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A novel and efficient synthesis of 3-aminomethyl-*N*-tosyl-indazoles

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ABSTRACT

A practical and environmentally friendly synthesis of 3-aminomethyl-*N*-tosyl-indazoles is developed. The in situ formed vinyl azines are reacted with amines to furnish amino functionalized *anti*-hydrazones in excellent yields. Subsequent copper-catalyzed cyclization at ambient temperature is effective and desired compounds are obtained in short reaction times. Also, the formation of bisindazoles is presented for the first time.

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1. Introduction

3-Substituted indazole is a fragment present in a number of biologically active compounds. Compound **1** has shown almost equal activity against P388 leukemia as adriomycin.[1] Indazole **2** has potent inhibitory activity against DNA gyrase[2] and 3-benzimidazole derivative **3** was developed as an inhibitor of receptor tyrosine kinases.[3] Fluoroindazole **4** was found to be a potent anticoagulant,[4] 3-amino indazole **5** has been identified as a MCHr1 antagonist,[5] and indazole **6** has proven to be a promising lead as an inhibitor of reverse transcriptase[6] (Fig. 1).

Due to the wide range of pharmaceutical applications of 3-substituted indazoles, several efficient methods have been developed to obtain these heterocycles.[7] Despite the variety of existing methods, routes to 3-aminomethylindazoles have remained relatively unexplored. To date, three distinct approaches have been utilized to access 3-aminomethylindazoles of general type **7** (Fig. 2).

3-Bromomethylindazole **8** can be obtained by radical bromination of 3-methylindazole.[1,2,6,8] Traditionally, the reaction has been performed in CCl_4 at reflux temperature for several hours. Usually the indazole N1 nitrogen has been protected with *tert*-butyloxycarbonyl (Boc) and the yields have been moderate (60%), due to formation of the dibrominated product. Substitution with primary or secondary amines at room temperature afforded **7** in 40–75% yields. Maryanoff et al.[9] utilized reductive amination during their synthesis of indazole based peptide mimetics. 3-Indazolecarboxaldehyde **10** was obtained by nitrosation-rearrangement[10] of the corresponding indole **11** under acidic conditions. The intermediates were used as obtained and yields of individual steps were not reported. In the third route **7** was obtained by reduction of the corresponding amide **12** with $LiAlH_4$.[11] 3-Indazolecarboxamide **12** can be prepared from isatin in five steps. Although the hydrolysis/diazotization/reduction protocol[12] usually gives the excellent yields (>90%) the total yield of **7** remains only moderate.

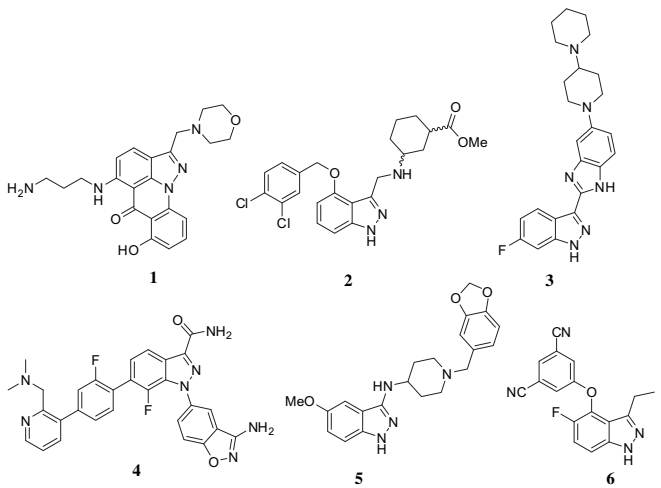

Fig. 1. Examples of pharmaceutically important indazoles.

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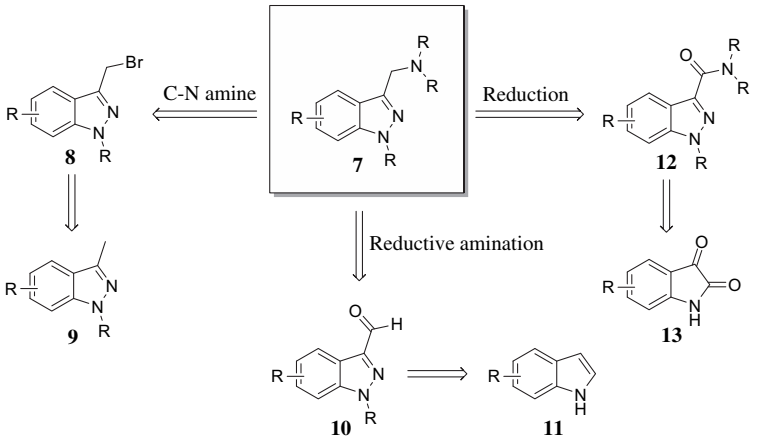
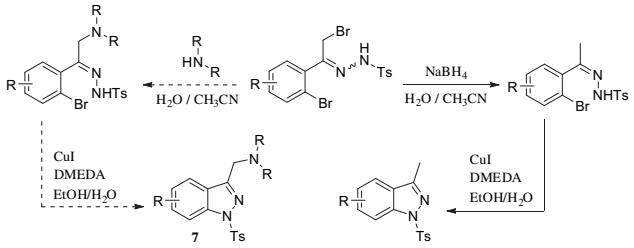


Fig. 2. Synthetic routes to 3-aminomethylindazoles.

Recently, we reported a practical and effective *Z*-selective synthesis of *o*-bromo-acetophenone *N*-tosylhydrazones and subsequent copper-catalyzed cyclization into 3-methylindazoles[13] (Scheme 1).

We reasoned that utilization of amines instead of sodium borohydride, followed by copper mediated cyclization would provide mild and rapid access to 3-aminomethylindazoles of general type **7**. Herein, we report our novel and environmentally friendly route to 3-aminomethylindazoles. According to our knowledge this is the first catalytic cyclization leading to 3-aminomethylindazoles.



Scheme 1. Synthesis of 3-methyindazoles and 3-aminomethylindazoles.

2. Results and discussion

2.1. Synthesis of *anti*-hydrazones

Hydrazones and oximes, possessing a leaving group at the α-position, undergo an elimination reaction when treated with basic reagents to form vinyl azines[14] and α-nitrososty renes,[15] respectively. These synthetically important conjugated dienes undergo 1,4-addition with nucleophiles producing predominantly the *anti*-products[16] (Fig. 3).

The anti-selectivity of this reaction has been explained by the higher reactivity of the *s-trans* conformation in comparison to the *s-cis* form.[15c,e]

Although the applications of nitrosostyrene are well reported by Gilchrist,[15f] Hassner,[17] Denmark,[18] and very recently by Weinreb,[19] the utilization of vinyl azines has remained relatively unexplored. Selective α-fuctionalization of vinyl azines has been utilized mainly in the field of carbohydrate chemistry.[14b–d] In those examples the intermediates have been isolated and reacted with different nucleophiles. We decided to use our own one-pot protocol,[13] and react the in situ formed vinyl azine with a range of amines. The amines used functioned both as a base, by performing the needed deprotonation, and as a nucleophile. Our investigation began with the preparation of five *anti*-aminomethyl *N*-tosylhydrazones **16a**–**e**. α-Brominated *o*-bromoacetophenones[20] **14a**–**d** were reacted with *p*-toluenesulfonylhydrazide at room temperature in the presence of acid. After stirring overnight, the intermediate products **15a**–**d** precipitated out as a mixture of isomers and were filtered. The intermediates were dissolved in acetonitrile, added to a stirred solution of the amine (2 equiv). According to TLC, the reactions were usually completed in 30 min. The results are summarized in Table 1.

With secondary amines the reaction proceeded smoothly, and the desired amino functionalized *anti*-hydrazones were obtained in excellent yields. After aqueous work-up, the products were isolated in pure form, and there was no need for chromatographic purifications.

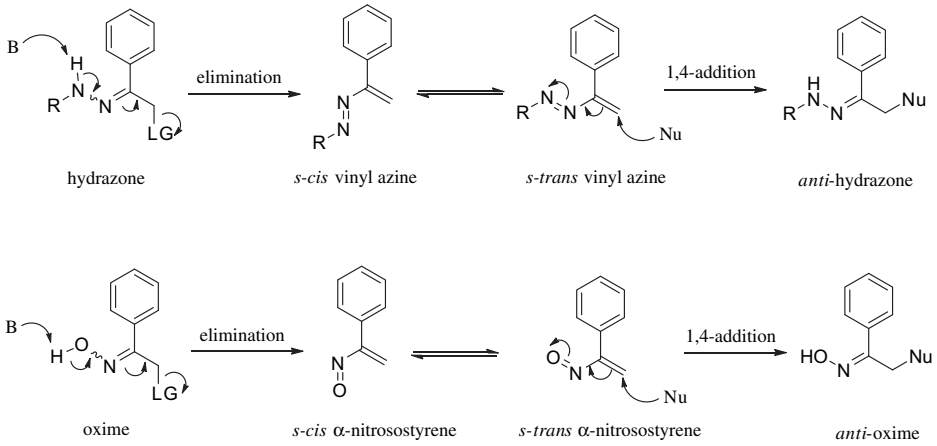
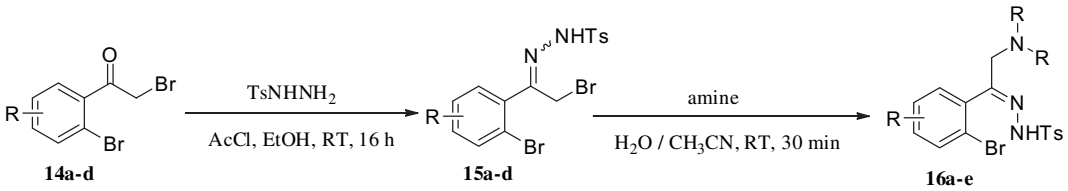
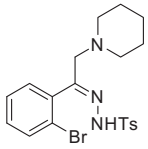
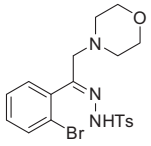
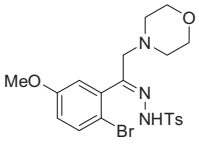
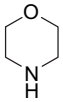
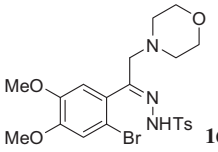
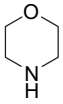
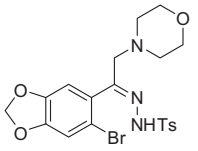


Fig. 3. Analogous formation of *anti*-hydrazones and *anti*-oximes.

Table 1
Synthesized *anti*-hydrazones



14a-d **15a-d** **16a-e**

Entry	Amine	Product	Yield[a] (%)
1		 **16a**	95
2		 **16b**	87
3		 **16c**	89
4		 **16d**	93
5		 **16e**	98

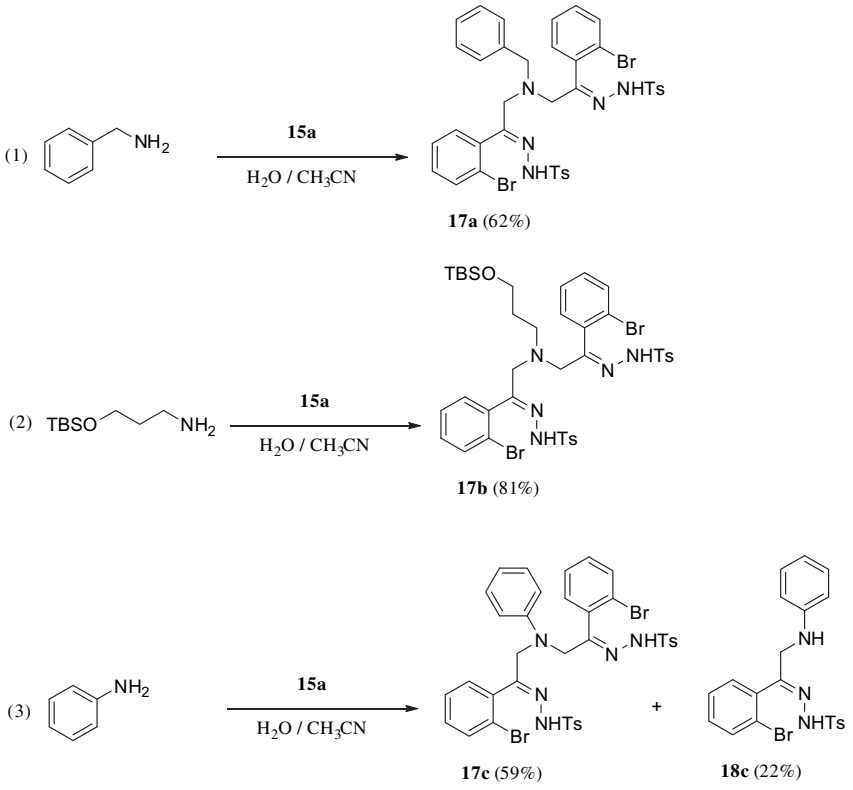
[a] Isolated yield after two steps.

Due to the success with secondary amines, we decided to investigate primary amines as nucleophiles First, **15a** was reacted with benzylamine and as before, the reaction was complete in 30 min as shown by TLC. After aqueous work-up the crude product was triturated with hexane/EtOAc-solution (1:1) and a white solid was obtained. ^{1}H NMR and ESI-MS indicated the formation of a dimer **17a** in 62% yield. For nitrosoalkenes the dimer- or trimer-formation has been reported,[15g] but according to our knowledge, this is the first example of *anti*-selective bishydrazone formation from vinyl azines. The reaction was next repeated with 3-(*tert*-butyldimethylsiloxy)-1-propylamine as the nucleophile giving **17b** in 81% isolated yield. When primary aromatic amine, aniline, was subjected to the reaction a complex mixture was obtained. Due to the lower basicity of aniline compared to aliphatic amines, it was not capable of abstracting the acidic proton and thus the vinyl azine intermediate was not formed. We decided to induce vinyl azine formation by the addition of DBU, which is known to be a strong base but a poor nucleophile. Our assumption was correct, and after 30 min **15a** was totally consumed giving bishydrazone **17c** in 59% isolated yield after column chromatography. In this case monohydrazone **18c** was also obtained in 22% yield (Scheme 2).

2.2. Copper-catalyzed cyclization of *anti*-hydrazones into 3-aminomethyl-*N*-tosyl-indazoles

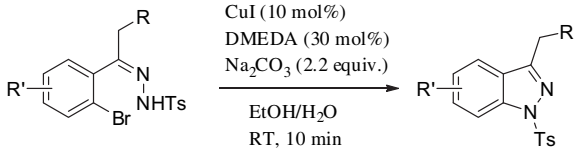
On the basis of our previous work on copper-catalyzed cyclizations,[13,20] we decided to utilize *N*,*N*′-dimethylethylenediamine, DMEDA, as a ligand and CuI as copper source. To our delight, the catalytic system was found suitable also for amino functionalized *anti*-hydrazones. The reactions were carried out at room temperature in air, and in all entries full conversion was achieved in less than 10 min with the results summarized in Table 2.

The starting materials **16a**–**e**, **17a**–**c**, and **18c** were simply slurried in EtOH/H_2O (1:1 for entries 1–5 and 2:1 for entries 6–9), treated with Na_2CO_3, and stirred for 2 min. DMEDA (0.7 M solution in EtOH) and CuI were added and the reactions monitored by TLC (hexane/EtOAc 1:1 or 2:1). After aqueous work-up products **19**–**25** and **27** were obtained in excellent yields with no need for chromatographic purification. Compound **26** was obtained in moderate yield, even though 100% conversion was observed, because a mixture of **17c** and **18c** was used as the starting material and chromatographic separation of **26** and **27** was difficult.

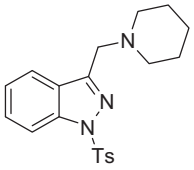
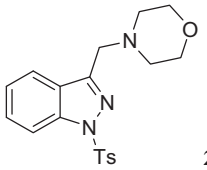
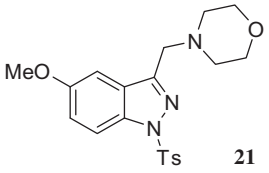


Scheme 2. anti-Selective formation of bishydrazones.

Table 2
Formation of 3-aminomethyl-*N*-tosyl-indazoles

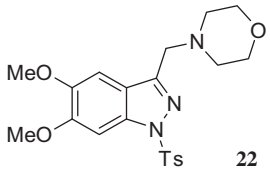
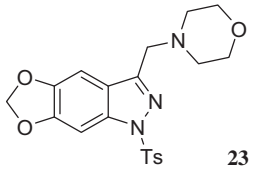
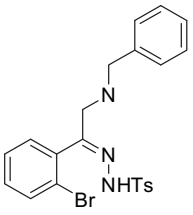
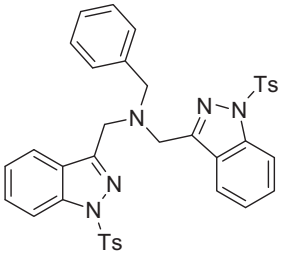
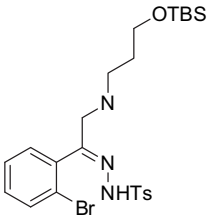
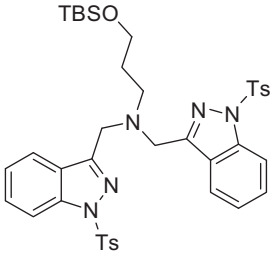
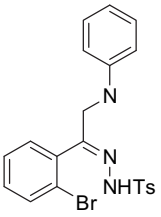
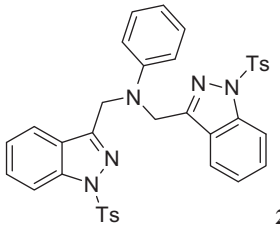
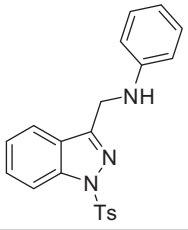


16a-e, **17a-c**, **18c** **19 - 27**

Entry	R	R′	Product	Yield[a] (%)
1		H	 **19**	92
2		H	 **20**	100
3		OMe	 **21**	99

(*continued on next page*)

Table 2 (*continued*)

Entry	R	R′	Product	Yield[a] (%)
4		di-OMe	 **22**	92
5		–OCH_2O–	 **23**	95
6		H	 **24**	98
7		H	 **25**	95
8		H	 **26**	54
9		H	 **27**	100

[a] Isolated yield.

3. Conclusion

In summary, we have extended our previously reported catalytic cyclization[13] method to the synthesis of 3-aminomethyl-*N*-tosylindazoles. This approach offers a rapid and convenient alternative to the existing synthetic routes toward 3-aminomethylindazole. The in situ formed highly reactive vinyl azines underwent 1,4-addition with a variety of amines producing, selectively, the *anti*-hydrazones. When primary amines were utilized as nucleophiles novel bishydrazones were formed in good yields. In case of aromatic amines addition of DBU was needed to induce the vinyl azine formation. Effective copper-catalyzed cyclizations were performed in aqueous conditions producing the desired indazoles in excellent yields. Further investigations to extend this strategy to other nucleophiles and utilization of bisindazoles as metal ligands are currently underway in our laboratory.

4. Experimental

4.1. General

All commercially available chemicals and solvents were used as received and reactions were carried out in air. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured using Varian Mercury

300 spectrometer. Chemical shifts are reported as δ values (ppm) relative to tetramethylsilane, which was used as internal standard. High resolution mass spectra were acquired with Micromass LCT instrument and ESI-MS with ESI-TOF Waters LCT Premier XE instrument. Thin-layer chromatography (TLC) was performed on precoated aluminum plates. Silica gel 60, particle size 0.040–0.063 mm, was used for column chromatography. Melting points were determined with a Stuart SMP10 apparatus and are uncorrected.

4.2. General procedure for the preparation of *anti*-hydrazones 16a–e

Acetyl chloride (0.4 g, 0.36 mL, 5.1 mmol, 5.1 equiv) was added slowly to 4 mL EtOH at 0 °C. Stirring was continued for 30 min at 0 °C and 30 min at room temperature. α-Bromo-acetophenones[20] (**14a**–**d**, 1.0 mmol, 1 equiv) were dissolved in ethanol (6 mL) and added to acidic EtOH-solution followed by *p*-toluenesulfonylhydrazide (0.48 g, 2.6 mmol, 2.6 equiv). The reactions were stirred overnight (ca. 18 h) at room temperature. The intermediate products (**15a**–**d**) precipitated out as a mixture of isomers and were filtered. Compounds **15a**–**d** (0.5 mmol, 1 equiv) were dissolved in acetonitrile (10 mL) and added portion wise to a stirred mixture of amine (1.0 mmol, 2 equiv) in water/CH_3CN (10 mL/10 mL). After 30 min stirring at room temperature, the reactions were complete according to TLC, wherein the mixtures were poured into water and the aqueous solutions extracted with EtOAc (3×20 mL). Combined organics were washed with water (20 mL) and saturated NaCl-solution (20 mL), dried over Na_2SO_4, and filtered. After removal of solvents the desired products (**16a**–**e**) were obtained in pure form.

*4.2.1. (E)-N′-(1-(2-Bromophenyl)-2-(piperidin-1-yl)ethylidene)-4-methylbenzenesulfonolhydrazide (**16a**).* Yellow solid, mp 144–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 7.81 (2H, d, *J* 8.3 Hz, Ar*H*), 7.57 (1H, d, *J* 8.0 Hz, Ar*H*), 7.36–7.25 (4H, m, Ar*H*), 6.96 (1H, d, *J* 7.5 Hz, Ar*H*), 3.33–3.13 (2H, m, N=CCH_2N), 2.42 (3H, s, *Me*), 2.26–2.21 (4H, m, 2×NCH_2CH_2), 1.45–1.32 (6H, m, 3×CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 152.9, 144.1, 135.3, 133.3, 131.3, 129.7, 129.5, 128.2, 120.2, 63.6, 54.4, 25.8, 24.1, 21.7. HRMS (ESI): MH^+, found 450.0862. $C_{20}H_{25}BrN_3O_2S$ requires 450.0851.

*4.2.2. (E)-N′-(1-(2-Bromophenyl)-2-morpholinoethylidene)-4-methylbenzenesulfonohydrazide (**16b**).* White solid, mp 161–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 7.80 (2H, d, *J* 8.3 Hz, Ar*H*), 7.60 (1H, d, *J* 8.0 Hz, Ar*H*), 7.41–7.26 (4H, m, Ar*H*), 6.97 (1H, d, *J* 7.5 Hz, Ar*H*), 3.54 (4H, t, *J* 4.6 Hz, 2×CH_2CH_2O), 3.25 (2H, m, N=CCH_2N), 2.43 (3H, s, *Me*), 2.37–2.31 (4H, m, 2×CH_2NCH_2). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 152.1, 144.2, 135.2, 133.4, 133.3, 131.4, 129.6, 129.5, 128.3, 128.2, 120.3, 66.9, 63.5, 53.5, 21.7. HRMS (EI): M^+, found 451.0571. $C_{19}H_{22}BrN_3O_3S$ requires 451.0565.

*4.2.3. (E)-N′-(1-(2-Bromophenyl-5-methoxyphenyl)-2-morpholinoethylidene)-4-methylbenzenesulfonohydrazide (**16c**).* Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 7.83 (2H, d, *J* 8.3 Hz, Ar*H*), 7.49 (1H, d, *J* 8.9 Hz, Ar*H*), 7.31 (2H, d, *J* 8.0 Hz, Ar*H*), 6.87 (1H, dd, *J* 8.9, 3.0 Hz, Ar*H*), 6.52 (1H, d, *J* 3.0 Hz, Ar*H*), 3.80 (3H, s, O*Me*), 3.58 (4H, t, *J* 5.1 Hz, 2×CH_2CH_2O), 3.26 (2H, m, N=CCH_2N), 2.43 (3H, s, *Me*), 2.43–2.35 (4H, m, 2×CH_2NCH_2). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 159.6, 151.7, 144.3, 135.3, 134.4, 134.1, 129.6, 128.4, 117.4, 115.1, 110.3, 66.9, 63.4, 55.8, 53.6, 21.8. HRMS (EI): M^+, found 481.0676. $C_{20}H_{24}BrN_3O_4S$ requires 481.0671.

*4.2.4. (E)-N′-(1-(2-Bromo-4,5-dimethoxyphenyl)-2-morpholinoethylidene)-4-methylbenzenesulfonohydrazide (**16d**).* Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 7.84 (2H, d, *J* 8.4 Hz, Ar*H*), 7.31 (2H, d, *J* 8.0 Hz, Ar*H*), 7.02 (1H, s, Ar*H*), 6.48 (1H, s, Ar*H*), 3.90 (3H, s, O*Me*), 3.83 (3H, s, O*Me*), 3.60–3.55 (4H, m, 2×CH_2CH_2O), 3.24 (2H, m, N=CCH_2N), 2.43 (3H, s, *Me*), 2.43–2.35 (4H, m, 2×CH_2NCH_2). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 150.9, 149.3, 144.3, 135.4, 131.5, 129.5, 128.4, 124.8, 115.8, 111.7, 110.7, 67.0, 63.7, 56.5, 56.3, 53.6, 21.8. HRMS (EI): M^+, found 511.0790. $C_{21}H_{26}BrN_3O_5S$ requires 511.0777.

*4.2.5. (E)-N′-(1-(6-Bromobenzo[d][1,3]dioxol-5-yl)-2-morpholinoethylidene)-4-methylbenzenesulfonohydrazide (**16e**).* Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 7.82 (2H, d, *J* 8.7 Hz, Ar*H*), 7.33–7.28 (2H, d, *J* 8.7 Hz, Ar*H*), 7.01 (1H, s, Ar*H*), 6.42 (1H, s, Ar*H*), 6.05 (2H, s, OCH_2O), 3.57 (4H, t, *J* 5.0 Hz, 2×CH_2CH_2O), 3.21 (2H, m, N=CCH_2N), 2.43 (3H, s, *Me*), 2.38–2.34 (4H, m, 2×CH_2NCH_2). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 156.0, 150.0, 148.4, 144.1, 135.4, 130.0, 128.2, 113.4, 111.4, 109.0, 102.6, 66.9, 53.6, 25.4, 21.7, 16.9. HRMS (EI): M^+, found 495.0470. $C_{20}H_{22}BrN_3O_5S$ requires 495.0464.

*4.2.6. (N′,N″E,N′,N″E)-N′,N″-((2,2-Benzylazanediyl)bis(1-(2-bromophenyl)ethan-2-yl-1-ylidene))bis(4-methylbenzenesulfonohydrazide) (**17a**).* Benzylamine (0.107 g, 1 mmol, 2 equiv) was dissolved in H_2O/CH_3CN (10 mL/10 mL). Compound **15a** (0.22 g, 0.5 mmol, 1 equiv) was dissolved in CH_3CN (10 mL) and added to the amine solution during 5 min. After 30 min stirring at room temperature the reaction was complete according to TLC (eluent hexane/EtOAc 1:1). Reaction mixture was poured in water and aqueous solution was extracted with EtOAc (3×25 mL). Combined organics were washed with brine (2×25 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was triturated with hexane/EtOAc-solution (1:1, 15 mL). Compound **17a** (0.13 g, 62%) was obtained as white powder after filtration. Mp 130–132 °C. ^{1}H NMR (300 MHz, acetone-d_6, 21 °C) δ (ppm): 7.82–7.77 (4H, m, Ar*H*), 7.56 (2H, t, *J* 7.9 Hz, Ar*H*), 7.38–7.17 (9H, m, Ar*H*), 7.12–6.99 (3H, m, Ar*H*), 6.89–6.73 (2H, m, Ar*H*), 6.57(2H, t, *J* 6.0 Hz, Ar*H*), 3.76–3.12 (6H, m, 2×N=CCH_2N and PhCH_2N), 2.35 (6H, s, 2×*Me*). ^{13}C NMR NMR (75 MHz, acetone-d_6, 21 °C) δ (ppm): 152.8, 152.4, 144.0, 143.9, 138.7, 137.5, 136.9, 136.8, 134.5, 134.1, 133.1, 133.0, 131.1, 131.0, 130.6, 130.3, 129.6, 128.8, 128.5, 128.3, 128.1, 127.9, 126.9, 120.6, 58.4, 57.2, 20.8. ESI-MS: M+Na^+, found 860.

*4.2.7. (N′,N″E,N′,N″E)-N′,N″-(2,2′-(3-(tert-Butyldimethylsilyloxy)propylazanediyl)bis(1-(2-bromophenyl)ethan-2-yl-1-ylidene))bis(4-methylbenzenesulfonohydrazide) (**17b**).* Compound **15a** (0.22 g, 0.5 mmol, 1 equiv) and 3-(*tert*-butyldimethylsiloxy)-1-propylamine (0.19 g, 1 mmol, 2 equiv) were subjected to conditions similar to **17a** described above. Crude product was purified by column chromatography (hexane/EtOAc 2:1→1:1). Compound **17b** (0.19 g, 81%) was obtained as a white solid. Mp 71–73 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 7.85 (4H, m, Ar*H*), 7.61–7.57 (2H, m, Ar*H*), 7.37–7.15 (10H, m, Ar*H*), 6.63–6.56 (2H, m, Ar*H*), 3.65–3.24 (6H, m, 2×N=CCH_2N and CH_2OSi), 2.73–2.27 (8H, m, NCH_2CH_2 and 2×*Me*), 1.39–1.19 (2H, m, CH_2CH_2CH_2), 0.89 (9H, s, 3×CCH_3), −0.01 (6H, s, m, 2×SiCH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 153.4, 152.9, 144.3, 144.2, 135.4, 135.4, 133.3, 133.0, 131.3, 130.2, 129.8, 129.7, 129.6, 128.3, 128.2, 128.1, 120.4, 120.0, 60.9, 60.5, 58.8, 26.1, 21.8, 18.3, −5.16, −7.91. ESI-MS: MH^+, found 920.

*4.2.8. (N′,N″E,N′,N″E)-N′,N″-(2,2′-(Phenylazanediyl)bis(1-(2-bromophenyl)ethan-2-yl-1-ylidene))bis(4-methylbenzenesulfonohydrazide) (**17c**) and (E)-N′-(1-(2-bromophenyl)-2-(phenylamino)ethylidene)-4-methylbenzenesulfonohydrazide (**18c**).* 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.09 mL, 0.6 mmol, 1.2 equiv) and aniline (0.093 g, 1 mmol, 2 equiv) were dissolved in H_2O/CH_3CN (10 mL/10 mL). Compound **15a** (0.22 g, 0.5 mmol, 1 equiv) was dissolved in CH_3CN (10 mL) and added to the amine solution during 5 min. After 30 min stirring at room temperature the reaction was complete according to TLC (eluent hexane/EtOAc 2:1). Reaction mixture was poured in water and aqueous solution was extracted with EtOAc (3×25 mL). Combined organics were washed with brine (2×25 mL) and dried over Na_2SO_4.

The solvent was evaporated in vacuo and the residue was triturated with hexane/EtOAc-solution (2:1, 15 mL). White solid **17c** (0.12 g, 59%) was filtered. Mp 194–195 °C. ^{1}H NMR (300 MHz, DMSO-d_6, 21 °C) δ (ppm): 10.4 (2H, m, N*H*), 7.63–7.54 (6H, m, Ar*H*), 7.34–7.20 (8H, m, Ar*H*), 6.89–6.40 (7H, m, Ar*H*), 4.00–3.68 (4H, m, 2×N=CCH_2N), 2.32 (6H, s, 2×*Me*). ^{13}C NMR (75 MHz, DMSO-d_6, 21 °C) δ (ppm): 151.2, 148.3, 143.1, 136.2, 133.7, 132.5, 131.1, 130.0, 129.2, 128.7, 127.9, 127.4, 120.5, 116.5, 111.8, 55.3, 55.2, 21.1. ESI-MS: M+Na$^+$, found 846. Compound **18c** (0.05 g, 22%) was obtained as a orange solid after column chromatography (hexane/EtOAc 2:1). Mp 134–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 7.76 (2H, d, *J* 8.3 Hz, Ar*H*), 7.59 (1H, d, *J* 7.6 Hz, Ar*H*), 7.44 (1H, br s, N*H*), 7.34–7.23 (4H, m, Ar*H*), 7.08 (2H, t, *J* 7.4 Hz, Ar*H*), 6.88 (1H, m, Ar*H*), 6.72–6.66 (1H, m, Ar*H*), 6.54 (2H, d, *J* 8.3 Hz, Ar*H*), 4.3–4.0 (3H, m, N=CCH_2N and N*H*), 2.42 (3H, s, *Me*). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 152.8, 147.2, 144.2, 135.2, 133.6, 132.7, 131.8, 129.6, 129.4, 129.2, 128.6, 128.0, 120.4, 117.8, 113.1, 48.9, 22.7. HRMS (EI): M$^+$, found 457.0465. $C_{21}H_{20}BrN_3O_2S$ requires 457.0460.

4.3. General procedure for the preparation of indazoles 19–27

Hydrazone (0.1 mmol, 1 equiv) was slurried in EtOH/H_2O (1:1, 1 mL) and Na_2CO_3 (0.22 mmol, 2.2 equiv) was added. The mixture was stirred at room temperature for 2 min, DMEDA (0.7 M solution in ethanol, 43 μl, 30 mol %) was added followed by CuI (2 mg, 10 mol %). After 10 min no starting material was observed on TLC. Reaction mixture was poured in water (50 mL) and the aqueous solution extracted with EtOAc (3×25 mL). The combined organics were washed with 5% aqueous NH_3-solution (3×10 mL), brine (2×25 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuo. Compounds **19**–**25** and **27** were obtained as pure form and compound **26** was purified by column chromatography (hexane/EtOAc 2:1).

*4.3.1. 3-(Piperidin-1-ylmethyl)-1-tosyl-1H-indazole (**19**).* Yellow solid, mp 112–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 8.17 (1H, d, *J* 8.5 Hz, Ar*H*), 7.95 (1H, d, *J* 8.0 Hz, Ar*H*), 7.82 (2H, d, *J* 8.4 Hz, Ar*H*), 7.52 (1H, m, ArH), 7.30 (1H, m, Ar*H*), 7.20 (2H, d, *J* 8.1 Hz, Ar*H*), 3.80 (2H, s, N=CCH_2N), 2.33–2.28 (7H, m, 2×NCH_2CH$_2$ and *Me*), 1.52–1.41 (4H, m, 2×NCH$_2$CH_2), 1.40–1.32 (2H, m, CH$_2$CH_2CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 152.1, 145.1, 141.7, 141.7, 134.6, 129.7, 129.2, 127.5, 126.2, 124.0, 122.3, 113.4, 54.6, 26.1. HRMS (ESI): MH$^+$, found 370.1574. $C_{20}H_{24}N_3O_2S$ requires 370.1589.

*4.3.2. 4-((1-Tosyl-1H-indazol-3-yl)methyl)morpholine (**20**).* White solid, mp 100 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 8.18 (1H, d, *J* 9.0 Hz, Ar*H*), 7.93 (1H, d, *J* 8.0 Hz, Ar*H*), 7.83 (2H, d, *J* 8.4 Hz, Ar*H*), 7.55 (1H, m, Ar*H*), 7.32 (1H, m, Ar*H*), 7.22 (2H, d, *J* 8.6 Hz, Ar*H*), 3.84 (2H, s, N=CCH_2N), 3.62 (4H, t, *J* 4.6 Hz, 2×CH$_2$CH_2O), 2.40 (4H, t, *J* 4.6 Hz, 2×CH$_2$NCH_2), 2.34 (3H, s, *Me*). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 151.1, 145.3, 141.7, 134.6, 129.8, 129.4, 127.5, 125.8, 124.1, 122.0, 113.5, 67.0, 55.5, 53.6, 21.7. HRMS (EI): M$^+$, found 371.1294. $C_{19}H_{21}N_3O_3S$ requires 371.1304.

*4.3.3. 4-((5-Methoxy-1-tosyl-1H-indazol-3-yl)methyl)morpholine (**21**).* Yellow sticky paste. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 8.06 (1H, d, *J* 8.8 Hz, Ar*H*), 7.79 (2H, d, *J* 8.3 Hz, Ar*H*), 7.23 (1H, m, Ar*H*), 7.20–7.15 (3H, m, Ar*H*), 3.85 (3H, s, O*Me*), 3.80 (2H, s, N=CCH_2N), 3.63 (4H, t, *J* 4.5 Hz, 2×CH$_2$CH_2O), 2.38 (4H, t, *J* 4.5 Hz, 2×CH$_2$NCH_2), 2.34 (3H, s, *Me*). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 156.9, 150.9, 145.2, 137.1, 130.0, 129.5, 127.8, 127.3, 126.8, 120.3, 115.0, 102.5 67.1, 56.0, 53.6, 21.7. HRMS (EI): M$^+$, found 401.1416. $C_{20}H_{23}N_3O_4S$ requires 401.1409.

*4.3.4. 4-((5,6-Dimethoxy-1-tosyl-1H-indazol-3-yl)methyl)morpholine (**22**).* Yellow sticky paste. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 7.78 (2H, d, *J* 8.4 Hz, Ar*H*), 7.61 (1H, s, Ar*H*), 7.25 (1H, s, Ar*H*), 7.21 (2H, d, *J* 8.0 Hz, Ar*H*), 4.04 (3H, s, O*Me*), 3.92 (3H, s, O*Me*), 3.77 (2H, s, N=CCH_2N), 3.62 (4H, t, *J* 4.6 Hz, 2×CH$_2$CH_2O), 2.38–2.34 (7H, m, 2×NCH_2CH$_2$ and *Me*). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 152.2, 151.0, 147.9, 145.2, 137.6, 129.8, 127.5, 118.8, 101.4, 95.5, 67.1, 56.6, 56.3, 55.7, 53.6, 21.7. HRMS (EI): M$^+$, found 431.1509. $C_{21}H_{25}N_3O_5S$ requires 431.1515.

*4.3.5. 3-(Morpholinomethyl)-1-tosyl-1H-[1,3]dioxolo[4,5-f]indazole (**23**).* Off-white solid, mp 150–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 7.8 (2H, d, *J* 8.4 Hz, Ar*H*), 7.58 (1H, s, Ar*H*), 7.23 (2H, d, *J* 8.6 Hz, Ar*H*), 7.18 (1H, s, Ar*H*), 6.07 (2H, s, OCH_2O), 3.72 (2H, s, N=CCH_2N), 3.62 (4H, t, *J* 4.6 Hz, 2×CH$_2$CH_2O), 2.38–2.34 (7H, m, 2×NCH_2CH$_2$ and *Me*). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 150.8, 146.2, 145.3, 138.5, 134.5, 129.8, 127.6, 120.4, 102.4, 99.1, 94.1, 67.1, 55.6, 53.6, 21.7. HRMS (EI): M$^+$, found 415.1206. $C_{20}H_{21}N_3O_5S$ requires 415.1202.

*4.3.6. N-Benzyl-1-(tosyl-1H-indazol-3-yl)-N-((1-tosyl-1H-indazol-3-yl)methyl)methanamine(**24**).* Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 8.16 (2H, d, *J* 8.3 Hz, Ar*H*), 7.72 (4H, d, *J* 8.4 Hz, Ar*H*), 7.50 (2H, t, *J* 7.1 Hz, Ar*H*), 7.23–7.20 (3H, m, Ar*H*), 7.07 (2H, t, *J* 8.3 Hz, Ar*H*), 6.99–6.92 (8H, m, Ar*H*), 3.74 (4H, s, 2×N=CCH_2N), 3.29 (2H, s, PhCH_2N), 1.97 (6H, s, 2×*Me*). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 152.3, 145.5, 142.2, 138.3, 134.2, 129.8, 129.7, 129.5, 128.4, 127.6, 127.4, 125.7, 124.2, 121.8, 113.8, 58.6, 50.0, 21.4. HRMS (ESI): MH$^+$, found 676.2054. $C_{37}H_{34}N_5O_4S_2$ requires 676.2052.

*4.3.7. 3-(tert-Butyldimethylsilyloxy)-N,N-bis((1-tosyl-1H-indazol-3-yl)methyl)propan-1-amine (**25**).* Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 8.26 (2H, d, *J* 8.4 Hz, Ar*H*), 7.88 (4H, d, *J* 8.4 Hz, Ar*H*), 7.63 (2H, t, *J* 7.1 Hz, Ar*H*), 7.38 (2H, d, *J* 7.1 Hz, Ar*H*), 7.24 (2H, t, *J* 7.1 Hz, Ar*H*), 7.15 (4H, d, *J* 8.4 Hz, Ar*H*), 3.90 (4H, s, 2×N=CCH_2N), 3.35–3.28 (2H, m, CH_2OSi), 2.51–2.45 (2H, m, NCH_2CH$_2$), 2.20 (6H, s, 2×*Me*), 1.75–1.62 (2H, m, CH$_2$CH_2CH$_2$), 0,88 (9H, s, 3×CCH_3), 0.00 (6H, s, 2×SiCH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 152.1, 145.3, 141.8, 134.2, 129.7, 129.3, 127.4, 125.5, 124.0, 121.7, 113.5, 61.2, 51.1, 50.7, 30.5, 25.9, 21.4, 18.2, −5.38. HRMS (ESI): MH$^+$, found 758.2852. $C_{39}H_{48}N_5O_5SiS_2$ requires 758.2866.

*4.3.8. N,N-Bis((1-tosyl-1H-indazol-3-yl)methyl)aniline (**26**).* Light yellow solid, mp 168–169 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 8.14 (2H, d, *J* 7.7 Hz, Ar*H*), 7.75 (4H, d, 8.3 Hz, Ar*H*), 7.51–7.41 (5H, m, Ar*H*), 7.18–7.01 (9H, m, Ar*H*), 6.89 (2H, d, *J* 7.8 Hz, Ar*H*), 6.74 (1H, t, *J* 7.3 Hz, Ar*H*), 4.72 (4H, s, 2×N=CCH_2N), 2.28 (6H, s, 2×*Me*). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 150.9, 145.3, 141.8, 134.4, 129.8, 129.8, 129.4, 129.2, 127.5, 125.0, 124.3, 121.2, 119.3, 116.1, 113.6, 49.0, 21.7. HRMS (ESI): MH$^+$, found 662.1897. $C_{36}H_{32}N_5O_4S_2$ requires 662.1896.

*4.3.9. N-((1-Tosyl-1H-indazol-3-yl)methyl)aniline (**27**).* Orange solid, mp 143–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C) δ (ppm): 8.19 (1H, d, *J* 9.3 Hz, Ar*H*), 7.81–7.71 (3H, m, Ar*H*), 7.51 (1H, m, Ar*H*), 7.27–7.11 (5H, m, Ar*H*), 7.10–6.65 (3H, m, Ar*H*), 4.82 (2H, br s, N=CCH_2NH), 2.34 (3H, s, *Me*). ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C) δ (ppm): 145.3, 134.5, 129.9, 129.6, 129.3, 127.5, 124.3, 120.9, 118.2, 113.7, 21.7. HRMS (EI): M$^+$, found 377.1199. $C_{21}H_{19}N_3O_2S$ requires 377.1198.

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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.2010.09.069.

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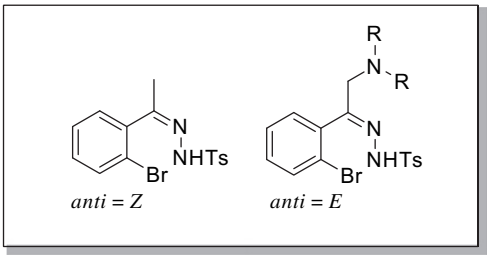
16. For clarity, we decided to use terms *anti*/*syn* instead of *E*/*Z* (see picture below). Throughout this article, anti refers to the isomer having the aminomethyl group trans to the hydrazone N–H. In other words, the hydrazone N–H is cis to the aromatic ring.



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