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 8.34–8.42 (m, 2 H, Ph), 7.53–7.62 (m, 3 H, Ph), 7.50 (s, 1 H), 3.52–3.62 (m, 4 H, NCH_2), 1.59–1.71 (m, 6 H, CH_2).

^{13}C NMR (DMSO-d_6): δ = 162.2 (C2), 156.9, 154.9, 135.7 ($C_{q,Ph}$), 132.3 (C_{Ph}), 129.0 (2 C, C_{Ph}), 128.8 (2 C, C_{Ph}), 125.6 (CNO_2), 67.6 ($CHCl_2$), 47.8 (2 C, NCH_2), 25.2 (2 C, NCH_2CH_2), 23.5 (CH_2CCH_2).

MS: *m/z* (%) = 366 [M^+] (4), 349 [M^+ – OH] (7), 294 (14), 105 (100).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_{17}Cl_2N_4O_2$: 367.07231; found: 367.07242.

4-(Dichloromethyl)-6-[4-(4-fluorophenyl)piperazin-1-yl]-2-methyl-5-nitropyrimidine (9)

Following the typical procedure for **6**, Method II gave **9** in 35% yield, whereas using Method I gave 32% yield; mp 97–98 °C (MeOH–$CHCl_3$, 2:1).

IR (KBr): 3068, 2820, 1568 (NO_2), 1510, 1460, 1333 (NO_2), 1219, 995, 922, 770, 748, 703, 673, 538 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.87–7.05 (m, 4 H, Ph), 6.99 (s, 1 H, $CHCl_2$), 3.70–3.81 (m, 4 H, NCH_2), 3.58–3.70 (m, 4 H, NCH_2), 2.64 (s, 3 H, Me).

^{13}C NMR ($CDCl_3$): δ = 168.7 (C2), 157.9 (CF, $^1J_{C\text{-}F}$ = 241 Hz), 156.7, 154.5, 146.6, 126.2 (CNO_2), 118.5 (2 C, $^3J_{C\text{-}F}$ = 8 Hz), 115.9 ($^2J_{C\text{-}F}$ = 22 Hz), 65.2 ($CHCl_2$), 50.1 (2 C, NCH_2), 46.3 (2 C, NCH_2), 26.1 (Me).

MS: *m/z* (%) = 399 [M^+] (9), 382 [M^+ – OH] (1), 364 [M^+ – Cl (2), 353 [M^+ – NO_2] (2), 303 [M^+ – PhF] (4), 150 (100).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_{17}Cl_2FN_5O_2$: 400.07378; found: 400.07373.

4-(4-Chlorophenylamino)-6-(dichloromethyl)-2-methyl-5-nitropyrimidine (10)

Following the typical procedure for **6**, Method II gave **10** in 85% yield, whereas using Method I gave 30% yield; mp 145–146 °C (MeOH–$CHCl_3$, 2:1).

IR (KBr): 3320, 1613, 1568 (NO_2), 1511, 1407, 1382 (NO_2), 1284, 1204, 1097, 1001, 856, 833, 785, 748, 710, 649, 510 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.73 (br s, 1 H, NH), 7.54 (d, *J* = 8.8 Hz, 2 H, CHCCl), 7.38 (d, *J* = 8.8 Hz, 2 H, CHCNH), 7.37 (s, 1 H, $CHCl_2$), 2.68 (s, 3 H, Me).

^{13}C NMR ($CDCl_3$): δ = 171.3 (C2), 160.6 (C6), 153.1 (C4), 134.9 ($HNC_{q,Ph}$), 131.4 ($ClC_{q,Ph}$), 129.2 (2 C, *C*HCCl), 128.7 (CNO_2), 124.3 (2 C, *C*HCNH), 66.5 ($CHCl_2$), 26.5 (Me).

MS: *m/z* (%) = 346 [M^+] (100), 329 [M^+ – OH] (4), 311 [M^+ – Cl] (2), 300 [M^+ – NO_2] (8).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{12}H_{10}Cl_3N_4O_2$: 346.98639; found: 346.98646.

***N*^{1}-[1-(1*H*-Benzotriazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-dienyl]benzamidine (11)**

To a suspension of **1** (5.00 g, 11.45 mmol) in MeCN (60 mL) was added benzamidine hydrochloride (2.07 g, 13.2 mmol) and $NaHCO_3$ (2.12 g, 25.2 mmol) suspended in MeCN (20 mL). The mixture was stirred at r.t. for 2 weeks. Subsequently, the precipitate was filtered off, washed with H_2O (2 × 50 mL), and dried in vacuo to give **11**; yield: 3.94 g (79%); mp 131–133 °C (MeOH–acetone, 3:1).

IR (KBr): 3154, 1678, 1558 (NO_2), 1449, 1433, 1375 (NO_2), 1290, 1255, 1219, 1085, 1020, 940, 854, 785, 711, 644, 612, 551 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.02 (d, *J* = 8.0 Hz, 1 H, Bzt-H), 7.58–7.68 (m, 3 H), 7.50–7.55 (m, 1 H), 7.40–7.48 (m, 2 H), 7.31–7.39 (m, 2 H), 6.55 (br s, 2 H, NH).

^{13}C NMR ($CDCl_3$): δ = 165.1 (C=NH), 147.9 (NHCN), 145.6 ($C_{q,Bzt}$), 132.9 (CH, C_{Ph}), 132.1 ($C_{q,Bzt}$), 131.3 ($C_{q,Ph}$), 129.5 (CH, Bzt), 129.2 (CCl), 129.0 (2 CH, C_{Ph}), 127.4 (2 CH, C_{Ph}), 126.9 (CCl_2), 125.4 (CH, Bzt), 123.4 (CNO_2), 120.5 (CH, Bzt), 111.7 (CH, Bzt).

MS: *m/z* (%) = 436 [M^+] (2), 401 [M^+ – Cl] (2), 78 (100).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{12}Cl_3N_6O_2$: 437.00818; found: 437.00842.

4-(1*H*-Benzotriazol-1-yl)-6-(dichloromethyl)-5-nitro-2-phenylpyrimidine (12)

Method I (from **1***)*: To a suspension of **1** (5.00 g, 11.45 mmol) in THF (60 mL) was added over 3 min a suspension of benzamidine hydrochloride (2.07 g, 13.2 mmol) and K_2CO_3 (3.48 g, 25.2 mmol)

in THF (20 mL) at r.t. The mixture was stirred for 2 d and the solvent was removed in vacuo. The residue then was treated with dil aq 5% HCl (200 mL). Finally, the crude product was extracted with CH_2Cl_2 (3 × 50 mL), washed with H_2O (2 × 100 mL), and dried over (anhyd $CaCl_2$). The solvent was removed under reduced pressure and the crude product purified by column chromatography (petroleum ether–EtOAc, 10:1) to give **12**; yield: 1.06 g (23%).

Method II (from **11***)*: At r.t., K_2CO_3 (0.35 g, 2.51 mmol) was added to a suspension of **11** (1.00 g, 2.28 mmol) in THF (20 mL); the mixture was stirred for 1 d. Workup and purification as described for Method I gave **12**; yield: 0.39 g (43%); mp 179–181 °C (MeOH–acetone, 3:1).

IR (KBr): 3026, 1597, 1556 (NO_2), 1487, 1402, 1356 (NO_2), 1212, 1088, 1005, 855, 812, 750, 698, 629 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.54–8.63 (m, 2 H), 8.49 (d, *J* = 8.3 Hz, 1 H), 8.20 (d, *J* = 8.3 Hz, 1 H), 7.76–7.87 (m, 1 H), 7.54–7.69 (m, 4 H), 7.07 (s, 1 H, $CHCl_2$).

^{13}C NMR ($CDCl_3$): δ = 165.5 (C2), 158.2, 148.5, 146.2 ($C_{q,Bzt}$), 134.5 ($C_{q,Bzt}$), 133.4 (CH, C_{Ph}), 131.1 ($C_{q,Ph}$), 130.7 (CH, Bzt), 130.3 (CNO_2), 129.5 (2 CH, C_{Ph}), 129.2 (2 CH, C_{Ph}), 126.5 (CH, Bzt), 121.0 (CH, Bzt), 114.0 (CH, Bzt), 64.9 ($CHCl_2$).

MS: *m*/*z* (%) = 400 [M^+] (15), 372 (10), 279 (28), 92 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{11}Cl_2N_6O_2$: 401.03151; found: 401.03148.

4-(4-Chlorophenylamino)-6-cyano-2-methyl-5-nitropyrimidine (13); Typical Procedure

To a soln of **10** (0.50 g, 1.44 mmol) in DMF (10 mL) at 0 °C was added NaN_3 (0.28 g, 4.31 mmol). The resulting mixture was stirred at 0 °C for 1 h and at r.t. for 30 min. Then ice cold H_2O (70 mL) was added and the soln was adjusted to pH 7 with 10% HCl soln. The resulting precipitate was filtered with suction, washed with H_2O (2 × 20 mL), dried in vacuo, and recrystallized (hexane–EtOAc, 1:1) to afford **13**; yield: 0.35 g (85%); mp 160–162 °C.

IR (KBr): 3319, 2127 (CN), 1609, 1576 (NO_2), 1520, 1494, 1408, 1273, 1215 (NO_2), 1090, 998, 857, 839, 788, 686, 510, 439 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 10.11 (br s, 1 H, NH), 7.53 (d, *J* = 8.8 Hz, 2 H, CHCCl), 7.41 (d, *J* = 8.8 Hz, 2 H, C*H*CNH), 2.65 (s, 3 H, Me).

^{13}C NMR ($CDCl_3$): δ = 172.2 (C2), 153.1 (C4), 138.6 (C6), 134.0 ($HNC_{q,Ph}$), 132.1 ($ClC_{q,Ph}$), 129.3 (2 C, *C*HCCl), 126.5 (CNO_2), 124.6 (2 C, *C*HCNH), 113.8 (CN), 26.3 (Me).

MS: *m*/*z* (%) = 289 [M^+] (100), 272 [M^+ – OH] (9), 254 [M^+ – Cl] (8), 243 [M^+ – NO_2] (12).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9ClN_5O_2$: 290.04393; found: 290.04391.

4-(4-Chlorophenylamino)-2-methyl-5-nitro-6-(1*H*-tetrazol-5-yl)pyrimidine (14)

Following the typical procedure for **13** using **13** at r.t. for 10 h; yield: 74%; mp 155–157 °C (MeOH–acetone, 1:1).

Following the typical procedure for **13** using **10** and NaN_3 (5 equiv) at r.t. for 10 h; yield: 65%.

IR (KBr): 3365, 2186, 2126, 1609, 1567 (NO_2), 1491, 1343, 1211 (NO_2), 1092, 1012, 831, 504 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 9.50 (br s, 1 H, N*H*-C_6H_4-Cl), 7.66 (d, *J* = 8.8 Hz, 2 H, CHCCl), 7.41 (d, *J* = 8.8 Hz, 2 H, C*H*CNH), 2.50 (s, 3 H, Me).

^{13}C NMR (DMSO-d_6): δ = 167.4 (C2), 156.2, 151.7, 148.5, 137.2 ($HNC_{q,Ph}$), 134.4 (CNO_2), 128.5 (2 C, *C*HCCl), 128.4 ($ClC_{q,Ph}$), 125.0 (2 C, *C*HCNH), 26.0 (Me).

MS: *m*/*z* (%) = 332 [M^+] (6), 289 (12), 286 [M^+ – NO_2] (4), 263 [M^+ – CHN_4] (10), 75 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}ClN_8O_2$: 333.06098; found: 333.06094.

6-(Dichloromethyl)-4-morpholino-5-nitro-2-(3-nitrophenyl)pyrimidine (15)

The nitration of pyrimidine **6** was accomplished by adding HNO_3 (5 mL) to **6** (0.20 g, 0.54 mmol) at 0 °C over 5 min. The mixture was stirred for 20 min at this temperature and an additional 10 min at 10 °C. Ice cold H_2O was added (50 mL) and the precipitate that formed was washed successively with H_2O (3 × 20 mL) and petroleum ether (2 × 10 mL). The crude product was dried and recrystallized (MeOH) to give dinitro compound **15**; yield: 0.16 g (73%); mp 162–163 °C.

IR (KBr): 2914, 2863, 1593, 1573, 1530 (NO_2), 1347 (NO_2), 1226, 1116, 1001, 951, 873, 837, 772, 737, 708, 659, 542 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 9.19 (dd, *J* = 2.1, 1.6 Hz, 1 H), 8.82 (ddd, *J* = 7.9, 1.6, 1.2 Hz, 1 H), 8.39 (ddd, *J* = 8.2, 2.1, 1.2 Hz, 1 H), 7.70 (dd, *J* = 8.2, 7.9 Hz, 1 H), 7.08 (s, 1 H, $CHCl_2$), 3.80–3.87 (m, 4 H, OCH_2), 3.68–3.75 (m, 4 H, NCH_2).

^{13}C NMR ($CDCl_3$): δ = 161.3 (C2), 157.6, 155.1, 148.6 ($C_{q,Ph}NO_2$), 137.4 ($C_{q,Ph}$), 134.9 (CH), 129.7 (CH), 126.6 (CNO_2), 126.4 (CH), 123.8 (CH), 66.2 (2 C, OCH_2), 65.5 ($CHCl_2$), 47.0 (2 C, NCH_2).

MS: *m*/*z* (%) = 413 [M^+] (11), 396 [M^+ – OH] (14), 378 [M^+ – Cl] (10), 322 [M^+ – NO_2] (8), 234 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}Cl_2N_5O_5$: 414.03665; found: 414.03678.

5-Amino-4-methyl-6-(morpholin-4-yl)-2-phenylpyrimidine (16)

To a soln of **6** (1.00 g, 2.70 mmol) in acetone (50 mL) were added $SnCl_2 \cdot 2\,H_2O$ (3.66 g, 16.20 mmol) and concd HCl (10 mL). The mixture was stirred at reflux for 6 h. The acetone was removed and then ice cold H_2O (200 mL) was added and the mixture was adjusted to pH 8 with 30% aq NaOH soln. The resulting precipitate was filtered off with suction, washed with H_2O (3 × 50 mL) and petroleum ether–Et_2O (5:1, 2 × 20 mL), and the crude product was recrystallized (hexane–EtOAc, 1:1) to give **16**; yield: 0.55 g (75%); mp 128–129 °C.

IR (KBr): 3426, 3327 (NH_2), 2957, 2859, 1618, 1583, 1558, 1430, 1287, 1243, 1116, 974, 864, 773, 708, 670, 551, 528 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.29–8.37 (m, 2 H, Ph), 7.35–7.47 (m, 3 H, Ph), 3.85–3.92 (m, 4 H, OCH_2), 3.52 (br s, 2 H, NH_2), 3.34–3.40 (m, 4 H, NCH_2), 2.45 (s, 3 H, Me).

^{13}C NMR ($CDCl_3$): δ = 154.9, 154.1, 149.5, 138.4 ($C_{q,Ph}$), 128.9 (CH, Ph), 128.2 (2 C, C_{Ph}), 127.7 (CNH_2), 127.1 (2 C, C_{Ph}), 66.9 (2 C, OCH_2), 48.1 (2 C, NCH_2), 19.8 (CH_3).

MS: *m*/*z* (%) = 270 [M^+] (100), 225 (48), 213 (82).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}N_4O$: 271.15534; found: 271.15533.

5-(Diacetylamino)-4-methyl-6-(morpholin-4-yl)-2-phenylpyrimidine (17)

To Ac_2O (50 mL) was added **16** (0.55 g, 2.03 mmol). The resulting mixture then was stirred at 105–110 °C for 3 h. The mixture was cooled to r.t. and ice cold H_2O (200 mL) was added. The resulting precipitate was filtered off with suction and treated with H_2O (3 × 50 mL) and petroleum ether (2 × 20 mL) and dried in vacuo to give **17**; yield: 0.55 g (76%); mp 149–150 °C (MeOH–$CHCl_3$, 2:1).

IR (KBr): 2964, 2865, 1716 (C=O), 1550, 1434, 1367, 1239, 1207, 1116, 1090, 983, 855, 776, 716, 586, 539 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.36–8.44 (m, 2 H, Ph), 7.43–7.49 (m, 3 H, Ph), 3.74–3.80 (m, 4 H, OCH_2), 3.52–3.58 (m, 4 H, NCH_2), 2.32 (s, 6 H, 2 Ac), 2.31 (s, 3 H, Me).

^{13}C NMR ($CDCl_3$): δ = 173.0 (C=O), 165.5, 162.4, 160.8, 137.2 ($C_{q,Ph}$), 130.7 (CH, Ph), 128.4 (2 C, C_{Ph}), 128.3 (2 C, C_{Ph}), 118.3 (C5), 66.7 (2 C, OCH_2), 47.7 (2 C, NCH_2), 25.8 (2 C, CH_3), 20.6 (CH_3).

MS: *m*/*z* (%) = 354 [M^+] (92), 311 [M^+ – Ac] (68), 268 [M^+ – morpholine] (73), 254 [M^+ – NAc_2] (39), 87 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{23}N_4O_3$: 355.17647; found: 355.17667.

_N_-[4-Methyl-6-(morpholin-4-yl)-2-phenylpyrimidin-5-yl]acetimidic Acid (18)

To a suspension of **17** (0.20 g, 0.56 mmol) in MeOH (10 mL) was added 64% hydrazine hydrate (0.084 g, 1.68 mmol) at 20 °C. The resulting mixture was stirred at 40–45 °C for 6 h and then cooled to r.t. Subsequently, the solvent was removed under reduced pressure. The mixture then was treated with ice cold H_2O (50 mL) to obtain a precipitate that was filtered off with suction and washed with H_2O (2 × 50 mL) then dried in vacuo to give **18**; yield: 0.16 g (93%); mixture of *E*- and *Z*-isomers, ratio 3:1 (^{1}H NMR); mp 160–161 °C ($MeOH–CHCl_3$, 1:1).

IR (KBr): 3226, 2847, 1651, 1560, 1438, 1371, 1289, 1224, 1118, 1021, 986, 835, 760, 701, 588, 549 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.32–8.42 (m, 2.72 H, Ph), 7.40–7.51 (m, 4.08 H, Ph), 6.98 (br s, 0.36 H, OH), 6.70 (br s, 1 H, OH), 3.75–3.83 (m, 5.44 H, OCH_2), 3.62–3.73 (m, 1.36 H, NCH_2). 3.50–3.59 (m, 4.08 H, NCH_2). 2.45 (s, 1.08 H, Me), 2.37 (s, 3 H, Me), 2.15 (s, 3 H, Me), 1.86 (s, 1.08 H, Me).

^{13}C NMR ($CDCl_3$): δ (major isomer) = 168.8, 165.3, 161.4, 161.0, 137.7 ($C_{q,Ph}$), 130.3 (1CH, Ph), 128.3 (2 CH, Ph), 128.1 (2 CH, Ph), 115.6 (C5), 66.7 (OCH_2), 47.9 (NCH_2), 23.2 (CH_3), 21.2 (CH_3); δ (minor isomer) = 172.9, 165.8, 161.6, 160.9, 137.3 ($C_{q,Ph}$), 130.6 (1CH, Ph), 128.4 (2 C, C_{Ph}), 128.2 (2 C, C_{Ph}), 115.4 (C5), 66.8 (2 C, OCH_2), 47.5 (2 C, NCH_2), 21.1 (CH_3), 20.2 (CH_3).

MS: *m*/*z* (%) = 312 [M^+] (14), 297 [M^+ – Me] (6), 254 [M^+ – ($CH_3C(OH)=N$)] (12), 226 [M^+ – morpholine] (8), 78 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{21}N_4O_2$: 313.16590; found: 313.16587.

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