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Regioselective synthesis of novel substituted indazole-5,6-diamine derivatives

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ABSTRACT

The synthesis of a series of novel indazole-5,6-diamine derivatives is described. This indazole ring system was incorporated in an octahydropyrrolo[3,4-*b*]phenazine scaffold and was diversely and regioselectively substituted on the nitrogen atoms at the 5- and 10-positions. Thus, the nitrogen atom at the 5-position was found to be more reactive toward electrophiles than the one at the 10-position. This difference of reactivity could be attributed to the electronic effect of the pyrazole moiety. Moreover, an unexpected tetrahydropyran protecting group migration was observed from the N-1 atom to the C-11 position of the octahydropyrrolo[3,4-*b*]phenazine scaffold.

1. Introduction

In the last decade, the extensive studies on drug-like properties of small organic molecules allowed the identification of privileged structures. The indazole ring system is among these bioactive scaffolds that have retained the attention of organic and medicinal chemists. Thus, numerous reports in the literature describe the synthesis and biological properties of indazole derivatives.[1–3] However, the discovery of new compounds containing the indazole scaffold remains a challenging area of research. In this context, we recently started to explore the synthesis of new indazole derivatives as potential kinase inhibitors and anti-tumor agents. Accordingly, we reported a preliminary work in the field on the synthesis and characterization of new pyrazolo[3,4-*g*]quinoxaline derivatives. These heterocyclic systems were prepared by reaction between 1*H*-indazole-5,6-diamine and α-chloroketones or 1,2-diketones.[4] We showed that some of the prepared compounds displayed interesting in vitro antiproliferative potency in the micromolar range toward PA1 cell line, as well as a moderate protein kinase inhibitory activity toward the third isoform of the Pim protein kinase family (Pim-3, provirus integration site of Moloney murine leukemia virus-3). The results obtained in this preliminary work have shown that compound **1** (Fig. 1) was the most potent of the series toward Pim-3. Thus, we decided to extend our study to the synthesis of novel derivatives of tetrahydro-1*H*-pyrazolo[3,4-*b*]phenazine **1**. More particularly, we considered that the pyrazine ring of compound **1** could be reduced, offering the opportunity to introduce various substituents on the two nitrogens at the 5- and 10-positions of the pyrazolophenazine scaffold. Herein we describe the synthesis of this unprecedented series of indazole derivatives represented by the general structure **A** (Fig. 1).

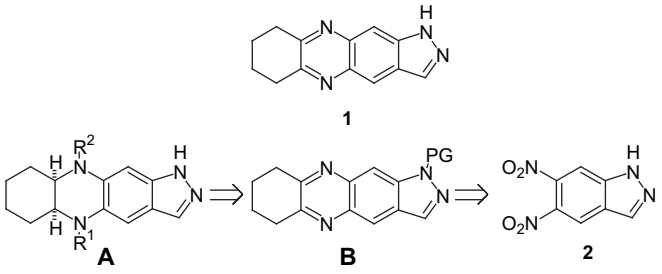

Fig. 1. Pyrazolo[3,4-*b*]phenazine derivative **1**. Retrosynthetic approach to the preparation of compound **A** from indazole **2**.

2. Results and discussion

A general access for the preparation of indazole derivative of general structure **A** (Fig. 1) could be the hydrogenation and subsequent nitrogen substitution of tetrahydro-1*H*-pyrazolo[3,4-*b*]phenazine **B**. This approach implies the introduction of a protecting group on the 1,2-diazole heterocycle, in order to prevent any regioselectivity complication due to competing pyrazole moiety during the substitution reactions on the nitrogen atoms at the 5- and 10-positions. In our previous study on the synthesis of pyrazolo[3,4-*g*]quinoxaline derivatives, compound **1** was prepared from 5,6-dinitroindazole **2** after reduction of the two nitro groups and condensation with 2-chlorocyclohexanone.[4] Therefore, we

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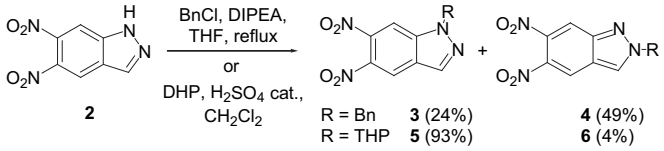
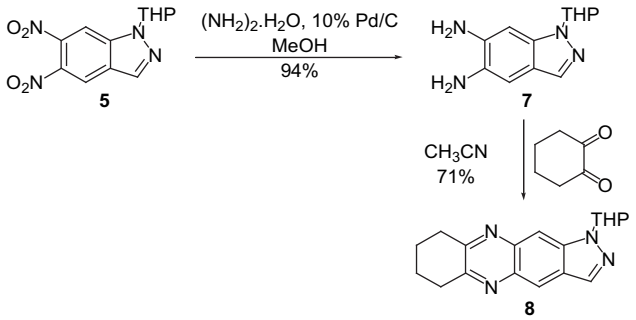
firstly examined the protection of indazole **2** prior to nitro group reduction. The protection reaction of the indazole ring system can proceed at N-1 or N-2 positions as it contains two non-equivalent nitrogen atoms. It has been shown that the regioselectivity of the reaction is highly dependent of the conditions used.[5–7] Thus, it was reported that indazoles were unselectively protected under strongly basic conditions. However, regioselective protection could be accomplished taking advantage of the higher nucleophilicity of the N-2 lone pair, by using a non-deprotonating base or by performing the reaction under acidic conditions. Nevertheless, as the reactivity of 5,6-dinitroindazole for protection reactions has never been examined, we decided to investigate the introduction of different protecting groups on this scaffold. When compound **2** was treated with acetic anhydride in the presence of sodium acetate at 100 °C, GC/MS analysis of the reaction mixture showed a single peak (m/z=250) corresponding to a monoacetylated compound. Nevertheless, this product was found to be too unstable for any chromatographic purification or further transformation. Similarly, the use of Boc_2O/K_2CO_3 in refluxing THF or BnOCOCl/NEt_3 in refluxing CH_2Cl_2 led to unstable regioisomeric mixtures of monosubstituted indazole derivatives (m/z=308 and 342, respectively). Conversely, the use of allyl or benzyl protecting groups yielded stable products but the regioisomeric ratio was function of the reaction conditions used, as it has already been observed for other indazole series. Thus, treatment of indazole **2** with allylbromide/K_2CO_3 in refluxing THF or benzylbromide/NaH in CH_2Cl_2 and subsequent GC/MS analysis showed an approximately 1:1 mixture of N-1 and N-2 protected regioisomers (m/z=248 and 298, for allyl and benzyl protecting groups, respectively). On the other hand, one regioisomer was favored using benzyl chloride/DIPEA in refluxing THF (GC/MS ratio: 3:1) (Scheme 1). Purification of the reaction mixture and subsequent identification of the products by NMR showed that the major isomer was the N-2 protected indazole **4**, obtained in 49% yield. Minor product **3** was isolated in 24% yield.



Scheme 1. Protection of indazole **2**.

Attempts to reduce the two nitro groups of **3** and **4** were performed using various reaction conditions. Unfortunately, we never managed to obtain the corresponding diamino products without removing the benzyl protecting group. Therefore, we looked for a protecting group inert in reduction conditions. Thus, indazole **2** was protected in a very regioselective fashion at the N-1 position to give compound **5** in 93% yield, using dihydropyran in CH_2Cl_2 in the presence of a catalytic amount of H_2SO_4 (Scheme 1). As it was found previously by Slade et al.[5], N-2 THP protected indazole **6** was quickly formed during the course of the reaction, and this compound was readily converted into the thermodynamic N-1 protected product **5**. Nevertheless, complete conversion was not observed and residual N-2 protected derivative **6** was isolated in 4% yield after chromatography. Using the mild acidic conditions proposed by Slade et al. (PPTS/DCM, room temperature), the N-2 protected isomer **6** was isolated as the major product in 91% yield after chromatography. In these conditions, compound **5** was also isolated in 3% yield.

As the two N-1 and N-2 THP protected regioisomers could be isolated in good yields, we decided to carry on the synthesis starting from the thermodynamically more stable indazole **5**, and considered the reduction of the two nitro groups. When the reaction was achieved in refluxing methanol in the presence of ammonium formate and 10% Pd/C, diamine **7** was isolated in 61% yield. A similar yield was obtained when the reduction was performed in the presence of $Na_2S_2O_4$/NaOH in EtOH at 50 °C. Ultimately, nitro groups were efficiently reduced in the presence of hydrazine hydrate and 10% Pd/C in refluxing methanol leading to protected indazole-5,6-diamine **7** in 94% yield (Scheme 2).

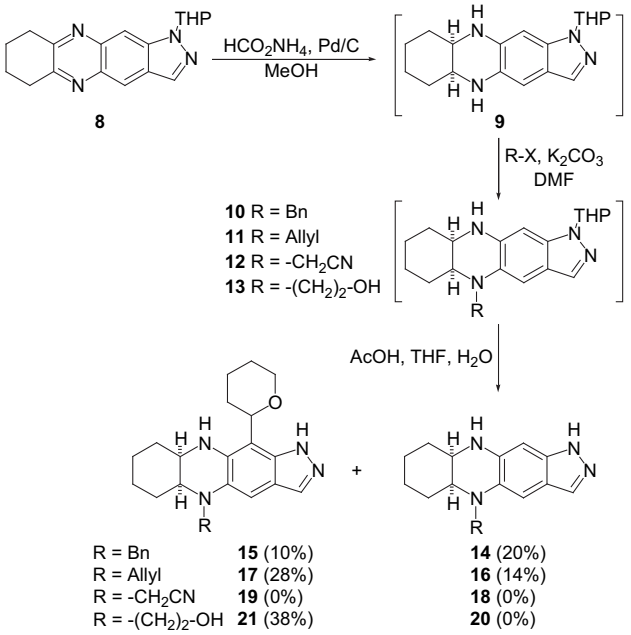


Scheme 2. Synthesis of tetrahydropyrazolo[3,4-*b*]phenazine **8**.

Indazole **7** was further used to complete the preparation of compound **8**. In our preceding study,[4] the synthesis of the non-protected tetrahydropyrazolo[3,4-*b*]phenazine **1** (Fig. 1), was performed by reaction between indazole-5,6-diamine and 2-chlorocyclohexanone in the presence of *p*-toluenesulfonic acid. In the current synthesis, the presence of the THP protecting group precludes the use of any acidic conditions. Moreover, the use of 2-chlorocyclohexanone under basic conditions in the presence of NEt_3 in acetonitrile led to product **8** in low yield. Consequently, the use of the cyclohexane-1,2-dione was preferred and the condensation reaction was accomplished in refluxing acetonitrile to give compound **8** in 71% yield (Scheme 2).

Hydrogenation of the pyrazine ring of compound **8** was a major issue for this approach because a non-stereoselective reaction would afford up to eight stereoisomers due to the presence of the THP group and two newly formed carbon stereocenters. The conversion of compounds containing a 2,3-disubstituted quinoxaline ring system to the corresponding tetrahydroquinoxaline derivatives has been described by a number of method including catalytic hydrogenation,[8–11] hydride reduction,[8,12–15] $BH_3\cdot THF$,[14] $TiCl_3$,[16] Na/EtOH,[17,18] or by the use of indium metal.[19] Whereas methods, such as hydrogenation preferentially give the cis product, no convenient reduction yielding the trans isomer has been described so far. As we needed a stereoselective method, we decided to apply simple catalytic hydrogenation. Thus, compound **8** was reduced using ammonium formate in refluxing methanol in the presence of 10% Pd/C (Scheme 3). In these reaction conditions, product **9** was obtained in high yield without need of chromatography. Nevertheless, ^1H NMR spectrum revealed a complex stereoisomeric mixture. Alternative methods using $BH_3\cdot THF$ or Wilkinson catalyst/H_2 led to similar ^1H NMR spectra but they yielded lower quantities of reduced product **9**.

The following alkylation and subsequent deprotection steps were carried out starting from compound **9**. Monoalkylation proceeded smoothly at room temperature with benzylbromide, allylbromide or bromoacetonitrile in DMF in the presence of K_2CO_3, leading to compounds **10**–**12**. However, in the case of bromoethanol, the reaction mixture needed to be heated at 120 °C to complete the reaction and to obtain the intermediate **13** after chromatography. In all cases, the formation of the disubstituted product was not observed. Deprotection of monosubstituted compounds **10** and **11** in the presence of acetic acid in THF/H_2O yielded compounds **14**–**17**. The expected deprotected products **14** and **16**, respectively substituted by benzyl and allyl groups, were isolated in 20% and 14% yields after three steps from starting material **8**. The

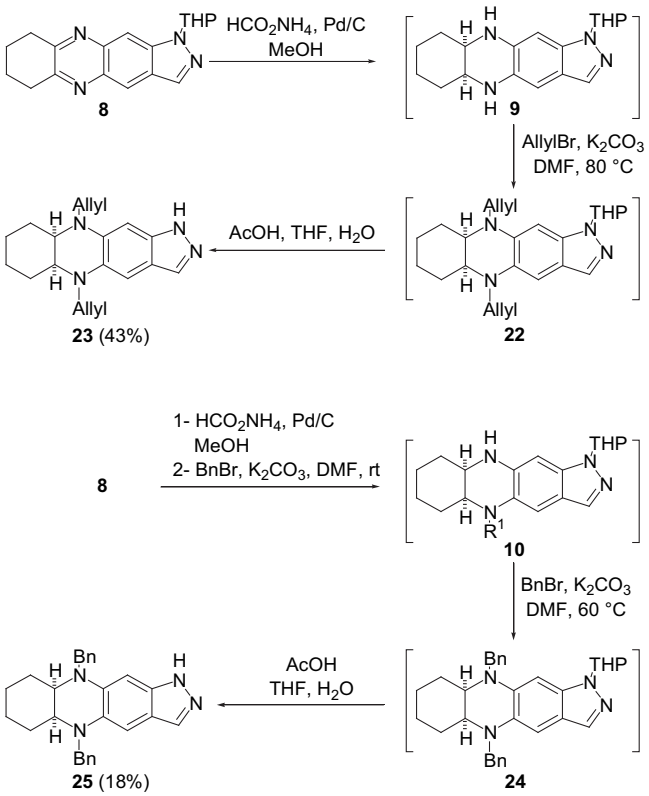


Scheme 3. Synthesis of monosubstituted derivatives **14**–**17** and **21**.

identity of these two products, as well as the cis stereochemistry of the fused six-membered ring were confirmed by analysis of the 1D and 2D NMR spectra (^{1}H, ^{13}C, ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC, ^{1}H–^{1}H NOESY). Monoalkylation was performed in a highly regioselective manner as only the N-5 alkylated compound was isolated. The regioselectivity of the alkylation step can be assessed on the basis of the electronic effect of the pyrazole moiety. It has been shown that the nucleophilicity of the amino groups of substituted benzene-1,2-diamines can be differentiated in function of the electronic effects of the benzene ring substituents.[20,21] Thus, an amino group is activated by the presence of an electron donating group at *para* position and/or of an electron withdrawing group at *meta* position. Accordingly, the pyrazole ring system directed the substitution reaction at the N-5 position of intermediates **9**.

Unexpectedly, two side products **15** and **17**, in which the THP group was found positioned at the C-11 carbon atom, were also isolated in 10% and 28% yields from compound **8**, respectively (~1:1 mixture of the two racemic *cis*-diastereoisomers). Regarding the 2-hydroxyethyl substituted intermediate **13**, the product of THP migration **21** was the only compound isolated after deprotection and chromatography (38% yield, ~1.4:1 mixture of the two racemic *cis*-diastereoisomers). On the other hand, due to the degradation of the reaction mixture during the deprotection step, neither the expected deprotected product **18** nor the THP side product at the C-11 position **19** were obtained from the cyanomethyl derivative **12**. The introduction of a THP group on a carbon atom as found in compounds **15**, **17**, and **21** was already reported by several authors during the THP protection/deprotection of phenolic derivatives. This reaction leads to the substitution *ortho* to the phenolic hydroxyl by a THP group.[22–26] To the best of our knowledge, the present report is the first one to describe this type of THP C-alkylation for compounds other than phenolic derivatives. In our case, the alkylation orientation at the C-11 position is probably due to the presence of the *ortho* non-substituted amino group at the 10-position of intermediates **10**, **11**, and **13**.

We carried on the synthesis of dialkylated derivatives at the N-5 and N-10 nitrogen atoms. A similar reaction procedure as for the preparation of monosubstituted compounds was performed from compound **8** (Scheme 4). Diallyl derivative was obtained by heating a solution of the hydrogenated intermediate **9** in DMF in the presence of K_2CO_3 and an excess of allylbromide. After deprotection, diallyl derivative **23** was isolated in 43% yield from compound **8**. Using similar alkylation conditions in the presence of benzylbromide, dibenzylated compound **25** could not be isolated in a pure form after deprotection and chromatography. Therefore, dibenzylation was performed stepwise: monobenzylated intermediate **10** was isolated prior to the second alkylation step, leading after benzylation and deprotection to the dibenzylated derivative **25** in 18% yield from **8**.

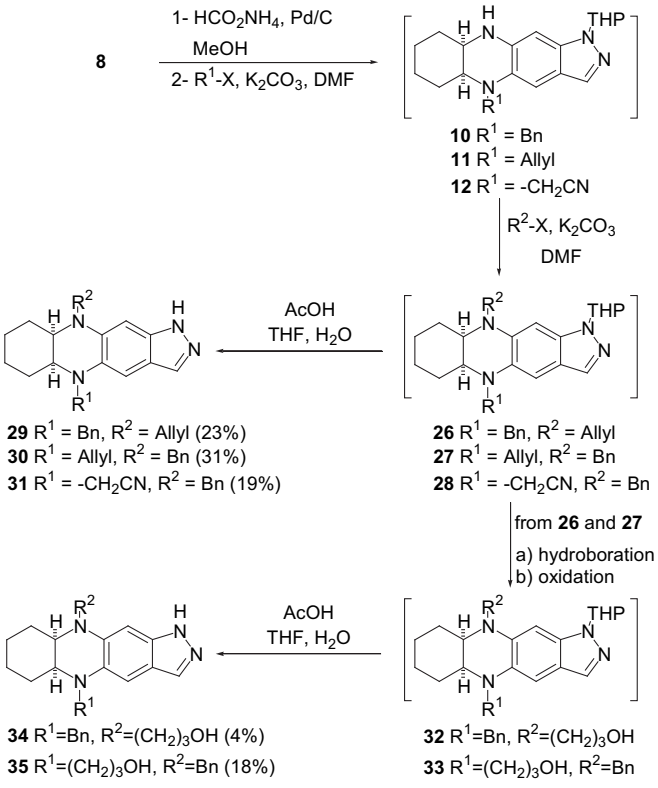


Scheme 4. Synthesis of dialkylated compounds **23** and **25**.

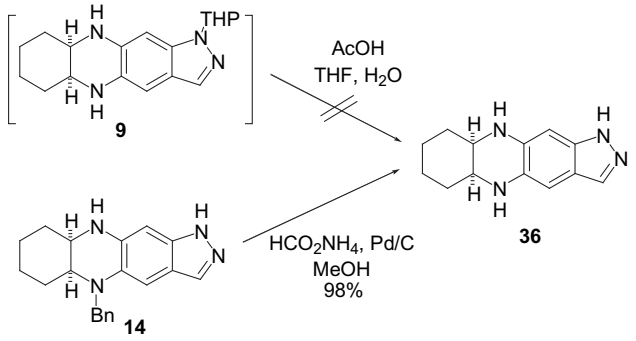
Contrarily to what was observed for the deprotection of monosubstituted derivatives **10**, **11**, and **13**, the THP migration products were not observed in the conditions used when the deprotection was performed from disubstituted intermediates (e.g., **22**, **24**, and disubstituted intermediates described below).

Taking advantage of the difference of nucleophilicity of the two N-5 and N-10 nitrogen atoms, distinct substituents were also introduced. The two alkylations were carried out consecutively after purification by chromatography of the monosubstituted intermediates **10**–**12** (Scheme 5). After a four-step sequence, compounds **29**–**31** were isolated in 23%, 31%, and 19% yields, respectively. We also proceeded in further functionalization through an additional hydroboration/oxidation sequence performed on allyl precursors **22**, **26**, and **27**. When hydroboration was performed on the diallyl intermediate **22** obtained during the preparation of compound **23**, no reaction was observed with 9-BBN. On the other hand, the use borane/THF complex led to a complex mixture after oxidation and deprotection steps. Conversely, hydroboration/oxidation of monoallyl intermediates **26** and **27** led to alcohol derivatives **34** and **35** in 4% and 18% yields, respectively, after a six-step sequence from starting material **8** (Scheme 5).

Finally, we prepared the non-alkylated analogue **36** (Scheme 6). Firstly, we attempted to prepare compound **36** by deprotection of compound **9** bearing a THP group at the N-1 position. Unfortunately, these conditions led to a mixture of degradation products. Therefore, compound **36** was readily prepared in 98% yield by hydrogenolysis of monobenzylated analogue **14**.



Scheme 5. Sequential regioselective alkylation. Synthesis of compounds **29**–**31**, **34**, and **35**. Hydroboration/oxidation: from **26**, (a) 9-BBN, THF (b) $NaBO_3 \cdot 4H_2O$; from **27**, (a) $BH_3 \cdot THF$ (b) $NaBO_3 \cdot 4H_2O$.



Scheme 6. Synthesis of compound **36**.

3. Conclusion

We have developed a straightforward protocol for the preparation of an unprecedented series of indazole-5,6-diamine derivatives of high interest for pharmaceutical research. This ring system was incorporated into an octahydropyrazolo[3,4-*b*]phenazine scaffold and we showed that nitrogen atoms at the 5- and 10-positions could be regioselectively substituted. We also described the migration of the THP protecting group, initially located at the N-1 indazole nitrogen atom, on a carbon atom during the deprotection step of monosubstituted derivatives. The synthetic pathway leading to the octahydropyrazolo[3,4-*b*]phenazine scaffold provides a regio-controlled access to N-5 and/or N-10 diversely substituted analogues with potential biological interest.

4. Experimental section

4.1. General

Starting materials were obtained from commercial suppliers and used without further purification. Solvents were distilled prior to use. IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer ($\bar{\nu}$ in cm^{-1}). NMR spectra were performed on a Bruker AVANCE 400 (^1H: 400 MHz, ^{13}C: 100 MHz), or a Bruker AVANCE 500 (^1H: 500 MHz, ^{13}C: 126 MHz); chemical shifts δ are indicated in parts per million and the following abbreviations are used: singlet (s), doublet (d), triplet (t), doublet of doublet (dd), multiplet (m), broad signal (br s). High resolution mass spectra (ESI^+) were determined on a high-resolution Micro Q-Tof apparatus (CRMP, Université Blaise Pascal, Clermont-Ferrand, France). GC/MS analyses were performed on an Agilent 6890N/5973N GC/MSD system using an Agilent HP-5ms (19091S-433) capillary column (He flow: 0.9 mL/min; injector temperature: 250 °C; temperature gradient: 1 min at 50 °C, 50 °C/min to 300 °C, and 5 min at 300 °C). Chromatographic purifications were performed by flash silica gel Geduran SI 60 (Merck) 0.040–0.063 mm column chromatography. Reactions were monitored by TLC using fluorescent silica gel plates (60 F_{254} from Merck). Melting points were measured on a Reichert microscope or on a Büchi B-540 apparatus and are uncorrected.

4.2. Procedure for preparation of compounds 3–8

*4.2.1. 1-Benzyl-5,6-dinitro-1H-indazole (**3**) and 2-benzyl-5,6-dinitro-2H-indazole (**4**).* To a solution of 5,6-dinitroindazole **2** (500 mg, 2.40 mmol) in THF (5 mL) was added *N*,*N*-diisopropylethylamine (0.5 mL, 2.9 mmol) and benzyl chloride (0.36 mL, 3.1 mmol). The mixture was refluxed for 48 h. After evaporation under reduced pressure, the residue was purified by flash chromatography (cyclohexane to EtOAc) to give **3** (172 mg, 0.58 mmol, 24%) and **4** (350 mg, 1.17 mmol, 49%) as yellow solids: compound **3**, mp=158–159 °C; IR (ATR): 1538, 1373, 1343 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 5.82 (2H, s), 7.30–7.43 (5H, m), 8.60 (1H, s), 8.90 (1H, s), 9.08 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): 52.5 (CH_2), 108.8, 121.8, 127.7 (2C), 127.9, 128.7 (2C), 137.2 (CH_{arom}), 122.9, 136.0, 136.3, 138.2, 141.8 (C_{arom}); HRMS (ESI^+) calcd for $C_{14}H_{10}N_4NaO_4$ $(M+Na)^+$ 321.0600, found 321.0610.

Compound **4**, mp=120–122 °C; IR (ATR): 1541, 1524, 1502, 1368, 1362 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 5.84 (2H, s), 7.25–7.39 (5H, m), 8.58 (1H, s), 8.87 (1H, s), 9.91 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): 57.3 (CH_2), 116.7, 123.2, 128.26 (2C), 129.29, 128.7 (2C), 130.5 (CH_{arom}), 120.1, 135.6, 136.4, 141.5, 145.7 (C_{arom}); HRMS (ESI^+) calcd for $C_{14}H_{10}N_4NaO_4$ $(M+Na)^+$ 321.0600, found 321.0609.

*4.2.2. 5,6-Dinitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (**5**) and 5,6-dinitro-2-(tetrahydro-2H-pyran-2-yl)-2H-indazole (**6**).* 3,4-Dihydro-2*H*-pyran (2 mL, 21.9 mmol) was added to a solution of 5,6-dinitroindazole **2** (3.0 g, 14.4 mmol) and H_2SO_4 (0.1 mL) in dichloromethane (35 mL) and the reaction mixture was stirred at room temperature for 5 days. The solution was evaporated and the residue was purified by flash chromatography (cyclohexane to EtOAc) to give **5** (3.9 g, 13.3 mmol, 93%) and **6** (168 mg, 0.57 mmol, 4%) as yellow solids: compound **5**, mp 97–98 °C; IR (ATR): 1611, 1538, 1456, 1373, 1351, 1342 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.56–1.64 (2H, m), 1.67–1.80 (1H, m), 1.98–2.07 (2H, m), 2.30–2.42 (1H, m), 3.77–3.85 (1H, m), 3.87–3.93 (1H, m), 6.08 (1H, d, *J*=9 Hz), 8.58 (1H, s), 8.78 (1H, s), 8.87 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): 21.9, 24.5, 28.8, 66.7 (CH_2), 84.5 (CH), 109.2, 121.7, 136.9 (CH_{arom}), 123.4, 136.3, 138.2, 141.8 (C_{arom}); HRMS (ESI^+) calcd for $C_{12}H_{12}N_4NaO_5$ $(M+Na)^+$ 315.0705, found 315.0708.

Compound **6**, mp 130–131 °C; IR (ATR): 1619, 1542, 1520, 1496, 1365, 1352, 1337 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.57–1.66 (2H, m), 1.67–1.81 (1H, m), 1.89–2.00 (1H, m), 2.08–2.19 (2H, m), 3.72–3.82 (1H, m), 3.97–4.05 (1H, m), 5.90–5.98 (1H, m), 8.64 (1H, s), 8.86 (1H, s), 9.04 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): 21.2, 24.4, 30.3, 67.1 (CH_2), 88.6 (CH), 117.3, 123.8, 129.1 (CH_{arom}), 119.6, 136.7, 141.8, 145.1 (C_{arom}); HRMS (ESI^+) calcd for $C_{12}H_{12}N_4NaO_5$ $(M+Na)^+$ 315.0705, found 315.0718.

*4.2.3. 1-(Tetrahydro-2H-pyran-2-yl)-1H-indazole-5,6-diamine (**7**).* Hydrazine monohydrate (2.6 mL, 2.7 g, 54 mmol) was slowly added to a mixture of **5** (1.6 g, 5.5 mmol) and 10% Pd/C (850 mg, 0.80 mmol) in methanol (25 mL) at 0 °C. The mixture was refluxed for 1 h and the catalyst was removed by filtration through a Celite pad, which was subsequently washed with methanol (30 mL). The filtrate was evaporated under reduced pressure to give **7** (1.2 g, 5.2 mmol, 94%) as a gray solid. Compound **7** was used directly for the next step without any further purification: mp 55–56 °C; IR (ATR): 3500–3125, 1640, 1608, 1506, 1489 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.49–1.60 (2H, m), 1.64–1.78 (1H, m), 1.83–1.93 (1H, m), 1.96–2.07 (1H, m), 2.29–2.42 (1H, m), 3.58–3.68 (1H, m), 3.82–3.91 (1H, m), 4.37 (2H, br s), 4.91 (2H, br s), 5.47 (1H, d, J=9 Hz), 6.66 (1H, s), 6.72 (1H, s), 7.55 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): 22.3, 24.9, 28.8, 66.3 (CH_2), 84.2 (CH), 92.0, 101.9, 131.3 (CH_{arom}), 116.8, 132.5, 135.5, 138.5 (C_{arom}); HRMS (ESI^+) calcd for $C_{12}H_{17}N_4O$ $(M+H)^+$ 233.1402, found 233.1409.

*4.2.4. 6,7,8,9-Tetrahydro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo [4,3-b]phenazine (**8**).* A solution of diamine **7** (1.6 g, 6.9 mmol) and 1,2-cyclohexanedione (1.15 g, 10.3 mmol) in acetonitrile (10 mL) was refluxed for 2 h. After evaporation, the residue was purified by flash chromatography (cyclohexane to EtOAc) to give **8** (1.5 g, 4.9 mmol, 71%) as a yellow solid: mp 147–148 °C; IR (ATR): 1629, 1495, 1437, 1426, 1411, 1396, 1319 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.57–1.65 (2H, m), 1.73–1.86 (1H, m), 1.94–2.01 (4H, m), 2.01–2.11 (2H, m), 2.42–2.54 (1H, m), 3.05–3.14 (4H, m), 3.78–3.86 (1H, m), 3.88–3.95 (1H, m), 6.01 (1H, d, J=9.5 Hz), 8.24 (1H, s), 8.44 (1H, s), 8.47 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): 22.17, 22.21, 22.23, 24.8, 28.8, 32.6, 32.9, 66.5 (CH_2), 84.2 (CH), 105.6, 119.3, 134.5 (CH_{arom}), 126.4, 135.3, 138.7, 138.8, 152.9, 155.1 (C_{arom}); HRMS (ESI^+) calcd for $C_{18}H_{21}N_4O$ $(M+H)^+$ 309.1715, found 309.1726.

4.3. General procedure for preparation of compounds 14–17, 21, 23, 28–31, 34, and 35

Step A: Ammonium formate (4 g, 63 mmol) was added to a mixture of **8** (1 g, 3.24 mmol) and 10% Pd/C (830 mg, 0.78 mmol) in methanol (50 mL). The mixture was refluxed for 2 h and the catalyst was removed by filtration through a Celite pad, which was subsequently washed with methanol (30 mL). After evaporation of the filtrate, the intermediate **9** (960 mg) was used directly for the next step without any further purification.

Step B: To a solution of the residue from *step A* in DMF was added potassium carbonate and the corresponding alkyl bromide. At the end of the reaction time, the mixture was diluted by addition of EtOAc (20 mL). The organic layer was washed with water (4×30 mL), dried over $MgSO_4$, and evaporated. The resulting dark-brown oil was purified by flash chromatography (cyclohexane to EtOAc).

Step C: To a solution of the monoalkylated diastereoisomer mixture from *step B* in DMF (2 mL) was added potassium carbonate and the corresponding alkyl bromide. The mixture was stirred for 16 h at 60 °C and then diluted by addition of EtOAc (20 mL). The organic layer was washed with water (4×30 mL), dried over $MgSO_4$, and evaporated. The resulting dark-brown oil was purified by flash chromatography (cyclohexane to EtOAc).

Step D: The residue from *step B* or from *step C* was solubilized in a 4:2:1 acetic acid/THF/water mixture (7 mL) and the solution was heated overnight at 60 °C. EtOAc (30 mL) was added and then a saturated aqueous $NaHCO_3$ solution (40 mL) was added. The aqueous layer was extracted with ethyl acetate (30 mL) and the combined organic fractions were dried over $MgSO_4$ and evaporated. The resulting yellow oil was purified by flash chromatography (cyclohexane to EtOAc).

*4.3.1. 5-Benzyl-5,5a,6,7,8,9,9a,10-octahydro-1H-pyrazolo[4,3-b] phenazine (**14**) and 5-benzyl-11-(tetrahydro-2H-pyran-2-yl)-5,5a,6,7,8,9,9a,10-octahydro-1H-pyrazolo[4,3-b]phenazine (**15**). Step A*; *step B*: Reduction product from *step A* (200 mg), K_2CO_3 (0.96 mmol), BnBr (0.64 mmol), DMF (4 mL), 1 h, rt, flash chromatography provided monoalkylated diastereoisomer mixture (125 mg); *step D*: mixture from *step B* (125 mg), flash chromatography provided **14** (42 mg, 0.13 mmol, 20% from **8**) and **15** (27 mg, 0.067 mmol, 10% from **8**) as green solids: compound **14**, mp=67–68 °C; IR (ATR): 1635, 1495, 1451, 1353, 1315, 1261 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.16–1.27 (1H, m), 1.29–1.38 (2H, m), 1.47–1.59 (2H, m), 1.59–1.71 (2H, m), 1.82–1.92 (1H, m), 3.17–3.24 (1H, m), 3.72 (1H, br s), 4.37 (1H, d, J=16.5 Hz), 4.42 (1H, d, J=16.5 Hz), 5.84 (1H, s), 6.28 (1H, s), 6.48 (1H, s), 7.18–7.24 (1H, m), 7.28–7.36 (4H, m), 7.43 (1H, s), 11.97 (1H, br s); ^{13}C NMR (126 MHz, DMSO-d_6): 19.2, 24.3, 24.4, 30.4, 53.5 (CH_2), 48.4, 57.7 (CH), 89.6, 98.4, 126.5, 126.7 (2C), 128.4 (2C), 131.6 (CH_{arom}), 115.5, 129.9, 135.7, 137.2, 139.5 (C_{arom}); HRMS (ESI^+) calcd for $C_{20}H_{23}N_4$ $(M+H)^+$ 319.1923, found 319.1919.

Compound **15**, IR (ATR): 1486, 1457, 1243 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.15–2.02 ($14H^a+14H^b$, m), 3.15–3.25 ($1H^a+1H^b$, m), 3.48–3.57 ($1H^a+1H^b$, m), 3.73–3.82 ($1H^a+1H^b$, m), 4.08–4.14 ($1H^a+1H^b$, m), 4.31–4.45 ($2H^a+2H^b$, m), 4.84–4.94 ($1H^a+1H^b$, m), 5.23, 5.43 ($1H^a+1H^b$, 2br s), 6.27, 6.31 ($1H^a+1H^b$, 2s), 7.19–7.25 ($1H^a+1H^b$, m), 7.28–7.37 ($4H^a+4H^b$, m), 7.47 ($1H^a+1H^b$, s), 11.76, 11.93 ($1H^a+1H^b$, 2br s); ^{13}C NMR (100 MHz, DMSO-d_6): 19.4 (×2), 23.2 (×2), 24.0, 24.1 (×2), 24.3, 25.6, 25.7, 28.9, 29.3, 30.5, 31.2, 54.08, 54.11, 68.4, 68.5 (CH_2), 48.6, 49.0, 56.8, 57.4, 75.4, 75.6 (CH), 98.1, 98.3, 126.7–126.9 (3C×2, peaks at 126.7, 126.8, and 126.9 ppm), 128.5 (2C×2), 131.7, 131.9 (CH_{arom}), 103.6, 104.1, 115.4, 115.5, 130.4, 130.6, 132.7, 133.5, 133.7, 133.9, 139.5 (×2) (C_{arom}); HRMS (ESI^+) calcd for $C_{25}H_{31}N_4O$ $(M+H)^+$ 403.2498, found 403.2489.

*4.3.2. 5-Allyl-5,5a,6,7,8,9,9a,10-octahydro-1H-pyrazolo[4,3-b]phenazine (**16**) and 5-allyl-11-(tetrahydro-2H-pyran-2-yl)-5,5a,6,7,8,9,9a, 10-octahydro-1H-pyrazolo[4,3-b]phenazine (**17**). Step A*; *step B*: Reduction product from *step A* (100 mg), K_2CO_3 (0.42 mmol), AllylBr (0.32 mmol), DMF (2 mL), 16 h, rt, flash chromatography provided monoalkylated diastereoisomer mixture (56 mg) and **8** (14 mg, 0.045 mmol); *step D*: mixture from *step B* (30 mg), flash chromatography provided **16** (7 mg, 0.026 mmol, 14% from **8**) as a black oil and **17** (18 mg, 0.051 mmol, 28% from **8**) as a yellow oil.

Compound **16**, IR (ATR): 1638, 1496, 1456, 1445 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.16–1.37 (3H, m), 1.44–1.69 (4H, m), 1.81–1.89 (1H, m), 3.11–3.17 (1H, m), 3.54–3.59 (1H, m), 3.75 (1H, dd, J=16.5, 5.5 Hz), 3.87 (1H, dd, J=16.5, 5 Hz), 5.14 (1H, dd, J=10.5, 1.5 Hz), 5.26 (1H, dd, J=17, 1.5 Hz), 5.75 (1H, s), 5.83–5.94 (1H, m), 6.45 (1H, s), 6.47 (1H, s), 7.52 (1H, s), 11.97 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6): 19.2, 24.2, 24.4, 30.4, 52.3 (CH_2), 48.3, 56.7 (CH), 89.6, 98.2, 131.6, 135.6 (=CH), 115.7, 115.8, 129.9, 135.7, 137.2 (=CH_2,C_{arom}); HRMS (ESI^+) calcd for $C_{16}H_{21}N_4$ $(M+H)^+$ 269.1766, found 269.1773.

Compound **17**, IR (ATR): 1486, 1261 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.15–1.99 ($14H^a+14H^b$, m), 3.11–3.19 ($1H^a+1H^b$, m), 3.47–3.57 ($1H^a+1H^b$, m), 3.58–3.67 ($1H^a+1H^b$, m), 3.69–3.79 ($1H^a+1H^b$, m), 3.81–3.91 ($1H^a+1H^b$, m), 4.06–4.14 ($1H^a+1H^b$, m), 4.84–4.92 ($1H^a+1H^b$, m), 5.15 ($1H^a+1H^b$, d, J=10 Hz), 5.19, 5.40 ($1H^a+1H^b$, 2s), 5.28 ($1H^a+1H^b$, d, J=17 Hz), 5.83–5.95 ($1H^a+1H^b$, m), 6.43, 6.45 ($1H^a+1H^b$, 2s), 7.56 ($1H^a+1H^b$, s), 11.77, 11.94 ($1H^a+1H^b$, 2br s); ^{13}C NMR (100 MHz, DMSO-d_6): 19.35, 19.39, 23.1 (2×), 23.96, 24.00, 24.1, 24.2, 25.4, 25.6, 28.9, 29.2, 30.4, 31.1, 52.6, 52.7, 68.28, 68.34 (CH_2), 48.4, 48.9, 55.7, 56.2, 75.2, 75.5 (CH), 97.8, 98.0, 131.6, 131.8, 135.6, 135.7 (=CH), 103.5, 104.0, 115.5, 115.6, 115.9, 116.0, 130.3, 130.4, 132.5, 133.3, 133.5, 133.7 (=CH_2, C_{arom}); HRMS (ESI^+) calcd for $C_{21}H_{29}N_4O$ $(M+H)^+$ 353.2341, found 353.2357.

*4.3.3. 2-[11-(Tetrahydro-2H-pyran-2-yl)-6,7,8,9,9a,10-hexahydro-1H-pyrazolo[4,3-b]phenazin-5(5aH)-yl]ethanol (**21**). Step A*; *step B*: Reduction product from *step A* (70 mg), K_2CO_3 (0.90 mmol), 2-bromoethanol (1.12 mmol), DMF (2 mL), 2 h, 120 °C, flash chromatography provided monoalkylated diastereoisomer mixture (44 mg); *step D*: mixture from step B (30 mg), flash chromatography provided **19** (22 mg, 0.062 mmol, 38% from **8**) as a yellow oil: IR (ATR): 3475, 1626, 1488, 1451 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6), H^a major diastereoisomer, H^b minor diastereoisomer: 1.14–1.98 ($14H^a+14H^b$, m), 3.10–3.22 ($2H^a+2H^b$, m), 3.26–3.38 ($1H^a+1H^b$, m), 3.47–3.65 ($4H^a+4H^b$, m), 4.06–4.14 ($1H^a+1H^b$, m), 4.64 ($1H^a+1H^b$, t, J=5.5 Hz), 4.83–4.92 ($1H^a+1H^b$, m), 5.16 ($1H^a$, br s), 5.34 ($1H^b$, br s), 6.47 ($1H^b$, s), 6.49 ($1H^a$, s), 7.57 ($1H^a+1H^b$, s), 11.77 ($1H^a$, br s), 11.91 ($1H^b$, br s); ^{13}C NMR (126 MHz, DMSO-d_6): 19.30, 19.34, 23.1 (×2), 24.1, 24.3, 24.5 (×2), 25.4, 25.5, 28.8, 29.2, 30.3, 31.1, 53.0 (×2), 58.1 (×2), 68.28, 68.33 (CH_2), 48.1, 48.5, 56.6, 57.1, 75.3, 75.4 (CH), 96.7, 96.9, 131.5, 131.8 (CH_{arom}), 103.6, 104.0, 115.6, 115.7, 130.3, 130.5, 132.4, 133.2, 133.1–133.4 (1C×2) (C_{arom}); HRMS (ESI^+) calcd for $C_{20}H_{29}N_4O_2$ $(M+H)^+$ 357.2291, found 357.2303.

*4.3.4. 5,10-Diallyl-5,5a,6,7,8,9,9a,10-octahydro-1H-pyrazolo[4,3-b]phenazine (**23**). Step A*; *step B*: Reduction product from *step A* (100 mg), K_2CO_3 (0.67 mmol), AllylBr (1.28 mmol), DMF (2 mL), 16 h, 80 °C, flash chromatography provided dialkylated diastereoisomer mixture (77 mg); *step D*: mixture from *step B* (55 mg), flash chromatography provided **23** (32 mg, 0.104 mmol, 43% from **8**) as a yellow oil: IR (ATR): 3350–3100, 1636, 1496 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.26–1.36 (2H, m), 1.47–1.63 (4H, m), 1.69–1.80 (2H, m), 3.35–3.40 (1H, m), 3.42–3.47 (1H, m), 3.66–3.75 (1H, m), 3.78–3.87 (1H, m), 4.08–5.98 (2H, m), 5.15–5.21 (2H, m), 5.23–5.32 (2H, m), 5.86–5.97 (2H, m), 6.41 (1H, s), 6.62 (1H, s), 7.57 (1H, s), 12.10 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6): 21.6, 22.0, 26.4, 27.0, 50.8, 51.5 (CH_2), 55.1, 56.7 (CH), 89.5, 99.4, 131.6, 134.8, 135.1 (=CH), 115.3, 116.0, 116.3, 132.3, 136.1, 137.5 (=CH_2, C_{arom}); HRMS (ESI^+) calcd for $C_{19}H_{25}N_4$ $(M+H)^+$ 309.2079, found 309.2068.

*4.3.5. 5,10-Dibenzyl-5,5a,6,7,8,9,9a,10-octahydro-1H-pyrazolo[4,3-b]phenazine (**25**). Steps A* and *B* as for the preparation of compound **14**; *step C*: mixture from *step B* (200 mg), K_2CO_3 (1.49 mmol), BnBr (1.24 mmol), flash chromatography provided dialkylated diastereoisomer mixture (220 mg); *step D*: mixture from *step C* (220 mg), flash chromatography provided **25** (80 mg, 0.20 mmol, 18% from **8**) as a white solid: mp=77–78 °C; IR (ATR): 1635, 1494, 1451 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.20–1.32 (2H, m), 1.44–1.55 (2H, m), 1.55–1.68 (2H, m), 1.75–1.89 (2H, m), 3.56–3.61 (1H, m), 3.64–3.70 (1H, m), 4.35 (1H, d, J=17 Hz), 4.50 (1H, d, J=17 Hz), 4.62–4.70 (2H, m), 6.31 (1H, s), 6.51 (s, 1H), 7.19–7.26 (2H, m), 7.31–7.40 (8H, m), 7.48 (1H, s), 12.02 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): 21.8, 22.0, 26.5, 27.1, 52.7, 52.9 (CH_2), 56.3, 57.7 (CH), 90.1, 99.7, 126.47 (3C), 126.53, 126.7 (2C), 128.38 (2C), 128.44 (2C), 131.6 (CH_{arom}), 115.4, 132.7, 135.9, 137.7, 139.1, 139.6 (C_{arom}); HRMS (ESI^+) calcd for $C_{27}H_{29}N_4$ $(M+H)^+$ 409.2392, found 409.2396.

*4.3.6. 10-Allyl-5-benzyl-5,5a,6,7,8,9,9a,10-octahydro-1H-pyrazolo[4,3-b]phenazine (**29**). Steps A* and *B* as for the preparation of compound **14**; *step C*: mixture from *step B* (100 mg), K_2CO_3 (0.50 mmol), AllylBr (0.75 mmol), flash chromatography provided dialkylated diastereoisomer mixture (68 mg); *step D*: mixture from *step C* (60 mg), flash chromatography provided **29** (40 mg, 0.11 mmol, 23% from 8) as a green oil: IR (ATR): 3350–3100, 1636, 1494, 1451 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): 1.20–1.35 (2H, m), 1.46–1.71 (5H, m), 1.84–1.93 (1H, m), 3.40–3.45 (1H, m), 3.56–3.61 (1H, m), 3.82–3.88 (1H, m), 4.06–4.13 (1H, m), 4.30 (1H, d, J=17 Hz), 4.57 (1H, d, J=17 Hz), 5.22 (1H, d, J=10.5 Hz), 5.30 (1H, d, J=17 Hz), 5.90–6.00 (1H, m), 6.44 (1H, s), 6.47 (1H, s), 7.19–7.24 (1H, m), 7.29–7.36 (4H, m), 7.48 (1H, s), 12.12 (1H, br s); ^{13}C NMR (126 MHz, DMSO-d_6): 21.5, 22.2, 25.9, 27.5, 51.3, 52.8 (CH_2), 56.3, 56.6 (CH), 89.8, 99.4, 126.5, 126.7 (2C), 128.4 (2C), 131.6, 134.9 (=CH), 115.2, 116.1, 132.4, 136.0, 137.8, 139.5 (=CH_2, C_{arom}); HRMS (ESI^+) calcd for $C_{23}H_{27}N_4$ $(M+H)^+$ 359.2236, found 359.2227.

*4.3.7. 5-Allyl-10-benzyl-5,5a,6,7,8,9,9a,10-octahydro-1H-pyrazolo[4,3-b]phenazine (**30**). Steps A* and *B* as for the preparation of compound **16**; *step C*: mixture from *step B* (84 mg), K_2CO_3 (0.48 mmol), BnBr (0.71 mmol), flash chromatography provided dialkylated diastereoisomer mixture (93 mg); *step D*: mixture from *step C* (50 mg), flash chromatography provided **30** (30 mg, 0.084 mmol, 31% from **8**) as a black oil: IR (ATR): 1636, 1495, 1451 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.21–1.37 (2H, m), 1.44–1.60 (3H, m), 1.60–1.76 (2H, m), 1.85–1.95 (1H, m), 3.50–3.56 (2H, m), 3.71–3.79 (1H, m), 4.07–4.15 (1H, m), 4.47 (1H, d, J=17 Hz), 4.59 (1H, d, J=17 Hz), 5.20 (1H, d, J=10 Hz), 5.32 (1H, d, J=17.5 Hz), 5.89–6.00 (1H, m), 6.23 (1H, s), 6.68 (1H, s), 7.19–7.25 (1H, m), 7.29–7.37 (4H, m), 7.57 (1H, s), 12.01 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6): 21.2, 22.5, 26.7, 26.9, 50.6, 53.0 (CH_2), 54.7, 58.0 (CH), 89.7, 99.6, 126.4 (2C), 126.5, 128.4 (2C), 131.6, 135.1 (=CH), 115.4, 116.3, 132.5, 135.9, 137.4, 138.9 (=CH_2,C_{arom}); HRMS (ESI^+) calcd for $C_{23}H_{27}N_4$ $(M+H)^+$ 359.2236, found 359.2220.

*4.3.8. 10-Benzyl-6,7,8,9,9a,10-hexahydro-1H-pyrazolo[4,3-b]phenazin-5(5aH)-ylacetonitrile (**31**). Step A*; *step B*: compound from *step A* (100 mg), K_2CO_3 (0.48 mmol), bromoacetonitrile (1.28 mmol), DMF (2 mL), 24 h, rt, flash chromatography provided monoalkylated diastereoisomer mixture (83 mg); *step C*: mixture from *step B* (60 mg), K_2CO_3 (0.34 mmol), BnBr (0.51 mmol), flash chromatography provided dialkylated diastereoisomer mixture (43 mg); *step D*: mixture from *step C* (42 mg), flash chromatography provided **31** (16 mg, 0.045 mmol, 19% from **8**) as a yellow oil: IR (ATR): 1637, 1496, 1452 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.21–1.46 (3H, m), 1.56–1.80 (4H, m), 2.07–2.16 (1H, m), 3.40–3.45 (1H, m), 3.53–3.60 (1H, m), 4.39 (1H, d, J=18.5 Hz), 4.56 (2H, s), 4.69 (1H, d, J=18.5 Hz), 6.23 (1H, s), 6.99 (1H, s), 7.20–7.26 (1H, m), 7.28–7.37 (4H, m), 7.68 (1H, s), 12.14 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6): 20.2, 23.1, 26.7, 27.0, 35.9, 52.8 (CH_2), 54.2, 58.6 (CH), 89.4, 101.5, 126.3 (2C), 126.6, 128.5 (2C), 132.0 (CH_{arom}), 114.7, 117.2, 130.2, 136.9, 137.1, 138.5 (CN, C_{arom}); HRMS (ESI^+) calcd for $C_{22}H_{24}N_5$ $(M+H)^+$ 358.2032, found 358.2043.

*4.3.9. 3-[5-Benzyl-5a,6,7,8,9,9a-hexahydro-1H-pyrazolo[4,3-b]phenazin-10(5H)-yl]propanol (**34**). Steps A, B, and C* as for the preparation of compound **29**. A solution of 9-BBN in THF (0.5 M, 2.26 mL, 1.13 mmol) was added to the mixture obtained from *step C* (100 mg). The solution was refluxed for 3 h and then $NaBO_3 \cdot 4H_2O$ (185 mg, 1.20 mmol) was added. After 4 h at room temperature, the mixture was evaporated under reduced pressure, water (10 mL) was added and, the mixture was extracted with EtOAc (2×20 mL). The combined organic fractions were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (cyclohexane to EtOAc) to give the intermediate mixture (28 mg) as an oil; *step D*: mixture from hydroboration/oxidation step (28 mg), flash chromatography provided **34** (12 mg, 0.032 mmol, 4% from **8**) as a green oil: IR (ATR): 3450–3125, 1610, 1496, 1451 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.19–1.29 (1H, m), 1.29–1.40 (1H, m), 1.43–1.62 (4H, m), 1.62–1.72 (1H, m), 1.72–1.81 (2H, m), 1.85–1.94 (1H, m), 3.22–3.56 (6H, m), 4.29 (1H, d, J=17 Hz), 4.57 (1H, d, J=17 Hz), 4.61 (1H, t, J=5 Hz), 6.44 (1H, s), 6.51 (1H, s), 7.18–7.24 (1H, m), 7.29–7.36 (4H, m), 7.47 (1H, s), 12.09 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6): 21.7, 21.9, 26.3, 27.1, 29.0, 45.0, 52.8, 58.6 (CH_2), 56.0, 56.2 (CH), 88.8, 99.4, 126.4, 126.7 (2C), 128.3 (2C), 131.6 (CH_{arom}), 114.9, 132.6, 136.2, 137.3,

139.6 (C_{arom}); HRMS (ESI^+) calcd for $C_{23}H_{29}N_4O$ $(M+H)^+$ 377.2341, found 377.2339.

*4.3.10. 3-[10-Benzyl-6,7,8,9,9a,10-hexahydro-1H-pyrazolo[4,3-b] phenazin-5(5aH)-yl]propanol (**35**). Steps A, B, and C* as for the preparation of compound **30**. A solution of BH_3 in THF (1 M, 1.0 mL, 1.0 mmol) was added to the mixture obtained from *step C* (30 mg). The solution was stirred at room temperature for 1 h and a solution of $NaBO_3 \cdot 4H_2O$ (209 mg, 1.36 mmol) in water (1 mL) was added. After 4 h at room temperature, the mixture was evaporated under reduced pressure, water (10 mL) was added, and the mixture was extracted with EtOAc (2×20 mL). The combined organic fractions were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (cyclohexane to EtOAc) to give the intermediate mixture (22 mg) as an oil; *step D*: mixture from hydroboration/oxidation step (22 mg), flash chromatography provided **35** (11 mg, 0.029 mmol, 18% from **8**) as a green oil: IR (ATR): 3500–3000, 1506, 1496, 1490, 1261 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): 1.21–1.29 (1H, m), 1.32–1.39 (1H, m), 1.44–1.58 (3H, m), 1.58–1.79 (4H, m), 1.87–1.95 (1H, m), 3.17–3.23 (1H, m), 3.43–3.55 (5H, m), 4.46 (1H, d, J=17.5 Hz), 4.57 (1H, t, J=5 Hz), 4.58 (1H, d, J=17.5 Hz), 6.22 (1H, s), 6.71 (1H, s), 7.19–7.24 (1H, m), 7.29–7.35 (4H, m), 7.57 (1H, s), 11.99 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6): 21.4, 22.3, 26.6, 26.9, 28.3, 44.5, 53.0, 58.8 (CH_2), 54.6, 57.7 (CH), 89.7, 98.7, 126.4 (2C), 126.5, 128.4 (2C), 131.6 (CH_{arom}), 115.5, 132.2, 135.7, 137.6, 139.0 (C_{arom}); HRMS (ESI^+) calcd for $C_{23}H_{29}N_4O$ $(M+H)^+$ 377.2341, found 377.2350.

4.4. Procedure for preparation of compound 36

*4.4.1. 5,5a,6,7,8,9,9a,10-Octahydro-1H-pyrazolo[4,3-b]phenazine (**36**).* Ammonium formate (117 mg, 1.86 mmol) was added to a mixture of **14** (40 mg, 0.126 mmol) and 10% Pd/C (16 mg, 15 μmol) in methanol (5 mL). The mixture was refluxed for 1 h and the catalyst was removed by filtration through a Celite pad, which was subsequently washed with methanol (20 mL). After evaporation of the filtrate, the residue was purified by flash chromatography (cyclohexane to EtOAc) to give **36** (28 mg, 0.123 mmol, 98%) as a gray solid: mp 215–217 °C; IR (ATR): 3400–3050, 1639, 1497, 1442, 1425 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.21–1.37 (2H, m), 1.46–1.73 (6H, m), 3.24 (1H, br s), 3.30–3.35 (1H, br s), 5.16 (1H, br s), 5.76 (1H, br s), 6.36 (1H, s), 6.51 (1H, s), 7.47 (1H, s), 11.91 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6): 21.7, 21.8, 29.6, 30.0 (CH_2), 48.8, 49.3 (CH), 89.5, 99.4, 131.1 (CH_{arom}), 115.3, 130.3, 135.9, 136.1 (C_{arom}); HRMS (ESI^+) calcd for $C_{13}H_{17}N_4$ $(M+H)^+$ 229.1453, found 229.1456.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.01.010.

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