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Electronic effects on the *cis*/*trans* selectivity in formation of isoxazolidine-fused eight-membered ring *via* an intramolecular nitrone-alkene cycloaddition

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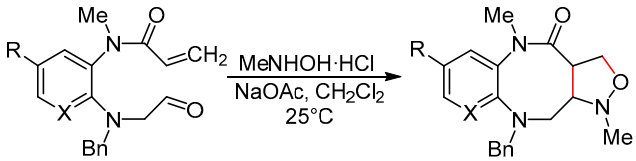


X = N, CH; R = CO_2Me, H, OMe, NO_2

An intramolecular nitrone-alkene cycloaddition involving *in situ* generated nitrones demonstrated reaction profiles different from those previously reported for pyrimidine system. Tuning the electron density of the benzene ring had a significant effect on *cis*/*trans* selectivity. These reactions were useful for the synthesis of novel tricyclic hexahydrobenzo[*b*]isoxazolo[3,4-*f*][1,4]diazocin-4(1*H*)-ones and hexahydroisoxazolo[3,4-*f*]pyrido[3,2-*b*][1,4]diazocin-4(1*H*)-one under mild reaction conditions in good yields.

Keywords: isoxazolidines, tricyclic compounds, *cis*/*trans* selectivity, eight-membered rings, electronic effects, fused-ring systems, nitrone-alkene cycloaddition.

Eight-membered heterocycles, which often occur in various natural products and pharmacologically active substances, have attracted considerable attention because of their unusual structural features and interesting biological effects.[1] For example, balasubramide (**1**) was isolated from *Clausena indica* that grows in the central mountain rainforests of Sri Lanka.[2] (–)-Heliannuol A (**2**) was isolated from aqueous extracts of fresh sunflower leaves (*Helianthus annuus* L. var. SH-222) and exhibits strong allelopathic activity.[3] Benzolactam-V8 (**3**) is a potent activator of protein kinase C.[4] Nefopam (**4**) is a centrally-acting non-opioid analgesic drug.[5] Buflavine (**5**) possesses interesting adrenolytic and antiserotonin activities.[6] Pyrimido[4,5-*b*]-[1,5]oxazocine derivative **6** has been observed to be a neurokinin-1 (NK_1) receptor antagonist[7] (Fig. 1).

1,3-Dipolar cycloadditions of nitrones are powerful synthetic methodologies and have often been utilized in the synthesis of natural products and biologically active molecules.[8] The intramolecular 1,3-dipolar cycloaddition between nitrones and alkenes can form two new rings simultaneously, providing direct access to fused or bridged polycyclic isoxazolidines of considerable complexity with high levels of regio- and stereocontrol.[8,9] Thus far, the intramolecular nitrone-alkene cycloaddition reaction have been successfully used for the construction of isoxazoli-

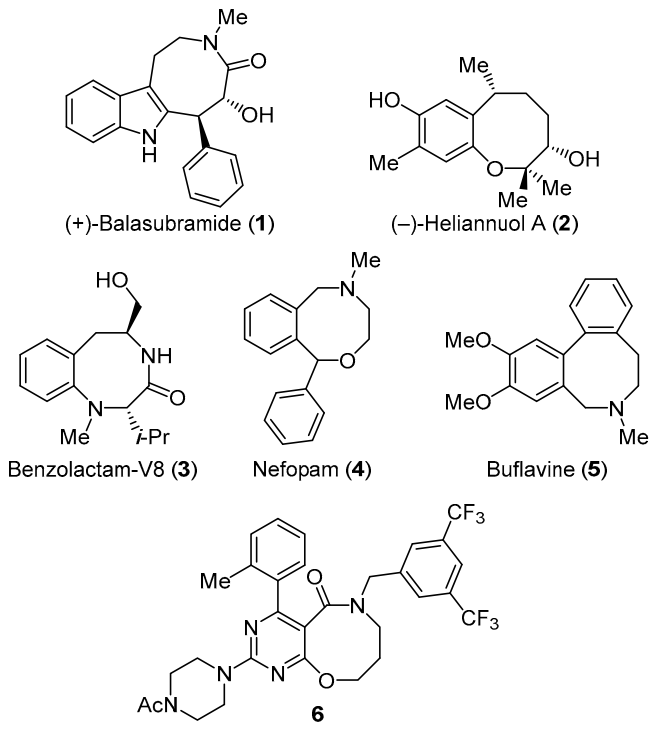
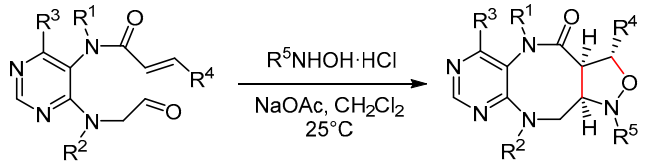


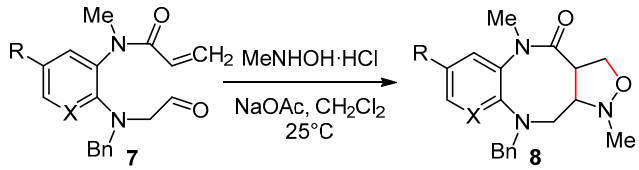
Figure 1. Natural and synthetic examples of 8-membered heterocycles.

Scheme 1



R^1 = Me, Bn, allyl; R^2 = Me, *cyclo*-Hex, Bn; R^3 = Cl, pyrrolidinyl, 4-$MeOC_6H_4S$; R^4 = H, Me, Bn; R^5 = Me, *cyclo*-Hex, Bn, Ph

Scheme 2



X = N or CH; R = CO_2Me, H, OMe, NO_2

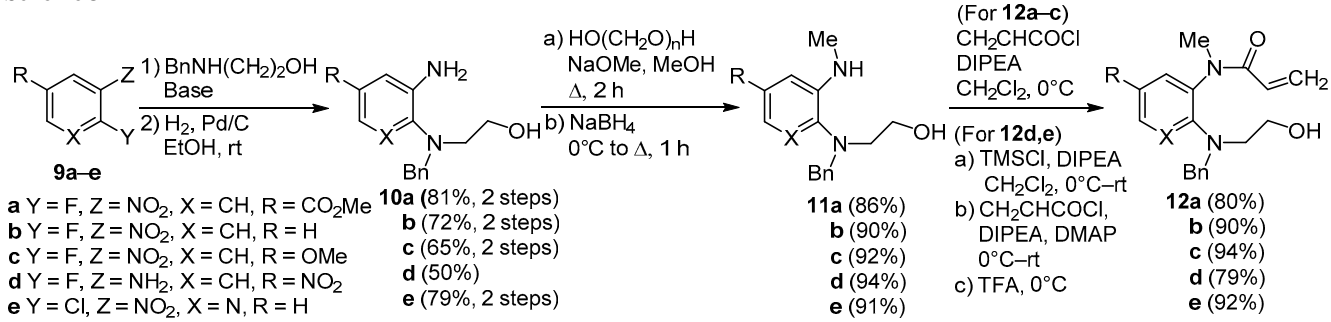
dines fused with 4- to 7-membered rings.[10] However, few examples have been reported where the synthesis of isoxazolidines fused with 8-membered rings has been achieved by intramolecular nitrone-alkene cycloaddition reactions.[11]

Recently, we communicated an intramolecular nitrone-alkene cycloaddition in pyrimidine derivatives leading to a novel *cis*-fused tricyclic compound containing an 8-membered ring and isoxazolidine system (Scheme 1).[12] It is worth noting that the desired tricyclic product was not obtained when *N*-allylamine analog was used. The results revealed that the electronic effects seem to be important for enhanced reactivity. Although the preliminary scope of the intramolecular nitrone-alkene cycloaddition was studied in the pyrimidine system, the electronic effects of other aromatic rings remained to be investigated. During our studies, we noticed that benzene derivatives demonstrated reaction profiles different from those of the pyrimidine system, and the tuning of electron density in the benzene ring had a significant effect on the *cis*/*trans* selectivity (Scheme 2). Herein, the details of these studies are presented.

Several key precursors **12a**–**c** were prepared in 37–66% overall yields from compounds **9a**–**c** as depicted in Scheme 3. Treatment of derivatives **9a**–**c**,**e** with 2-(benzylamino)ethan-1-ol followed by reduction yielded compounds **10a**–**c**,**e**. Compound **10d** was obtained by reacting nitroaniline **9d** with 2-(benzylamino)ethan-1-ol. Reductive amination of compounds **10a**–**c** resulted in substituted amines **11a**–**c**. Direct acylation of compounds **11a**–**c** afforded products **12a**–**c**. However, a direct acylation of compound **11d** proved to be problematic.[12] The selective protection of the hydroxyl group in compounds **11d**,**e** with TMSCl, subsequent acylation of the amino group with acryloyl chloride and TFA removal of TMS gave compounds **12d**,**e**.

Oxidation of compounds **12a**–**c** under the Parikh–Doering conditions cleanly generated the respective aldehydes **7a**–**c**, which were used immediately without further purification (Table 1). Initially, the cyclization reaction of crude aldehyde **7a** with *N*-methylhydroxylamine hydrochloride was investigated under our previously reported reaction

Scheme 3



9a–e

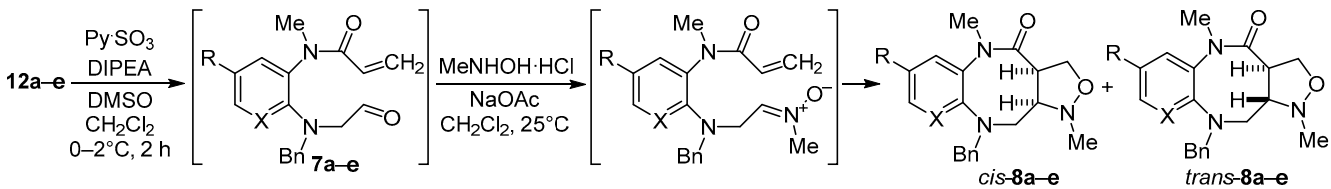
a Y = F, Z = NO_2, X = CH, R = CO_2Me
b Y = F, Z = NO_2, X = CH, R = H
c Y = F, Z = NO_2, X = CH, R = OMe
d Y = F, Z = NH_2, X = CH, R = NO_2
e Y = Cl, Z = NO_2, X = N, R = H

10a (81%, 2 steps)
b (72%, 2 steps)
c (65%, 2 steps)
d (50%)
e (79%, 2 steps)

11a (86%)
b (90%)
c (92%)
d (94%)
e (91%)

12a (80%)
b (90%)
c (94%)
d (79%)
e (92%)

Table 1. Synthesis of benzo[*b*]isoxazolo[3,4-*f*][1,4]diazocin-4(1*H*)-ones **8***



7a–e

cis-**8a–e** + *trans*-**8a–e**

Entry	X	R	Time, h	*cis*-**8** isomer (Yield, %)	*trans*-**8** isomer (Yield, %)	*cis*-**8** : *trans*-**8** ratio
1	CH	CO_2Me	10	**a** (62)	**a** (5)	93:7
2	CH	H	24	**b** (39)	**b** (28)	58:42
3	CH	OMe	28	**c** (20)	**c** (35)	36:64
4	CH	NO_2	8	**d** (71)	**d** (0)	100:0
5	N	H	3	**e** (65)	**e** (0)	100:0

* Overall yield (three steps) from compound **12** and isolated using flash chromatography.

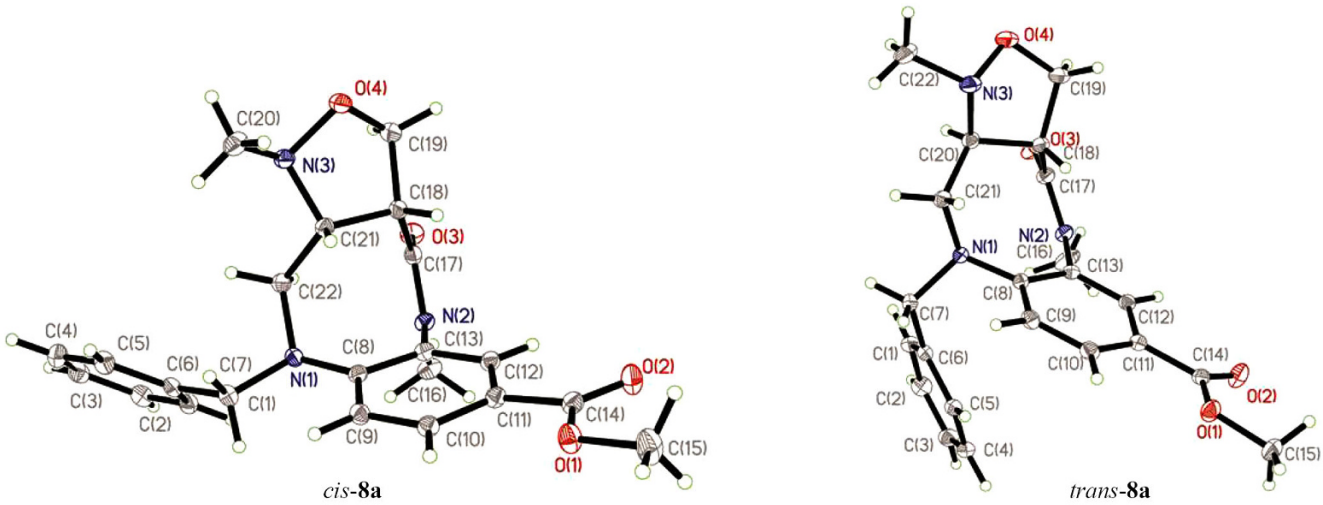


Figure 2. X-ray crystallography data for compounds *cis*-**8a** and *trans*-**8a** with atoms represented by thermal vibration ellipsoids of 30% probability.

conditions using NaOAc in CH_2Cl_2, giving 62% isolated yield of ester *cis*-**8a** ($J_{3a,11a}$ = 8.4 Hz) and 5% isolated yield of ester *trans*-**8a** ($J_{3a,11a}$ = 6.9 Hz) (entry 1). This result was quite different from the previously reported case when only *cis*-isomer was obtained from analogous pyrimidine derivative. To unambiguously determine the configuration of both cycloadducts, X-ray crystallographic analyses of compounds *cis*-**8a** and *trans*-**8a** were performed (Fig. 2). The electronic effects on the *cis*/*trans* selectivity were further explored by using benzene derivatives with substituents of different electronic profiles or a pyridine derivative, and the results are summarized in Table 1.

As shown in Table 1, good overall yields (55–71%) of the desired products **8** were obtained for the three reaction steps (oxidation of alcohols to aldehydes, formation of nitrones, and cycloaddition). The reaction was sensitive to electronic factors of the benzene ring substituents. The reaction proceeded faster when electron-withdrawing group was attached to benzene ring (entries 1 and 4 vs entries 2 and 3). It is noteworthy that tuning the electron density of the benzene ring had a significant effect on the *cis*/*trans* selectivity. The presence of an electron-withdrawing group favored the *exo* adducts *cis*-**8** (entries 4 and 1), while an electron-donating group favored the *endo* adducts *trans*-**8** (entry 3), which indicated that decreasing the electron density of the aromatic ring leads to a higher amount of the *exo* diastereomer being formed. As expected, only the product *cis*-**8e** was obtained in 65% yield when precursor **12e** was used (entry 5). These results are in line with those previously reported for the intermolecular nitrone-alkene cycloaddition.[13] Minor variations in the electronic properties of dipolarophiles led to important changes in the ratio of the *cis*/*trans* isomers formed, possibly through secondary orbital interactions that may occur in the transition state.[8g,13c]

In conclusion, novel tricyclic isoxazolidine-fused eight-membered rings were successfully constructed *via* an intramolecular nitrone-alkene cycloaddition. The benzene derivatives used as substrates demonstrated reaction profiles different from those previously reported for pyrimidine substrates, and the tuning of electron density in the benzene ring had a significant effect on the *cis*/*trans* selectivity of these cycloaddition reactions.

Experimental

^{1}H and ^{13}C NMR data were obtained on a Varian Mercury 300 NMR spectrometer (300 and 75 MHz, respectively) with TMS as internal standard and $CDCl_3$ as solvent unless otherwise stated. HRMS analysis was performed on an Agilent 1290-micrOTOF-Q II mass spectrometer. Melting points were determined with a Beijing Keyi Electro-Optical Factory XT5 melting point apparatus and are uncorrected. Dichloromethane was dried over CaH_2 and distilled prior to use. DMSO was dried over 4 Å molecular sieves. All other commercial reagents were used as received without additional purification.

Methyl 3-amino-4-[benzyl(2-hydroxyethyl)amino]-benzoate (10a). Anhydrous K_2CO_3 (8.292 g, 60 mmol) was added to a stirred solution of methyl 4-fluoro-3-nitro-benzoate (**9a**) (3.983 g, 20 mmol) and $BnNH(CH_2)_2OH$ (4.536 g, 30 mmol) in THF (20 ml). The resulting solution was stirred for 5 h at 60°C. The precipitate was collected by filtration. The resulting clear solution was concentrated *in vacuo* and CH_2Cl_2 (300 ml) was added. The organic layer was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether–EtOAc, 4:1 to 1:1 v/v) afforded methyl 4-(benzyl(2-hydroxyethyl)amino)-3-nitrobenzoate (6.440 g), which was dissolved in EtOH (150 ml). The resulting solution was hydrogenated over Pd/C catalyst (1.288 g, 10% w/w) by stirring for 2 h under a hydrogen atmosphere (balloon). The Pd/C catalyst was then filtered off. The resulting clear solution was concentrated *in vacuo*. Purification by flash chromatography (petroleum ether–EtOAc, 1:1 to 1:5 v/v) afforded the desired product **10a**. Yield 4.866 g (81%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.16 (2H, t, *J* = 5.4, C$\underline{H_2}$OH); 3.57 (2H, t, *J* = 5.4, NC$\underline{H_2}$CH$_2$OH); 3.87 (3H, s, CH_3); 4.18 (2H, s,

$PhCH_2$); 7.01–7.07 (1H, m, H Ar); 7.19–7.31 (5H, m, H Ar); 7.38–7.42 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 52.0; 55.3; 58.1; 59.9; 116.7; 120.3; 123.0; 126.9; 127.4; 128.4; 128.9; 137.8; 141.2; 142.8; 167.3. Found, *m*/*z*: 301.1554 $[M+H]^+$. $C_{17}H_{21}N_2O_3$. Calculated, *m*/*z*: 301.1547.

2-[(2-Aminophenyl)(benzyl)amino]ethan-1-ol (10b). A stirred solution of 1-fluoro-2-nitrobenzene (**9b**) (7.055 g, 50 mmol) in pyridine (5 ml, 62 mmol) was treated by the addition of $BnNH(CH_2)_2OH$ (9.374 g, 62 mmol). The resulting solution was stirred for 2 h at reflux. The solvent was removed *in vacuo* and CH_2Cl_2 (500 ml) was added. The organic layer was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (4:1 to 1:1 petroleum ether–EtOAc, v/v) afforded 2-[benzyl(2-nitrophenyl)amino]ethan-1-ol (12.030 g), which was dissolved in EtOH (250 ml). The resulting solution was hydrogenated over Pd/C catalyst (2.406 g, 10% w/w) by stirring for 2.5 h under a hydrogen atmosphere (balloon). The Pd/C catalyst was filtered off. The resulting clear solution was concentrated *in vacuo*. Purification by flash chromatography (petroleum ether–EtOAc, 1:1 to 1:5 v/v) afforded the desired product **10b**. Yield 8.723 g (72%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.12 (2H, t, *J* = 5.4, $C\underline{H}_2OH$); 3.49 (2H, t, *J* = 5.4, $NC\underline{H}_2CH_2OH$); 4.10 (2H, s, $PhCH_2$); 6.71–6.79 (2H, m, H Ar); 6.98 (1H, td, *J* = 7.5, *J* = 1.5, H Ar); 7.09 (1H, dd, *J* = 7.8, *J* = 1.5, H Ar); 7.23–7.29 (5H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 56.6; 60.0; 60.2; 115.9; 119.2; 124.0; 126.0; 127.2; 128.4; 129.0; 136.8; 138.5; 143.6. Found, *m*/*z*: 243.1498 $[M+H]^+$. $C_{15}H_{19}N_2O$. Calculated, *m*/*z*: 243.1492.

2-[(2-Amino-4-methoxyphenyl)(benzyl)amino]ethan-1-ol (10c). A stirred solution of 1-fluoro-4-methoxy-2-nitrobenzene (**9c**) (8.555 g, 50 mmol) in pyridine (5 ml, 62 mmol) was treated by the addition of $BnNH(CH_2)_2OH$ (9.374 g, 62 mmol). The resulting solution was stirred for 4 h at reflux. The solvent was removed *in vacuo* and CH_2Cl_2 (500 ml) was added. The organic layer was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (4:1 to 1:1 petroleum ether–EtOAc, v/v) afforded 2-[benzyl(4-methoxy-2-nitrophenyl)amino]ethan-1-ol (12.990 g), which was dissolved in EtOH (250 ml). The resulting solution was hydrogenated over 10% Pd/C catalyst (2.598 g) by stirring for 3 h under a hydrogen atmosphere (balloon). The Pd/C catalyst was filtered off. The resulting clear solution was concentrated *in vacuo*. Purification by flash chromatography (1:1 to 1:5 petroleum ether–EtOAc, v/v) afforded the desired product **10c**. Yield 8.850 g (65%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.06 (2H, t, *J* = 5.4, $C\underline{H}_2OH$); 3.45 (2H, t, *J* = 5.4, $NC\underline{H}_2CH_2OH$); 3.74 (3H, s, CH_3); 4.03 (2H, s, $PhCH_2$); 6.25 (1H, d, *J* = 2.7, H Ar); 6.33 (1H, dd, *J* = 8.7, *J* = 2.7, H Ar); 7.01 (1H, d, *J* = 8.7, H Ar); 7.20–7.30 (5H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 55.2; 57.1; 60.2; 60.6; 101.2; 104.3; 124.8; 127.1; 128.2; 129.0; 129.9; 138.7; 144.9; 157.8. Found, *m*/*z*: 273.1607 $[M+H]^+$. $C_{16}H_{21}N_2O_2$. Calculated, *m*/*z*: 273.1598.

2-[(2-Amino-4-nitrophenyl)(benzyl)amino]ethan-1-ol (10d). A stirred solution of 2-fluoro-5-nitroaniline (**9d**) (7.805 g, 50 mmol) in pyridine (5 ml, 62 mmol) was treated by the addition of $BnNH(CH_2)_2OH$ (9.374 g, 62 mmol). The resulting solution was stirred for 6 days at reflux. The solvent was removed *in vacuo* and CH_2Cl_2 (400 ml) was added. The organic layer was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether–EtOAc, 4:1 to 1:1 v/v) afforded the desired product **10d**. Yield 7.155 g (50%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.21 (2H, t, *J* = 5.4, $C\underline{H}_2OH$); 3.67 (2H, t, *J* = 5.4, $NC\underline{H}_2CH_2OH$); 4.26 (2H, s, $PhCH_2$); 7.01 (1H, d, *J* = 9.0, H Ar); 7.19–7.31 (5H, m, H Ar); 7.52–7.56 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 54.5; 56.7; 59.8; 109.8; 113.5; 122.4; 127.5; 128.5; 128.6; 137.4; 142.9; 143.0; 144.5. Found, *m*/*z*: 288.1351 $[M+H]^+$. $C_{15}H_{18}N_3O_3$. Calculated, *m*/*z*: 288.1343.

2-[(3-Aminopyridin-2-yl)(benzyl)amino]ethan-1-ol (10e). A stirred solution of 2-chloro-3-nitropyridine (**9e**) (7.925 g, 50 mmol) and $BnNH(CH_2)_2OH$ (8.316 g, 55 mmol) in *n*-BuOH (100 ml) was treated by the addition of Et_3N (8.36 ml, 60 mmol). The resulting solution was stirred for 4 h at reflux. The solvent was removed *in vacuo* and CH_2Cl_2 (500 ml) was added. The organic layers were washed with saturated $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether–EtOAc, 4:1 to 1:1 v/v) afforded 2-[benzyl(3-nitropyridin-2-yl)amino]ethan-1-ol (11.9 g), which was dissolved in EtOH (300 ml). The resulting solution was hydrogenated over 10% Pd/C catalyst (2.38 g) and stirred for 3 h under a hydrogen atmosphere (balloon). The Pd/C catalyst was filtered off. The resulting clear solution was concentrated *in vacuo*. Purification by flash chromatography (petroleum ether–EtOAc, 1:1 to 1:5 v/v) afforded the desired product **10e**. Yield 9.611 g (79%), white solid, mp 61–63°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.40 (2H, t, *J* = 4.8, $C\underline{H}_2OH$); 3.74 (2H, t, *J* = 4.8, $NC\underline{H}_2CH_2OH$); 4.37 (2H, s, $PhCH_2$); 6.86 (1H, dd, *J* = 7.8, *J* = 4.8, H Ar); 6.97 (1H, dd, *J* = 7.8, *J* = 1.5, H Ar); 7.24–7.41 (5H, m, H Ar); 7.74 (1H, dd, *J* = 4.8, *J* = 1.5, H Ar). ^{13}C NMR spectrum, δ, ppm: 51.8; 52.8; 59.1; 119.8; 122.6; 127.2; 127.6; 128.7; 136.4; 136.6; 138.6; 150.0. Found, *m*/*z*: 244.1452 $[M+H]^+$. $C_{14}H_{18}N_3O$. Calculated, *m*/*z*: 244.1444.

Synthesis of compounds 11a–e (General method). Sodium methoxide (6.482 g, 120 mmol) was added to a stirred solution of the appropriate compound **10a**–**e** (20 mmol) and paraformaldehyde (3.6 g, 120 mmol) in MeOH (320 ml). The resulting solution was stirred for 2 h at reflux. When the solution was cooled to 0°C, $NaBH_4$ (4.536 g, 120 mmol) was added portionwise to the mixture within 10 min. The resulting solution was then stirred for 1 h at reflux. When the solution was cooled to 0°C, the reaction mixture was treated with saturated aqueous citric acid to adjust pH to 7. The solvent was removed *in vacuo* and water (100 ml) was added. Then the aqueous phase was extracted with CH_2Cl_2 (3×100 ml). The combined CH_2Cl_2 layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether–EtOAc, 1:1 to 1:5 v/v) afforded the desired product **11a**–**e**.

Methyl 4-[benzyl(2-hydroxyethyl)amino]-3-(methylamino)benzoate (11a). Yield 5.407 g (86%), pale-yellow

oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.82 (3H, s, NCH_3); 3.11 (2H, t, *J* = 5.4, $C\underline{H}_2OH$); 3.51–3.54 (2H, m, $NC\underline{H}_2CH_2OH$); 3.88 (3H, s, CO_2CH_3); 4.11 (2H, s, $PhCH_2$); 7.01 (1H, d, *J* = 8.1, H Ar); 7.15–7.18 (2H, m, H Ar); 7.20–7.29 (4H, m, H Ar); 7.36 (1H, dd, *J* = 8.1, *J* = 1.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.5; 51.9; 55.1; 58.2; 59.8; 110.9; 118.4; 122.2; 127.1; 127.3; 128.3; 128.8; 137.6; 140.8; 145.4; 167.7. Found, *m*/*z*: 315.1709 $[M+H]^+$. $C_{18}H_{23}N_2O_3$. Calculated, *m*/*z*: 315.1703.

2-{Benzyl[2-(methylamino)phenyl]amino}ethan-1-ol (11b). Yield 4.613 g (90%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.73 (3H, s, NCH_3); 3.09 (2H, t, *J* = 5.1, $C\underline{H}_2OH$); 3.45 (2H, t, *J* = 5.1, $NC\underline{H}_2CH_2OH$); 4.05 (2H, s, $PhCH_2$); 6.63 (1H, dd, *J* = 8.4, *J* = 1.5, H Ar); 6.73 (1H, td, *J* = 7.8, *J* = 1.5, H Ar); 7.06–7.12 (2H, m, H Ar); 7.19–7.31 (5H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.7; 56.5; 60.2; 60.3; 110.6; 117.3; 123.4; 126.4; 127.3; 128.3; 129.1; 136.3; 138.4; 146.5. Found, *m*/*z*: 257.1650 $[M+H]^+$. $C_{16}H_{21}N_2O$. Calculated, *m*/*z*: 257.1648.

2-{Benzyl[4-methoxy-2-(methylamino)phenyl]amino}-ethan-1-ol (11c). Yield 5.269 g (92%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.68 (3H, s, NCH_3); 3.05 (2H, t, *J* = 4.5, $C\underline{H}_2OH$); 3.43 (2H, t, *J* = 5.1, $NC\underline{H}_2CH_2OH$); 3.78 (3H, s, OCH_3); 3.99 (2H, s, $PhCH_2$); 6.15 (1H, d, *J* = 2.7, H Ar); 6.25 (1H, dd, *J* = 8.4, *J* = 2.7, H Ar); 6.99 (1H, d, *J* = 8.4, H Ar); 7.20–7.31 (5H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.5; 55.3; 57.1; 60.3; 61.0; 97.3; 101.2; 124.2; 127.2; 128.3; 129.1; 129.6; 138.6; 147.9; 158.6. Found, *m*/*z*: 287.1759 $[M+H]^+$. $C_{17}H_{23}N_2O_2$. Calculated, *m*/*z*: 287.1754.

2-{Benzyl[2-(methylamino)-4-nitrophenyl]amino}ethan-1-ol (11d). Yield 5.664 g (94%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.89 (3H, s, NCH_3); 3.17 (2H, t, *J* = 5.4, $C\underline{H}_2OH$); 3.64 (2H, t, *J* = 5.4, $NC\underline{H}_2CH_2OH$); 4.21 (2H, s, $PhCH_2$); 6.98 (1H, d, *J* = 8.7, H Ar); 7.16–7.19 (2H, m, H Ar); 7.24–7.29 (3H, m, H Ar); 7.40 (1H, d, *J* = 2.7, H Ar); 7.51 (1H, dd, *J* = 8.7, *J* = 2.7, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.3; 54.6; 56.8; 59.7; 104.0; 111.8; 121.6; 127.5; 128.4; 128.6; 137.2; 142.5; 145.2; 145.4. Found, *m*/*z*: 302.1502 $[M+H]^+$. $C_{16}H_{20}N_3O_3$. Calculated, *m*/*z*: 302.1499.

2-{Benzyl[3-(methylamino)pyridin-2-yl]amino}ethan-1-ol (11e). Yield 4.682 g (91%), white solid, mp 105–107°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.80 (3H, s, NCH_3); 3.35 (2H, t, *J* = 4.8, $C\underline{H}_2OH$); 3.72 (2H, t, *J* = 4.8, $NC\underline{H}_2CH_2OH$); 4.29 (2H, s, $PhCH_2$); 6.84 (1H, dd, *J* = 7.8, *J* = 1.5, H Ar); 6.97 (1H, dd, *J* = 7.8, *J* = 4.8, H Ar); 7.26–7.37 (5H, m, H Ar); 7.68 (1H, dd, *J* = 4.8, *J* = 1.5, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.4; 52.0; 53.3; 59.0; 116.4; 120.4; 127.2; 127.8; 128.7; 134.2; 138.6; 139.5; 149.9. Found, *m*/*z*: 258.1606 $[M+H]^+$. $C_{15}H_{20}N_3O$. Calculated, *m*/*z*: 258.1601.

Synthesis of compounds 12a–c (General method). DIPEA (0.784 ml, 4.5 mmol) was added to a stirred solution of the appropriate compound **11a–c** (3.0 mmol) in CH_2Cl_2 (30 ml). The resulting solution was cooled to 0°C, and a solution of acryloyl chloride (0.292 ml, 3.6 mmol) in anhydrous CH_2Cl_2 (30 ml) was added dropwise over 2 h. The reaction mixture was washed with saturated aqueous Na_2CO_3 (50 ml). The water layer was extracted with CH_2Cl_2 (4×20 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether–EtOAc, 3:1 to 1:4 v/v) afforded the desired product **12a–c** .

Methyl 4-[benzyl(2-hydroxyethyl)amino]-3-(*N*-methylacrylamido)benzoate (12a). Yield 884 mg (80%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.23–3.30 (2H, m, $C\underline{H}_2OH$); 3.35 (3H, s, NCH_3); 3.67 (2H, t, *J* = 5.7, $NC\underline{H}_2CH_2OH$); 3.89 (3H, s, CO_2CH_3); 4.33–4.44 (2H, m, $PhCH_2$); 5.58 (1H, dd, *J* = 10.2, *J* = 2.1) and 6.46 (1H, dd, *J* = 16.8, *J* = 1.8, $COCH=C\underline{H}_2$); 6.12 (1H, dd, *J* = 16.8, *J* = 10.2, $COC\underline{H}=CH_2$); 7.09 (1H, d, *J* = 8.7, H Ar); 7.12–7.20 (2H, m, H Ar); 7.24–7.32 (3H, m, H Ar); 7.75 (1H, d, *J* = 2.1, H Ar); 7.91 (1H, dd, *J* = 8.7, *J* = 2.1, H Ar). ^{13}C NMR spectrum, δ, ppm: 35.8; 52.1; 52.8; 56.3; 59.8; 121.1; 123.4; 127.5; 127.9; 128.0; 128.3; 128.5; 130.0; 131.9; 134.4; 137.1; 151.1; 166.1; 166.2. Found, *m*/*z*: 369.1821 $[M+H]^+$. $C_{21}H_{25}N_2O_4$. Calculated, *m*/*z*: 369.1809.

***N*-{2-[Benzyl(2-hydroxyethyl)amino]phenyl}-*N*-methylacrylamide (12b)**. Yield 838 mg (90%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.08–3.20 (2H, m, $C\underline{H}_2OH$); 3.38 (3H, s, NCH_3); 3.61 (2H, t, *J* = 5.4, $NC\underline{H}_2CH_2OH$); 4.19 (2H, s, $PhCH_2$); 5.55 (1H, dd, *J* = 10.2, *J* = 2.1) and 6.45 (1H, dd, *J* = 16.8, *J* = 2.1, $COCH=C\underline{H}_2$); 6.13 (1H, dd, *J* = 16.8, *J* = 10.2, $COC\underline{H}=CH_2$); 7.08–7.17 (4H, m, H Ar); 7.22–7.32 (5H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.4; 53.0; 57.7; 59.8; 123.0; 123.8; 127.6; 128.2; 128.4; 128.6; 128.8; 129.0; 130.2; 137.2; 137.4; 147.6; 166.1. Found, *m*/*z*: 311.1762 $[M+H]^+$. $C_{19}H_{23}N_2O_2$. Calculated, *m*/*z*: 311.1754.

***N*-{2-[Benzyl(2-hydroxyethyl)amino]-5-methoxyphenyl}-*N*-methylacrylamide (12c)**. Yield 960 mg (94%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.02–3.08 (2H, m, $C\underline{H}_2OH$); 3.36 (3H, s, NCH_3); 3.56 (2H, t, *J* = 5.4, $NC\underline{H}_2CH_2OH$); 3.79 (3H, s, OCH_3); 4.05 (2H, s, $PhCH_2$); 5.53 (1H, dd, *J* = 10.2, *J* = 2.1) and 6.44 (1H, dd, *J* = 16.8, *J* = 2.1, $COCH=C\underline{H}_2$); 6.12 (1H, dd, *J* = 16.8, *J* = 10.2, $COC\underline{H}=CH_2$); 6.68 (1H, d, *J* = 3.0, H Ar); 6.85 (1H, dd, *J* = 9.0, *J* = 3.0, H Ar); 7.07 (1H, d, *J* = 9.0, H Ar); 7.13–7.16 (2H, m, H Ar); 7.22–7.31 (3H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.6; 54.0; 55.7; 58.9; 59.7; 114.1; 115.2; 124.6; 127.5; 128.0; 128.4 (2C); 129.1; 137.4; 139.0; 140.9; 156.3; 166.0. Found, *m*/*z*: 341.1868 $[M+H]^+$. $C_{20}H_{25}N_2O_3$. Calculated, *m*/*z*: 341.1860.

Synthesis of compounds 12d,e. A solution of trimethylsilyl chloride (0.573 ml, 4.5 mmol) in anhydrous CH_2Cl_2 (4.5 ml) was added dropwise to a stirred solution of compound **11d**,**e** (3.0 mmol) and DIPEA (0.784 ml, 4.5 mmol) in anhydrous CH_2Cl_2 (9 ml) at 0°C. The resulting solution was allowed to warm to 25°C. After 2 h, DIPEA (0.836 ml, 4.8 mmol) and DMAP (73 mg, 0.6 mmol) were added, the resulting solution was cooled to 0°C, and a solution of acryloyl chloride (0.39 ml, 4.8 mmol) in anhydrous CH_2Cl_2 (9 ml) was added dropwise. The reaction mixture was then allowed to warm to 25°C. After 2 h, a solution of TFA (2.23 ml, 30 mmol) in CH_2Cl_2 (4.5 ml) was added dropwise at 0°C. The resulting solution was stirred for 30 min at 0°C. The reaction mixture was then diluted with CH_2Cl_2 (30 ml), washed with saturated aqueous Na_2CO_3 (50 ml). The water

layer was extracted with CH_2Cl_2 (4×20 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (3:1 to 1:4 petroleum ether–EtOAc, v/v) afforded the desired product **12 d**,**e**.

***N*-{2-[Benzyl(2-hydroxyethyl)amino]-5-nitrophenyl}-*N*-methylacrylamide (12d)**. Yield 842 mg (79%), yellow solid, mp 89–90°C. ^{1}H NMR (6.10 ppm/6.66 ppm) indicated the ratio of two rotamers of compound **12d** to be 4:1. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.33 (2.61H, s, NCH_3); 3.35–3.44 (1.95H, m, CH_2OH); 3.47 (0.67H, s, NCH_3); 3.66–3.80 (1.94H, m, NCH_2CH_2OH); 4.21–4.43 (0.36H, m, $PhCH_2$); 4.45–4.58 (1.64H, m, $PhCH_2$); 5.62 (0.81H, dd, *J* = 10.2, *J* = 1.8) and 6.48 (0.82H, dd, *J* = 16.8, *J* = 1.8, $COCH=CH_2$); 5.89 (0.20H, dd, *J* = 9.9, *J* = 1.8) and 6.55 (0.18H, d, *J* = 2.1, $COCH=CH_2$); 6.10 (0.80H, dd, *J* = 16.8, *J* = 10.2, $COCH=CH_2$); 6.66 (0.20H, dd, *J* = 16.5, *J* = 10.2, $COCH=CH_2$); 7.07–7.18 (3.38H, m, H Ar); 7.28–7.34 (2.75H, m, H Ar); 7.94 (0.56H, d, *J* = 2.7, H Ar); 8.07 (0.17H, d, *J* = 2.4, H Ar); 8.10 (0.82H, dd, *J* = 9.0, *J* = 2.7, H Ar). ^{13}C NMR spectrum (major rotamer), δ, ppm: 35.7; 53.0; 56.0; 60.0; 120.4; 124.3; 126.7; 127.7; 127.8; 128.1; 128.8; 129.4; 133.3; 136.7; 140.6; 152.7; 166.1. Found, *m*/*z*: 356.1620 $[M+H]^+$. $C_{19}H_{22}N_3O_4$. Calculated, *m*/*z*: 356.1605.

***N*-{2-[Benzyl(2-hydroxyethyl)amino]pyridin-3-yl}-*N*-methylacrylamide (12e)**. Yield 859 mg (92%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.16 (3H, s, NCH_3); 3.58–3.79 (4H, m, NCH_2CH_2OH); 4.49–4.64 (2H, m, $PhCH_2$); 5.43 (1H, dd, *J* = 10.2, *J* = 2.1) and 6.30 (1H, dd, *J* = 16.8, *J* = 2.1, $COCH=CH_2$); 5.71 (1H, dd, *J* = 16.8, *J* = 10.2, $COCH=CH_2$); 6.85 (1H, dd, *J* = 7.5, *J* = 4.8, H Ar); 7.14–7.17 (2H, m, H Ar); 7.19–7.29 (4H, m, H Ar); 8.20 (1H, dd, *J* = 4.8, *J* = 1.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 35.6; 53.2; 53.8; 60.7; 116.1; 127.0; 127.2; 127.7; 127.9 (2C); 128.4; 138.3; 138.9; 146.5; 156.1; 166.0. Found, *m*/*z*: 312.1715 $[M+H]^+$. $C_{18}H_{22}N_3O_2$. Calculated, *m*/*z*: 312.1707.

Synthesis of compounds 8a–e (General method). Compound **12a**–**e** (0.50 mmol) in CH_2Cl_2 (20 ml) was treated with DIPEA (0.697 ml, 4.0 mmol) and DMSO (0.709 ml, 10 mmol). The reaction mixture was cooled to 0–2°C and SO_3-pyridine (320 mg, 2.0 mmol) was added in two portions. The resulting solution was stirred for 2 h at 0–2°C. The reaction mixture was then diluted with CH_2Cl_2 (20 ml), washed with 0.2 M aqueous $KHSO_4$ (20 ml), water (20 ml), and brine (20 ml), dried over $MgSO_4$, filtered, and diluted with CH_2Cl_2 to give a solution of crude aldehyde **7a**–**e** in CH_2Cl_2 (50 ml). NaOAc (49 mg, 0.60 mmol) and *N*-methylhydroxylamine hydrochloride (50 mg, 0.60 mmol) were added to the above solution. The mixture was stirred for the corresponding time at 25°C, then washed with saturated aqueous Na_2CO_3 (25 ml), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether–EtOAc, 5:1 to 1:2 v/v) afforded the desired product **8a**–**e**.

Methyl (3a*R,11a*R**)-10-benzyl-1,5-dimethyl-4-oxo-1,3,3a,4,5,10,11,11a-octahydrobenzo[*b*]isoxazolo[3,4-*f*]-[1,4]diazocine-7-carboxylate (*cis*-8a)**. Yield 122 mg (62%), white solid, mp 133–134°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.44 (3H, s, $ONCH_3$); 2.51 (1H, br. s, CH_3NCH); 3.07 (1H, d, *J* = 14.4) and 3.58 (1H, dd, *J* = 14.7, *J* = 9.9, $BnNCH_2CH$); 3.17 (3H, s, $CONCH_3$); 3.51 (1H, dd, *J* = 17.1, *J* = 8.4, COCH); 3.89 (3H, s, CO_2CH_3); 3.95 (1H, t, *J* = 8.4) and 4.39 (1H, t, *J* = 8.1, $NOCH_2$); 4.51–4.69 (2H, m, $PhCH_2$); 7.14 (1H, d, *J* = 8.7, H Ar); 7.23–7.26 (2H, m, H Ar); 7.30–7.39 (3H, m, H Ar); 7.76 (1H, d, *J* = 2.1, H Ar); 7.89 (1H, dd, *J* = 8.7, *J* = 2.1, H Ar). ^{13}C NMR spectrum, δ, ppm: 37.0; 43.5; 49.8; 52.1; 52.8; 59.4; 66.7; 70.2; 119.8; 122.7; 127.5; 128.0; 129.0; 130.6; 131.5; 132.2; 137.3; 150.8; 166.1; 170.3. Found, *m*/*z*: 396.1924 $[M+H]^+$. $C_{22}H_{26}N_3O_4$. Calculated, *m*/*z*: 396.1918.

Methyl (3a*R,11a*S**)-10-benzyl-1,5-dimethyl-4-oxo-1,3,3a,4,5,10,11,11a-octahydrobenzo[*b*]isoxazolo[3,4-*f*]-[1,4]diazocine-7-carboxylate (*trans*-8a)**. Yield 9 mg (5%), pale-yellow solid, mp 125–126°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.57 (3H, s, $ONCH_3$); 2.81 (2H, dd, *J* = 18.6, *J* = 6.9, $BnNCH_2CH$); 3.13 (1H, ddd, *J* = 15.0, *J* = 8.4, *J* = 6.3, CH_3NCH); 3.25 (3H, s, $CONCH_3$); 3.23 (1H, dd, *J* = 10.2, *J* = 6.9, COCH); 3.78 (1H, t, *J* = 8.4) and 4.42 (1H, t, *J* = 7.2, $NOCH_2$); 3.93 (3H, s, CO_2CH_3); 4.20 (2H, s, $PhCH_2$); 7.18–7.26 (4H, m, H Ar); 7.27–7.31 (1H, m, H Ar); 7.61 (1H, d, *J* = 8.4, H Ar); 7.88 (1H, d, *J* = 2.1, H Ar); 8.01 (1H, dd, *J* = 8.4, *J* = 2.1, H Ar). ^{13}C NMR spectrum, δ, ppm: 37.3; 44.2; 51.2; 52.5; 56.9; 61.1; 68.3; 72.7; 127.8; 128.1; 128.6; 128.7; 128.8; 129.2; 130.1; 138.0; 142.0; 153.1; 165.9; 170.6. Found, *m*/*z*: 396.1924 $[M+H]^+$. $C_{22}H_{26}N_3O_4$. Calculated, *m*/*z*: 396.1918.

(3a*R,11a*R**)-10-Benzyl-1,5-dimethyl-3,3a,5,10,11,11a-hexahydrobenzo[*b*]isoxazolo[3,4-*f*][1,4]diazocin-4(1*H*)-one (*cis*-8b)**. Yield 66 mg (39%), pale-yellow solid, mp 97–98°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.47 (1H, br. s, CH_3NCH); 2.52 (3H, s, $ONCH_3$); 3.00 (1H, d, *J* = 13.2) and 3.42–3.47 (1H, m, $BnNCH_2CH$); 3.09 (3H, s, $CONCH_3$); 3.36–3.39 (1H, m, COCH); 3.95 (1H, t, *J* = 8.4) and 4.38 (1H, t, *J* = 8.1, $NOCH_2$); 4.36 (1H, d, *J* = 15.3) and 4.55 (1H, d, *J* = 15.0, $PhCH_2$); 6.97–7.08 (2H, m, H Ar); 7.19–7.25 (4H, m, H Ar); 7.28–7.36 (3H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.9; 43.7; 50.0; 53.4; 60.3; 67.0; 70.0; 122.9; 123.1; 127.6; 127.9; 128.8 (2C); 129.2; 135.5; 138.2; 147.0; 170.7. Found, *m*/*z*: 338.1871 $[M+H]^+$. $C_{20}H_{24}N_3O_2$. Calculated, *m*/*z*: 338.1863.

(3a*R,11a*S**)-10-Benzyl-1,5-dimethyl-3,3a,5,10,11,11a-hexahydrobenzo[*b*]isoxazolo[3,4-*f*][1,4]diazocin-4(1*H*)-one (*trans*-8b)**. Yield 47 mg (28%), pale-yellow solid, mp 109–110°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.55 (3H, s, $ONCH_3$); 2.72–2.83 (2H, m, $BnNCH_2CH$); 3.13–3.21 (1H, m, CH_3NCH); 3.22 (3H, s, $CONCH_3$); 3.24–3.31 (1H, m, COCH); 3.78 (1H, t, *J* = 8.1) and 4.42 (1H, t, *J* = 8.4, $NOCH_2$); 4.18 (2H, s, $PhCH_2$); 7.17–7.25 (4H, m, H Ar); 7.26–7.31 (3H, m, H Ar); 7.33–7.39 (1H, m, H Ar); 7.55 (1H, dd, *J* = 8.1, *J* = 1.5, H Ar). ^{13}C NMR spectrum, δ, ppm: 37.2; 44.2; 51.0; 56.8; 61.4; 68.3; 73.0; 126.4; 127.2; 127.5; 127.7; 128.5; 128.7; 129.2; 138.6; 141.8; 148.8; 170.8. Found, *m*/*z*: 338.1873 $[M+H]^+$. $C_{20}H_{24}N_3O_2$. Calculated, *m*/*z*: 338.1863.

(3a*R,11a*R**)-10-Benzyl-7-methoxy-1,5-dimethyl-3,3a,5,10,11,11a-hexahydrobenzo[*b*]isoxazolo[3,4-*f*][1,4]-diazocin-4(1*H*)-one (*cis*-8c)**. Yield 37 mg (20%), pale-

yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.48 (1H, br. s, $CH_3NC\underline{H}$); 2.55 (3H, s, $ONCH_3$); 2.92–2.99 (1H, m) and 3.30–3.37 (1H, m, $BnNC\underline{H}_2CH$); 2.99 (3H, s, $CONCH_3$); 3.26–3.29 (1H, m, COCH); 3.79 (3H, s, OCH_3); 3.97 (1H, t, *J* = 8.7) and 4.42 (1H, t, *J* = 8.1, $NOCH_2$); 4.19 (1H, d, *J* = 14.4,) and 4.35 (1H, d, *J* = 14.1, $PhCH_2$); 6.60 (1H, d, *J* = 3.0, H Ar); 6.85 (1H, dd, *J* = 9.0, *J* = 3.0, H Ar); 7.19–7.33 (6H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 37.0; 44.0; 50.0; 54.2; 55.7; 61.3; 67.2; 69.7; 112.6; 115.0; 126.4; 127.5; 128.4; 128.6; 138.0; 138.7; 139.9; 156.4; 170.7. Found, *m*/*z*: 368.1977 $[M+H]^+$. $C_{21}H_{26}N_3O_3$. Calculated, *m*/*z*: 368.1969.

(3a*R,11a*S**)-10-Benzyl-7-methoxy-1,5-dimethyl-3,3a,5,10,11,11a-hexahydrobenzo[*b*]isoxazolo[3,4-*f*][1,4]-diazocin-4(1*H*)-one (*trans*-8c)**. Yield 64 mg (35%), white solid, mp 124–125°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.56 (3H, s, $ONCH_3$); 2.70–2.81 (2H, m, $BnNC\underline{H}_2CH$); 3.13–3.18 (1H, m, $CH_3NC\underline{H}$); 3.19 (3H, s, $CONCH_3$); 3.23 –3.27 (1H, m, COCH); 3.74–3.79 (1H, m) and 4.41 (1H, t, *J* = 6.9, $NOCH_2$); 3.80 (3H, s, OCH_3); 4.15 (2H, s, $PhC\underline{H}_2$); 6.66 (1H, d, *J* = 3.0, H Ar); 6.90 (1H, dd, *J* = 9.0, *J* = 3.0, H Ar); 7.17–7.25 (4H, m, H Ar); 7.27–7.30 (1H, m, H Ar); 7.45 (1H, d, *J* = 9.0, H Ar). ^{13}C NMR spectrum, δ, ppm: 37.0; 44.2; 51.1; 55.6; 57.1; 61.6; 68.3; 73.2; 111.0; 114.9; 127.4; 128.3; 128.4; 128.7; 138.8; 141.5; 142.6; 158.1; 170.8. Found, *m*/*z*: 368.1977 $[M+H]^+$. $C_{21}H_{26}N_3O_3$. Calculated, *m*/*z*: 368.1969.

(3a*R,11a*R**)-10-Benzyl-1,5-dimethyl-7-nitro-3,3a,5,10,11,11a-hexahydrobenzo[*b*]isoxazolo[3,4-*f*][1,4]diazocin-4(1*H*)-one (*cis*-8d)**. Yield 136 mg (71%), yellow solid, mp 169–170°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.41 (3H, s, $ONCH_3$); 2.52 (1H, br. s, $CH_3NC\underline{H}$); 3.14 (1H, d, *J* = 15.3) and 3.67 (1H, dd, *J* = 15.0, *J* = 9.6, $BnNC\underline{H}_2CH$); 3.21 (3H, s, $CONCH_3$); 3.51–3.60 (1H, m, COCH); 3.98 (1H, t, *J* = 8.4) and 4.41 (1H, t, *J* = 8.1, $NOCH_2$); 4.63 (1H, d, *J* = 15.9) and 4.70 (1H, d, *J* = 16.2, $PhCH_2$); 7.15 (1H, d, *J* = 9.3, H Ar); 7.24–7.26 (2H, m, H Ar); 7.31–7.42 (3H, m, H Ar); 8.01 (1H, d, *J* = 2.7, H Ar); 8.11 (1H, dd, *J* = 9.3, *J* = 2.7, H Ar). ^{13}C NMR spectrum, δ, ppm: 37.3; 43.4; 49.7; 52.8; 59.5; 66.6; 70.2; 118.9; 125.1; 126.4; 127.4; 128.3; 129.2; 131.0; 136.3; 140.1; 152.4; 170.1. Found, *m*/*z*: 383.1715 $[M+H]^+$. $C_{20}H_{23}N_4O_4$. Calculated, *m*/*z*: 383.1714.

(3a*R,11a*R**)-10-Benzyl-1,5-dimethyl-3,3a,5,10,11,11a-hexahydroisoxazolo[3,4-*f*]pyrido[3,2-*b*][1,4]diazocin-4(1*H*)-one (*cis*-8e)**. Yield 110 mg (65%), white solid, mp 202–203°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.22 (3H, s, $ONCH_3$); 2.26 (1H, br. s, $CH_3NC\underline{H}$); 3.13 (1H, d, *J* = 15.3) and 3.52 (1H, dd, *J* = 15.3, *J* = 9.6, $BnNC\underline{H}_2CH$); 3.19 (3H, s, $CONCH_3$); 3.43–3.49 (1H, m, COCH); 3.89 (1H, t, *J* = 8.4) and 4.37 (1H, t, *J* = 7.2, $NOCH_2$); 4.67 (1H, d, *J* = 14.7) and 5.18 (1H, d, *J* = 14.7, $PhCH_2$); 6.80 (1H, dd, *J* = 7.5, *J* = 4.8, H Ar); 7.27–7.36 (4H, m, H Ar); 7.37–7.43 (2H, m, H Ar); 8.25 (1H, dd, *J* = 4.8, *J* = 1.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 37.2; 43.2; 49.8; 50.0; 55.2; 66.5; 70.3; 115.2; 125.2; 127.6; 128.7 (2C); 137.8; 138.7; 147.7; 155.8; 170.5. Found, *m*/*z*: 339.1823 $[M+H]^+$. $C_{19}H_{23}N_4O_2$. Calculated, *m*/*z*: 339.1816.

X-ray structural study of compounds *cis*-8a and *trans*-8a. Crystals of compound *cis*-**8a** suitable for X-ray structural analysis were obtained by slow evaporation from CH_2Cl_2/petroleum ether. Crystals of compound *trans*-**8a** suitable for X-ray structural analysis were obtained by slow evaporation from EtOAc/petroleum ether. The X-ray structural study was performed on an automated Rigaku R-AXIS RAPID IP diffractometer (graphite monochromator, λ(MoKα), ω-scanning). Empirical accounting for absorption and the correction of systematic errors were performed with the SADABS software. The structure was solved by a direct method and refined by full matrix method of least squares by F^2_{hkl} with anisotropic thermal parameters for all non-hydrogen atoms, using the SHELXTL package.[14] The hydrogen positions at the carbon atoms were calculated. The complete crystallographic dataset was deposited at the Cambridge Crystallographic Data Center (the deposit numbers are CCDC 1010955 (compound *cis*-**8a**) and CCDC 1010956 (compound *trans*-**8a**)).

The Supplementary information file containing NMR spectra of the synthesized compounds is available at http://link.springer.com/journal/10593.

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