The Free Internet Journal
for Organic Chemistry

Paper

Archive for
Organic Chemistry

Arkivoc **2017**, part v, 20-31

Ultrasound-assisted, $ZnBr_2$-catalyzed regio- and stereoselective synthesis of novel 3,3′-dispiropyrrolidine bisoxindole derivatives via 1,3-dipolar cycloaddition reaction of an azomethine ylide

Mostafa Kiamehr,[a,*] Mohammad R. Khodabakhshi,[b] Firouz M. Moghaddam,[c] Alexander Villinger,[d] and Peter Langer [d,e]

[a] *Department of Chemistry, Faculty of Science, University of Qom, Ghadir Blvd, Qom, Iran*

[b] *Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran*

[c] *Laboratory of Organic Synthesis and Natural Products, Department of Chemistry , Sharif University of Technology, P. O. Box 11155-9516 Tehran, Iran*

[d] *Institut für Chemie der Universität Rostock, Albert-Einstein-Strasse 3a, D-18059 Rostock, Germany*

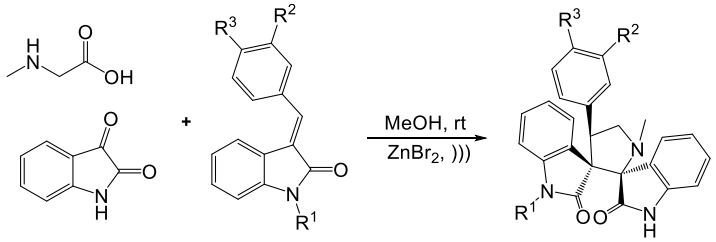
[e] *Leibniz Institut für Katalyse an der Universität Rostock, Albert-Einstein-Strasse 29a, D-18059 Rostock, Germany*

Email: mkiamehr@yahoo.com m.kiamehr@qom.ac.ir

Received 02-02-2017 **Accepted** 03-14-2017 **Published on line** 06-27-2017

Abstract

Ultrasound irradiation in presence of 20% $ZnBr_2$ effectively promotes regio- and stereo-selective cycloaddition reaction of azomethine ylide with a series of *(E)*-3-benzylideneindolin-2-ones to afford 3,3′-dispiropyrrolidine bisoxindole derivatives in excellent yields in methanol at room temperature. The factors affecting the cycloaddition reaction, for example solvent, catalyst, ultrasonic irradiation, are examined in detail to find the mildest conditions and highest reaction yields. The structure and stereochemistry of cycloadducts were determined by spectroscopic data and confirmed by X-ray crystallographic analysis.



Keywords: Ultrasonic irradiation, azomethine ylide, 1,3-dipolar cycloaddition, dispiro oxindole, $ZnBr_2$

DOI: https://doi.org/10.24820/ark.5550190.p010.046

Introduction

The 1,3-dipolar cycloaddition reaction of azomethine ylides is a powerful tool for the construction of various types of complex polyheterocyclic frameworks.[1-3] In recent years the azomethine ylide has gained a vital place in the synthesis of heterocyclic compounds as it serves as an important building block for the construction of nitrogen-containing five membered heterocycles,[4-8] which are often an integral part of many natural products and bioactive molecules.[9,10] The 3,3′-spirocyclooxindole skeleton is found in a growing number of natural or synthetic products presenting various biological activities.[11-13] In particular, the spiropyrrolidinyloxindole, due to its presence in a large number of bioactive alkaloids, such as coerulescine[14,15] (**1**), inhibitor of the MDM2–p53[16,17] (**2**), alstonisine[18,19] (**3**) and strychnofoline[20] (**4**) display a broad range of biological activity (Figure 1). Some spiropyrrolidines are potential antileukaemic and anticonvulsant agents[21] and possess antiviral and local anaesthetic activities,[15] and this has attracted considerable attention from organic chemists. The challenges associated with the synthesis of spiro- or dispiro-heterocycles containing the 3,3′-pyrrolidinyl-spirooxindole core have made them the subject of several elegant synthetic investigations.[22-32]

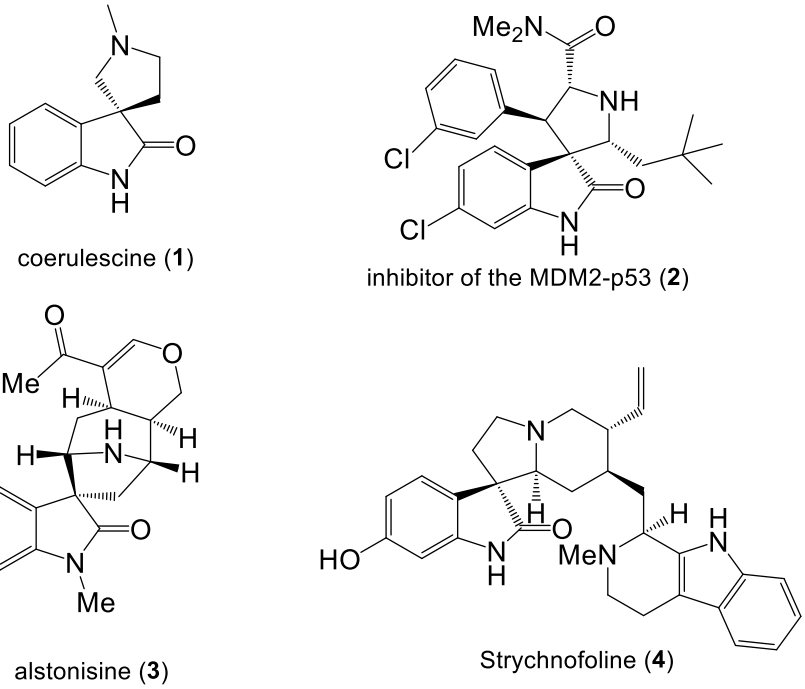
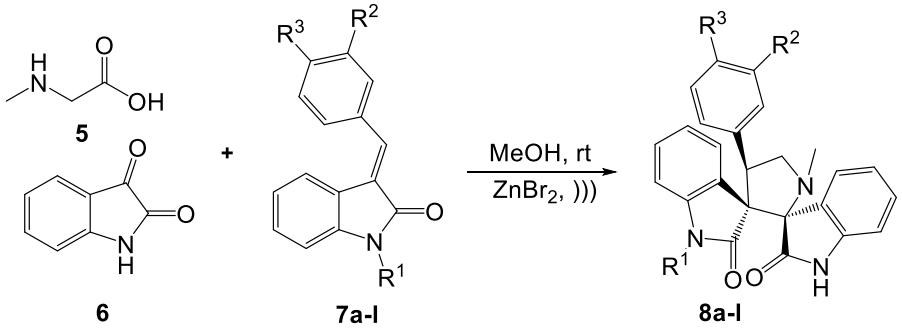


Figure 1. Biologically important molecules containing spiropyrrolidinyloxindole skeleton.

Ultrasound irradiation has increasingly been used as a powerful tool for the preparation of organic molecules either in homogeneous or in heterogeneous liquid reaction systems.[33,34] The success and advantages of this method include shorter reaction time, higher yield, higher product purity, improved selectivity, reduced side product formation, and use of milder reaction conditions when compared with conventional heating.[35,36] Therefore, recently, ultrasonic irradiation has received considerable attention of researchers and numerous examples under this condition for constructing heterocycles with interesting properties have been reported.[37-39] Zinc halides, particularly $ZnBr_2$, are very interesting catalysts due to their low toxicity, low cost, ease of handling, stability in air and water, recoverability and use in numerous chemical transformations.[40]

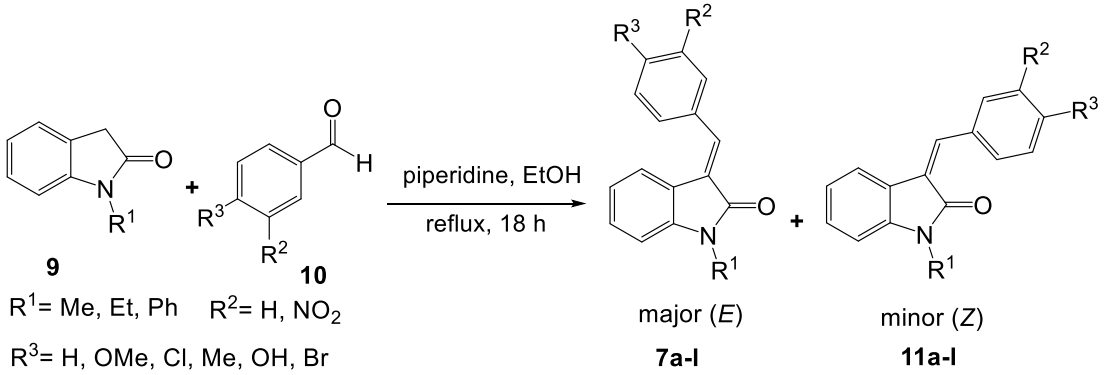
In continuation of our interest in the cycloaddition reaction to synthesis of novel polycyclic nitrogen heterocycles[41-43] and as part of our concern in the using catalyst,[44,45] herein we report an efficient, highly atom-economic and regioselective synthesis of novel 3,3′-dispiropyrrolidine bisoxindoles **8a-l** via the one-pot, three-component condensation of azomethine ylide (generated *in situ* from sarcosine **5** and isatin **6**) with the Knoevenagel adduct *(E)*-3-benzylideneindolin-2-ones **7a-l** (Scheme 1). The reaction is performed under ultrasound irradiation, in the presence of 20% $ZnBr_2$ as a catalyst in methanol at ambient temperature.



Scheme 1. Synthesis of 3,3′-dispiropyrrolidine bisoxindole derivatives **8a-l**.

Results and Discussion

The *(E)*-3-benzylideneindolin-2-ones **7a-l** were prepared according to the reported procedure via condensation of indolin-2-ones **9** and various aromatic aldehydes **10** with the predominant formation of *E* isomer (Scheme 2).[46] These diastereomers were separated by column chromatography to give pure compounds *(E)* and *(Z)*-3-benzylideneindolin-2-ones **7** and **11** in good yields. The structure of the isomers was deduced on the basis of ^{1}H NMR spectral data.[47,48]



Scheme 2. Synthesis of (*E*) and (*Z*)-3-benzylideneindolin-2-ones.

We studied the effect of solvents, catalysts and ultrasound irradiation on cycloaddition reaction of the 1,3-dipole generated from isatin **6** and sarcosine **5** with the Knoevenagel adduct *(E)*-3-benzylidene-indolin-2-one **7a** (Table 1). Initially a series of solvents were investigated to find the best reaction conditions (Entries 1-7). Among the solvents used, methanol at 65 °C (reflux temp.) was found to be the best one in terms of highest yield and shortest reaction time (Entry 7). Then this reaction was examined in some different catalysts under refluxing methanol. The results showed that $ZnBr_2$ is the best catalyst to achieve the desired product in the highest yield and the shortest reaction time (Entry 11). Increasing and reducing the amount of $ZnBr_2$ from 100

mol% to 20 mol% did not have any effect on the yield of reaction (Entries 13 and 14), but reducing the amount of $ZnBr_2$ to 10 mol% shows little negative effect (Table 1, entry 15). To evaluate the effects of ultrasound irradiation on the reactivity of reagents, this reaction was performed in methanol and $ZnBr_2$ (20 mol%) under ultrasound irradiation conditions at room temperature (Table 1, entry 16). The 1,3-dipole generated from isatin **6** and sarcosine **5** reacted readily with the adduct *(E)*-3-benzylideneindolin-2-one **7a** under ultrasound irradiation to give 3,3′-dispiropyrrolidine bisoxindole **8a** in 98% yield through an intermolecular 1,3-dipolar cycloaddition reaction with high regio- and stereoselectivity in presence of 20% $ZnBr_2$ in methanol within 30 minute. The reaction produced a single product in all cases, as which was confirmed by TLC and 1H NMR spectral data. Comparison of $ZnBr_2$ catalyzed ultrasonic irradiation and classical reactions showed that the reaction time is reduced from 90 minutes to only 30 minutes by ultrasonic irradiation at room temperature, which indicates that the ultrasonic irradiation plays an important role in the rate and yield enhancement.

Table1. Effect of solvent, catalyst and ultrasound irradiation on the yield of product **8a**

Entry	Solvent	Catalyst	Temp. (°C)	Time (min)	Yield[a] (%)
1	CH_3CN	-	Reflux	180	50
2	Toluene	-	Reflux	300	14
3	Benzene	-	Reflux	300	25
4	1,4-Dioxane	-	Reflux	300	50
5	CH_3CH_2OH	-	Reflux	180	60
6	CH_3OH	-	rt	300	10
7	CH_3OH	-	Reflux	180	82
8	CH_3OH	SiO_2 (50 mol%)	Reflux	90	88
9	CH_3OH	$ZnCl_2$ (50 mol%)	Reflux	90	84
10	CH_3OH	$ZrOCl_2$ (50 mol%)	Reflux	90	85
11	CH_3OH	$ZnBr_2$ (50 mol%)	Reflux	90	92
12	CH_3OH	ZnO (50 mol%)	Reflux	90	82
13	CH_3OH	$ZnBr_2$ (100 mol%)	Reflux	90	92
14	CH_3OH	$ZnBr_2$ (20 mol%)	Reflux	90	92
15	CH_3OH	$ZnBr_2$ (10 mol%)	Reflux	90	87
16[b]	CH_3OH	$ZnBr_2$ (20 mol%)	rt	30	98

[a] Isolated product. [b] This reaction was conducted under ultrasound irradiation.

The scope of the reaction was extended by reacting various *(E)*-3-benzylideneindolin-2-ones **7a-l** with azomethine ylide generated from isatin **6**, and sarcosine **5** to give 3,3′-dispiropyrrolidine bisoxindole derivatives **8a-l** in excellent yields (Table 2). The reaction proceeded smoothly and a single regioisomer was isolated in all the cases studied.

The structures and regiochemistry of cycloadducts **8a–l** were characterized by IR, ^1H/ ^{13}C NMR, GCMS and HRMS data. For instance, the IR spectrum of cycloadduct **8a** showed three characteristic peaks at 1698 (for other derivatives are separated) and 3168 cm^{-1} corresponding to the two oxindole ring carbonyls and the secondary amide NH groups, respectively. In the ^1H NMR spectrum of **8a** two singlets appeared at δ 2.30 and

Table 2. Structures of synthesized compounds **8a-l**[a]

Entry	R^1	R^2	R^3	Product	Yield[b] (%)
1	CH_3	H	H	**8a**	98
2	CH_3	H	OCH_3	**8b**	90
3	CH_3	H	Cl	**8c**	92
4	CH_3	NO_2	H	**8d**	88
5	C_2H_5	NO_2	H	**8e**	85
6	C_2H_5	H	CH_3	**8f**	92
7	C_2H_5	H	Cl	**8g**	95
8	C_2H_5	H	OH	**8h**	88
9	C_2H_5	H	Br	**8i**	97
10	C_6H_5	H	CH_3	**8j**	90
11	C_6H_5	H	OCH_3	**8k**	86
12	C_6H_5	H	Cl	**8l**	94

[a] All the reactions were conducted under ultrasound irradiation, using 20 mol% $ZnBr_2$ in methanol at room temperature for 30 minute. [b] Isolated product.

2.96 for two $-NCH_3$ protons of the pyrrolidine ring and oxindole ring, respectively. The $-NCH_2$ protons and benzylic proton of pyrrolidine ring appeared as multiplet and triplet at δ 4.47-4.53 and 3.73 which explained the regiochemistry of the cycloaddition. In contrast, if the other regionisomer had been formed, the benzylic proton would have appeared as a singlet in the ^{1}H NMR spectrum. The –NH proton of the oxindole showed a broad singlet at δ 7.93 ppm. For the ^{13}C NMR spectrum of **8a**, the two spiro quaternary carbons resonated at 64.9, 79.5 ppm and the oxindoles carbonyl carbons resonated at 177.5 and 179.0 ppm. Finally the regiochemistry and formation of the products **8** was confirmed by the structure determined from an X-ray crystallographic study of the single crystal of **8i** (Figure 2).[49]

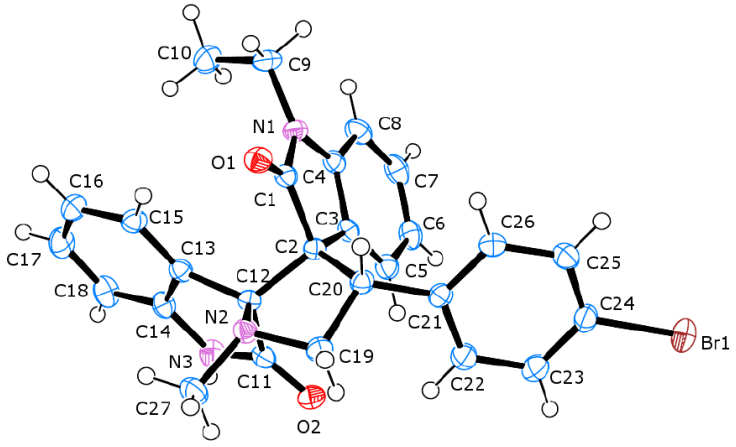
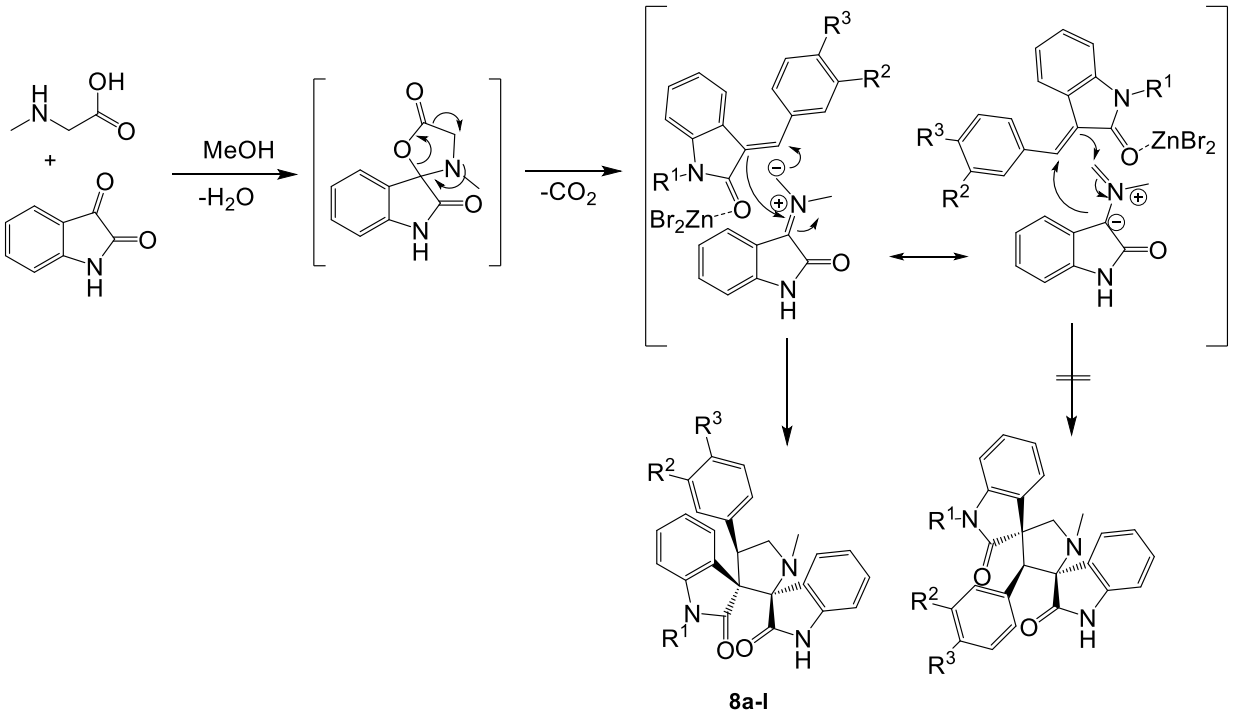


Figure 2. ORTEP diagram of **8i.**

Based on the literature reports,[50] the mechanism involves the formation of an oxazolidinone intermediate. In the presence of activated *(E)*-3-benzylideneindolin-2-ones with $ZnBr_2$, it undergoes loss of CO_2 via a

stereospecific 1,3-cycloreversion forming the azomethine ylide, which undergoes 1,3-dipolar cycloaddition to give the dispiro compounds **8a-l** (Scheme 3).



Scheme 3. Mechanism for the formation of compounds **8a-l**.

Conclusions

This letter describes a facile, high yield and efficient method for the synthesis of novel dispiro compounds via 1,3-dipolar cycloaddition reaction of azomethine ylide generated from isatin and sarcosine with different *(E)*-3-benzylideneindolin-2-ones by $ZnBr_2$ catalyzed ultrasonic irradiation. The products were isolated by recrystallization in methanol without need for further purification. The synthetic route involves a regio- and stereo-controlled fashion as determined by NMR and confirmed by X-ray crystallographic analysis.

Experimental Section

General. The reagents and solvents were commercially available and purchased from Sigma–Aldrich and Merck, and were used without any additional purification. Ultrasonication was performed in a Parsonic 7500s ultrasonic bath with a frequency of 28 kHz and a power of 100 W. The liquid holding capacity of the ultrasonic cleaner tank was 6L. TLC: Silica-gel plates 60 F_{254} (SiO_2; Merck). M.p.: Büchi melting point B-540 apparatus; in sealed capillaries. ^{1}H and ^{13}C NMR Spectra: Bruker (DRX-500 Avance) spectrometer at 500 and 300 (^{1}H) and 125 and 75.5 (^{13}C) MHz, in $CDCl_3$ soln., at ambient temp.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. Signals of the ^{13}C NMR spectra corresponding to CH, CH_2 , or CH_3 groups are assigned from DEPT. Infrared spectra were recorded in an ATR apparatus. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI).

General procedure for synthesis of the 3,3′-dispiropyrrolidine bisoxindole (8a-l). A mixture of *(E)*-3-benzylideneindolin-2-one **7a-l** (1 mmol), isatin (147 mg, 1 mmol), sarcosine (89 mg, 1 mmol) and anhydrous $ZnBr_2$ (20%, 45 mg, 0.2 mmol) in methanol (10 mL) was sonicated for 30 minute at room temperature (25-30 ^oC). After completion of the reaction as monitored by TLC, the mixture was poured in ice cold water and the precipitates were filtered and air dried. Then the product was recrystallized from methanol to afford the pure product **8a-l**.

(3R*,3′′S*,4′R*)-1′,1′′-Dimethyl-4′-phenyldispiro[indole-3,2′-pyrrolidine-3′,3′′-indole]-2,2′′(1*H*,1′′*H*)-dione (8a). Pale yellow solid, yield 98% (401 mg); mp 206-208 ^oC. IR (KBr, ν, cm^{-1}): 3168 (m), 1698 (s), 1609 (s), 1468 (s). ^1H NMR (500 MHz, $CDCl_3$): δ 7.93 (s, 1H, NH), 7.53 (d, *J* 7.6 Hz, 1H, Ar-H), 7.26 (d, *J* 7.4 Hz, 2H, Ar-H), 7.11-7.14 (m, 3H, Ar-H), 7.06 (t, *J* 7.2 Hz, 1H, Ar-H), 6.98 (t, *J* 7.6 Hz, 1H, Ar-H), 6.92 (t, *J* 7.6 Hz, 1H, Ar-H), 6.71 (d, *J* 7.2 Hz, 1H, Ar-H), 6.55 (d, *J* 7.6 Hz, 1H, Ar-H), 6.42 (t, *J* 7.1 Hz, 2H, Ar-H), 4.47-4.53 (m, 2H, CH_2), 3.73 (t, *J* 5.4 Hz, 1H, CH), 2.96 (s, 3H, NMe), 2.30 (s, 3H, NMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.0 (C, N-C=O), 177.5 (C, N-C=O), 144.2 (C), 142.0 (C), 138.4 (C), 130.0 (CH), 129.9 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.2 (CH), 127.1 (CH), 125.5 (C), 125.0 (C), 122.8 (CH), 122.0 (CH), 109.7 (CH), 107.4 (CH), 79.5 (C), 64.9 (C), 57.2 (CH_2), 49.8 (NCH_3), 35.8 (CH), 26.6 (NCH_3). MS (GC, 70eV): *m/z* (%) = 409 (M^+, 2), 235 (31), 234 (22), 174 (100), 159 (18). HRMS (ESI): calcd for $C_{26}H_{24}N_3O_2$ (M+H) 410.1863, found 410.1872.

(3R*,3′′S*,4′R*)-4′-(4-Methoxyphenyl)-1′,1′′-dimethyldispiro[indole-3,2′-pyrrolidine-3′,3′′-indole]-2,2′′(1*H*,1′′*H*)-dione (8b). Yellow solid, yield 90% (396 mg); mp 216-218 ^oC. IR (KBr, ν, cm^{-1}): 3165 (m), 1702 (s), 1609 (s), 1493 (m). ^1H NMR (500 MHz, $CDCl_3$): δ 7.66 (s, 1H, NH), 7.55 (d, *J* 7.5 Hz, 1H, Ar-H), 7.22 (d, *J* 8.6 Hz, 2H, Ar-H), 7.15 (t, *J* 7.5 Hz, 1H, Ar-H), 7.01 (t, *J* 7.6 Hz, 1H, Ar-H), 6.97 (t, *J* 7.8 Hz, 1H, Ar-H), 6.78 (d, *J* 7.5 Hz, 1H, Ar-H), 6.70 (d, *J* 8.6 Hz, 2H, Ar-H), 6.56 (d, *J* 7.6 Hz, 1H, Ar-H), 6.52 (t, *J* 7.6 Hz, 1H, Ar-H), 6.45 (d, *J* 7.7 Hz, 1H, Ar-H), 4.42-4.48 (m, 2H, CH_2), 3.72-3.80 (m, 4H, OMe, CH), 3.00 (s, 3H, NMe), 2.35 (s, 3H, NMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.4 (C, N-C=O), 162.8 (C, N-C=O), 158.6 (C), 143.3 (C), 142.1 (C), 130.8 (C), 130.4 (C), 129.8 (CH), 129.0 (CH), 128.3 (CH), 127.6 (CH), 125.6 (CH), 125.4 (C), 122.8 (CH), 121.8 (CH), 113.7 (CH), 109.6 (CH), 107.4 (CH), 79.4 (C), 64.6 (C), 57.6 (CH_2), 55.5 (OCH_3), 49.2 (CH), 35.8 (NCH_3), 34.9 (NCH_3). MS (GC, 70eV): *m/z* (%) = 439 (M^+, 2), 277 (5), 265 (28), 264 (23), 174 (100), 159 (19). HRMS (ESI): calcd for $C_{27}H_{26}N_3O_3$ (M+H) 440.1968, found 440.1973.

(3R*,3′′S*,4′R*)-4′-(4-Chlorophenyl)-1′,1′′-dimethyldispiro[indole-3,2′-pyrrolidine-3′,3′′-indole]-2,2′′(1*H*,1′′*H*)-dione (8c). White solid, yield 92% (408 mg); mp 231-233 ^oC. IR (KBr, ν, cm^{-1}): 3231 (m), 1709 (s), 1695 (s), 1610 (m), 1369 (s). ^1H NMR (500 MHz, $CDCl_3$): δ 7.69 (s, 1H, NH), 7.53 (d, *J* 7.6 Hz, 1H, Ar-H), 7.24 (d, *J* 8.4 Hz ,2H, Ar-H), 7.13-7.17 (m, 3H, Ar-H), 6.98-7.03 (m, 2H, Ar-H), 6.71 (d, *J* 7.5 Hz, 1H, Ar-H), 6.53-6.57 (m, 2H, Ar-H), 6.47 (d, *J* 7.7 Hz, 1H, Ar-H), 4.42-4.47 (m, 2H, CH_2), 3.78 (m, 1H, CH), 3.01 (s, 3H, NCH_3), 2.34 (s, 3H, NCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.7 (C, N-C=O), 177.3 (C, N-C=O), 144.2 (C), 141.9 (C), 136.9 (C), 132.9 (C), 131.4 (CH), 130.0 (CH), 128.7 (CH), 128.4 (CH), 127.6 (CH), 127.1 (CH), 125.3 (C), 124.6 (C), 122.9 (CH), 122.2 (CH), 109.5 (CH), 107.4 (CH), 79.4 (C), 64.7 (C), 57.4 (CH_2), 49.1 (CH), 35.7 (NCH_3), 26.6 (NCH_3). MS (GC, 70eV): *m/z* (%) = 443 (M^+, 1), 269 (32), 268 (14), 174 (100), 159 (17). HRMS (ESI): calcd for $C_{26}H_{23}ClN_3O_2$ (M+H) 444.1473, found 444.1476.

(3R*,3′′S*,4′R*)-1′,1′′-Dimethyl-4′-(3-nitrophenyl)dispiro[indole-3,2′-pyrrolidine-3′,3′′-indole]-2,2′′-(1*H*,1′′*H*)-dione (8d). Bold yellow solid, yield 88% (400 mg); mp 201-203 ^oC. IR (KBr, ν, cm^{-1}): 3170 (m), 1712 (s), 1608 (m), 1524 (s). ^1H NMR (500 MHz, $CDCl_3$): δ 8.53 (s, 1H, NH), 7.37 (d, *J* 7.6 Hz, 1H, Ar-H), 7.01 (t, *J* 7.7 Hz, 2H, Ar-H), 6.96 (t, *J* 7.6 Hz, 2H, Ar-H), 6.85 (t, *J* 7.6 Hz, 1H, Ar-H), 6.80 (d, *J* 7.6 Hz, 1H, Ar-H), 6.54 (t, *J* 7.7 Hz, 1H, Ar-H), 6.48 (d, *J* 7.7 Hz, 1H, Ar-H), 6.45 (d, *J* 7.6 Hz, 1H, Ar-H), 6.41 (d, *J* 7.7 Hz, 1H, Ar-H), 6.17-6.18 (m, 1H, Ar-H), 4.31 (t, *J* 7.4 Hz, 1H, CH), 4.24 (t, *J* 8.7 Hz, 1H, CH_2), 3.71 (t, *J* 8.2 Hz, 1H, CH), 2.94 (s, 3H, NCH_3), 2.23 (s, 3H, NCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.3 (C, N-C=O), 177.0 (C, N-C=O), 153.2 (C), 148.5 (C), 144.3 (C), 142.8 (C), 141.4 (CH), 139.7 (CH), 135.2 (C), 129.8 (CH), 128.6 (CH), 127.1 (CH), 126.8 (CH), 125.0 (C), 122.3

(CH), 122.1 (CH), 110.3 (CH), 109.6 (CH), 108.7 (CH), 107.3 (CH), 79.1 (C), 62.7 (C), 56.8 (CH_2), 43.3 (NCH_3), 35.6 (CH), 26.4 (NCH_3). MS (GC, 70eV): *m/z* (%) = 454 (M^+, 2), 280 (37), 174 (100), 159 (19). HRMS (ESI): calcd for $C_{26}H_{23}N_4O_4$ (M+H) 455.1713, found 455.1706.

(3R*,3′′S*,4′R*)-1′′-Ethyl-1′-methyl-4′-(3-nitrophenyl)dispiro[indole-3,2′-pyrrolidine-3′,3′′-indole]-2,2′′-(1*H*,1′′*H*)-dione (8e). Pale brown solid. yield 85% (398 mg); mp 208-210 °C. IR (KBr, ν, cm^{-1}): 3213 (m), 1708 (s), 1608 (m), 1525 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H, NH), 8.11 (s, 1H, Ar-H), 7.93 (d, *J* 6.9 Hz, 1H, Ar-H), 7.54 (d, *J* 7.6 Hz, 1H, Ar-H), 7.46 (d, *J* 7.6 Hz, 1H, Ar-H), 7.27 (t, *J* 8.0 Hz, 1H, Ar-H), 7.13 (t, *J* 7.6 Hz, 1H, Ar-H), 6.98 (t, *J* 7.6 Hz, 1H, Ar-H), 6.94 (t, *J* 7.7 Hz, 1H, Ar-H), 6.64 (d, *J* 7.6 Hz, 1H, Ar-H), 6.59 (d, *J* 7.7 Hz, 1H, Ar-H), 6.48 (d, *J* 7.8 Hz, 1H, Ar-H), 6.44 (t, *J* 7.5 Hz, 1H, Ar-H), 4.52 (q, *J* 7.1 Hz, 2H, NCH_2), 3.78 -3.82 (m, 2H, CH_2), 3.40-3.42 (m, 1H, CH), 2.33 (s, 3H, NMe), 0.94 (t, *J* 7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.0 (C, N-C=O), 177.6 (C, N-C=O), 148.4 (C), 143.5 (C), 142.1 (C), 141.0 (CH), 136.3 (CH), 130.2 (CH), 129.1 (CH), 128.9 (CH), 128.5 (CH), 127.6 (CH), 124.9 (C), 124.8 (CH), 124.4 (C), 123.1 (CH), 122.2 (CH), 122.0 (CH), 109.9 (C), 108.0 (CH), 79.6 (C), 64.1 (C), 57.2 (CH_2), 49.7 (CH_2), 35.6 (NCH_3), 35.1 (CH), 12.8 (CH_3). MS (GC, 70eV): *m/z* (%) = 468 (M^+, 2), 294 (21), 279 (13), 174 (100). HRMS (ESI): calcd for $C_{27}H_{25}N_4O_4$ (M+H) 469.1870, found 469.1878.

(3R*,3′′S*,4′R*)-1′′-Ethyl-1′-methyl-4′-(4-methylphenyl)dispiro[indole-3,2′-pyrrolidine-3′,3′′-indole]-2,2′′(1*H*,1′′*H*)-dione (8f). White solid, yield 92% (402 mg); mp 205-207 °C. IR (KBr, ν, cm^{-1}): 3231 (m), 1712 (s), 1699 (s), 1609 (s), 1467 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (s, 1H, NH), 7.58 (d, *J* 7.5 Hz, 1H, Ar-H), 7.12-7.16 (m, 3H, Ar-H), 7.00-7.02 (m, 1H, Ar-H), 6.93-6.96 (m, 3H, Ar-H), 6.79 (d, *J* 7.6 Hz, 1H, Ar-H), 6.59 (d, *J* 7.6 Hz, 1H, Ar-H), 6.43-6.47 (m, 2H, Ar-H), 4.48 (m, 2H, NCH_2), 3.70-3.83 (m, 2H, CH_2), 3.37-3.44 (m, 1H, CH), 2.34 (s, 3H, NCH_3), 2.25 (s, 3H, NCH_3), 0.94 (t, *J* 7.2 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.3 (C, N-C=O), 178.0 (C, N-C=O), 143.3 (C), 142.1 (C), 136.3 (C), 135.2 (C), 129.7 (CH), 129.6 (CH), 129.1 (CH), 129.0 (CH), 128.3 (CH), 127.7 (CH), 125.8 (C), 125.4 (C), 122.8 (CH), 121.7 (CH), 109.6 (CH), 107.3 (CH), 79.5 (C), 64.6 (C), 57.3 (CH_2), 49.7 (CH), 35.8 (NCH_3), 34.9 (CH_2), 21.4 (CH_3), 12.8 (CH_3). MS (GC, 70eV): *m/z* (%) = 437 (M^+, 3), 291 (8), 263 (30), 174 (100). HRMS (ESI): calcd for $C_{28}H_{28}N_3O_2$ (M+H) 438.2176, found 438.2182.

(3R*,3′′S*,4′R*)-4′-(4-Chlorophenyl)-1′′-ethyl-1′-methyldispiro[indole-3,2′-pyrrolidine-3′,3′′-indole]-2,2′′(1*H*,1′′*H*)-dione (8g). White solid, yield 95% (435 mg); mp 209-211 °C. IR (KBr, ν, cm^{-1}): 3274 (m), 1709 (s), 1682 (s), 1606 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (s, 1H, NH), 7.44 (d, *J* 7.6 Hz, 1H, Ar-H), 7.19 (d, *J* 8.4 Hz, 2H, Ar-H), 7.08 (d, *J* 8.4 Hz, 2H, Ar-H), 7.05 (t, *J* 7.6 Hz, 1H, Ar-H), 6.97 (t, *J* 7.6 Hz, 1H, Ar-H), 6.88 (t, *J* 7.6 Hz, 1H, Ar-H), 6.80 (d, *J* 7.6 Hz, 1H, Ar-H), 6.55 (d, *J* 7.7 Hz, 1H, Ar-H), 6.52 (t, *J* 7.7 Hz, 1H, Ar-H), 6.47 (d, *J* 7.7 Hz, 1H, Ar-H), 4.46 (t, *J* 8.5 Hz, 1H, CH), 4.37 (t, *J* 8.0 Hz, 1H, CH_2), 3.72-3.79 (m, 1H, NCH_2), 3.66 (t, *J* 8.0 Hz, 1H, CH_2), 3.34-3.41 (m, 1H, NCH_2), 2.29 (s, 3H, NMe), 0.90 (t, *J* 7.2 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.1 (C, N-C=O), 182.0 (C, N-C=O), 148.2 (C), 144.2 (C), 142.1 (C), 137.2 (C), 137.1(CH), 136.0 (C), 134.5 (CH), 133.7 (CH), 133.3 (CH), 133.0 (CH), 131.8 (CH), 130.0 (C), 126.8 (CH), 126.3 (CH), 114.6 (CH), 112.3 (CH), 83.9 (C), 68.9 (C), 62.1 (CH_2), 54.3 (NCH_3), 40.4 (CH), 39.6 (CH_2), 17.5 (CH_3). MS (GC, 70eV): *m/z* (%) = 457 (M^+, 3), 291 (16), 283 (15), 175 (14), 174 (100), 159 (12). HRMS (ESI): calcd for $C_{27}H_{25}ClN_3O_2$ (M+H) 458.1629, found 458.1639.

(3R*,3′′S*,4′R*)-1′′-Ethyl-4′-(4-hydroxyphenyl)-1′-methyldispiro[indole-3,2′-pyrrolidine-3′,3′′indole]-2,2′′-(1*H*,1′′*H*)-dione (8h). Pale brown solid, yield 88% (387 mg); mp 217-219 °C. IR (KBr, ν, cm^{-1}): 3516 (m), 3252 (w), 1697 (s), 1681 (s), 1610 (s), 1467 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.10 (s, 1H, OH), 7.84 (s, 1H, NH), 7.52 (d, *J* 7.5 Hz, 1H, Ar-H), 7.31 (d, *J* 8.0 Hz, 1H, Ar-H), 6.86 (t, *J* 7.6 Hz ,1H, Ar-H), 6.69-6.73 (m, 3H, Ar-H), 6.63 (t, *J* 7.4 Hz, 1H, Ar-H), 6.39 (d, *J* 7.8 Hz, 1H, Ar-H), 6.31 (d, *J* 7.6 Hz, 1H, Ar-H), 6.20-6.24 (m, 3H, Ar-H), 4.40 (m, 2H, CH_2), 3.43-3.52 (m, 3H, CH_2, CH), 2.12 (s, 3H, NMe), 0.73 (t, *J* 7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.9 (C, N-C=O), 177.3 (C, N-C=O), 156.0 (C), 144.0 (C), 143.3 (C), 129.3 (CH), 128.4 (CH), 127.5 (CH), 127.3 (CH), 127.0 (CH), 126.4 (C), 125.6 (C), 125.5 (C), 120.5 (CH), 118.8 (CH), 114.5 (CH), 109.4 (CH), 106.5 (CH), 79.0 (C), 63.5 (C), 57.7 (CH_2), 42.8 (CH), 35.7 (NCH_3), 34.4 (CH_2), 12.5 (CH_3). MS (GC, 70eV): *m/z* (%) = 439 (M^+, 6), 368 (9), 174 (100), 159 (11), 111 (15). HRMS (ESI): calcd for $C_{27}H_{26}N_3O_3$ (M+H) 440.1968, found 440.1968.

(3R*,3′′S*,4′R*)-4′-(4-Bromophenyl)-1′′-ethyl-1′-methyldispiro[indole-3,2′-pyrrolidine-3′,3′′-indole]-2,2′′-(1*H*,1′′*H*)-dione (8i). White solid, yield 97% (487 mg); mp 216-218 °C. IR (KBr, ν, cm^{-1}): 3269 (m), 1709 (s), 1681 (s), 1606 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, *J* 7.4 Hz,1H, Ar-H), 7.26 (s, 1H, NH), 7.16-7.20 (m, 2H, Ar-H), 7.02-7.08 (m, 3H, Ar-H), 6.91 (tt, *J* 7.7 Hz, 1.4 Hz, 2H, Ar-H), 6.69 (dd, 1H, *J* 7.7 Hz, 0.7 Hz, Ar-H), 6.39-6.50 (m, 3H, Ar-H), 4.32-4.36 (m, 2H, CH_2), 3.61-3.77 (m, 2H, NCH_2, CH), 3.24-3.36 (m, 1H, NCH_2), 2.25 (s, 3H, NCH_3), 0.83 (t, *J* 7.3 Hz, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 177.8 (C, N-C=O), 176.9 (C, N-C=O), 143.0 (C), 141.4 (C), 137.1 (C), 131.2 (CH), 131.0 (CH), 129.5 (CH), 128.4 (CH), 128.2 (CH), 127.2 (CH), 125.0 (C), 124.5 (C), 122.6 (CH), 121.5 (CH), 120.6 (C), 109.2 (CH), 107.3 (CH), 78.9 (C), 64.0 (C), 56.9 (CH_2), 49.1 (CH), 35.3 (NCH_3), 34.6 (CH_2), 12.4 (CH_3). MS (GC, 70eV): *m/z* (%) = 501 (M^+, 1), 329 (27), 327 (27), 174 (100), 159 (24). HRMS (ESI): calcd for $C_{27}H_{25}BrN_3O_2$ (M+H) 502.1130, found 502.1133.

(3R*,3′′S*,4′R*)-1′-Methyl-4′-(4-methylphenyl)-1′′-phenyldispiro[indole-3,2′-pyrrolidine-3′,3′′-indole]-2,2′′-(1*H*,1′′*H*)-dione (8j). Pale yellow solid, yield 90% (437 mg); mp 227-228 °C. IR (KBr, ν, cm^{-1}): 3263 (m), 1721 (s), 1703 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (s, 1H, NH), 7.52 (d, *J* 7.5 Hz, 1H, Ar-H), 7.40 (t, *J* 7.5 Hz, 2H, Ar-H), 7.34 (t, *J* 7.3 Hz, 1H, Ar-H), 7.15-7.22 (m, 3H, Ar-H), 6.94-7.02 (m, 5H, Ar-H), 6.79-6.82 (m, 2H, Ar-H), 6.59 (d, *J* 7.6 Hz, 1H, Ar-H), 6.45-6.48 (m, 1H, Ar-H), 6.28 (d, *J* 8.0 Hz, 1H, Ar-H), 4.53-4.60 (m, 1H, CH), 3.71-3.74 (m, 2H, CH_2), 2.34 (s, 3H, NMe), 2.24 (s, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.5 (C, N-C=O), 178.1 (C, N-C=O), 144.5 (C), 142.3 (C), 136.5 (C), 135.0 (C), 134.8 (C), 129.9 (CH), 129.8 (CH), 129.7 (CH), 129.1 (CH), 129.0 (CH), 128.5 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 125.5 (C), 124.9 (C), 122.9 (CH), 122.2 (CH), 109.7 (CH), 108.6 (CH), 79.8 (C), 65.1 (C), 57.3 (CH_2), 49.8 (NCH_3), 35.8 (CH), 21.5 (CH_3). MS (GC, 70eV): *m/z* (%) = 485 (M^+, 1), 312 (22), 311 (100), 310 (51), 174 (90). HRMS (ESI): calcd for $C_{32}H_{28}N_3O_2$ (M+H) 486.217, found 486.2180.

(3R*,3′′S*,4′R*)-4′-(4-Methoxyphenyl)-1′-methyl-1′′-phenyldispiro[indole-3,2′-pyrrolidine-3′,3′′-indole]-2,2′′(1*H*,1′′*H*)-dione (8k). Bold yellow solid, yield 86% (431 mg); mp 215-217 °C. IR (KBr, ν, cm^{-1}): 3235 (m), 1712 (s), 1696 (s), 1609 (m), 1511 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (s, 1H, Ar-H), 7.56 (d, *J* 7.5 Hz, 1H, Ar-H), 7.45 (t, *J* 7.3 Hz ,2H, Ar-H), 7.37-7.40 (m, 1H, Ar-H), 7.27-7.30 (m, 2H, Ar-H), 7.21 (t, *J* 7.5 Hz, 1H, Ar-H), 7.00-7.04 (m, 3H, Ar-H), 6.85-6.90 (m, 2H, Ar-H), 6.75 (d, *J* 8.6 Hz, 2H, Ar-H), 6.63 (d, *J* 7.6 Hz, 1H, Ar-H), 6.56 (t, *J* 7.6 Hz, 1H, Ar-H), 6.34 (d, *J* 7.7 Hz, 1H, Ar-H), 4.60 (dd, *J* 9.2, 8.7 Hz, 1H, CH_2), 4.52 (dd, *J* 9.3, 9.2 Hz, 1H, CH_2), 3.77-3.80 (m, 4H, OMe, CH), 2.38 (s, 3H, NCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.0 (C, N-C=O), 177.1 (C, N-C=O), 158.7 (C), 144.4 (C), 142.0 (C), 134.9 (C), 130.9 (CH), 130.2 (C), 129.9 (CH), 129.7 (CH), 129.0 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.6 (CH), 125.6 (C), 124.9 (C), 123.0 (CH), 122.3 (CH), 113.8 (CH), 109.6 (CH), 108.6 (CH), 79.8 (C), 65.1 (C), 57.6 (CH_2), 55.4 (OCH_3), 49.5 (CH), 35.8 (NCH_3). MS (GC, 70eV): *m/z* (%) = 501 (M^+, 2), 328 (47), 327 (100), 326 (57), 284 (29), 174 (99). HRMS (ESI): calcd for $C_{32}H_{28}N_3O_3$ (M+H) 502.2125, found 502.2121.

(3R*,3′′S*,4′R*)-4′-(4-Chlorophenyl)-1′-methyl-1′′-phenyldispiro[indole-3,2′-pyrrolidine-3′,3′′-indole]-2,2′′(1*H*,1′′*H*)-dione (8l). Pale gray solid, yield 94% (476 mg); mp 214-216 °C. IR (KBr, ν, cm^{-1}): 3245 (m), 1708 (s), 1688 (s), 1608 (m), 1493 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (s, 1H, NH), 7.42 (d, *J* 7.4 Hz, 1H, Ar-H), 7.33 (t, *J* 7.3 Hz, 2H, Ar-H), 7.28 (d, *J* 7.3 Hz, 1H, Ar-H), 7.19 (d, *J* 7.8 Hz, 2H, Ar-H), 7.07-7.12 (m, 3H, Ar-H), 6.87-6.92 (m, 3H, Ar-H), 6.77 (t, *J* 7.4 Hz, 1H, Ar-H), 6.68 (d, *J* 7.2 Hz, 1H, Ar-H), 6.51 (d, *J* 7.7 Hz, 1H, Ar-H), 6.39 (t, *J* 7.6 Hz, 1H, Ar-H), 6.23 (d, *J* 7.8 Hz, 1H, Ar-H), 4.40-4.48 (m, 2H, CH_2), 3.60-3.67 (m, 1H, CH), 2.25 (s, 3H, NMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.0 (C, N-C=O), 178.0 (C, N-C=O), 144.5 (C), 142.3(C) , 136.9 (C), 134.7 (C), 133.0 (C), 131.3 (CH), 130.1 (CH), 129.8 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 127.5 (CH), 125.3 (C), 124.5 (C), 123.0 (CH), 122.4 (CH), 109.8 (CH), 108.8 (CH), 79.8 (C), 64.9 (C), 57.3(CH_2), 49.5(CH), 35.7(NCH_3). MS (GC, 70eV): *m/z* (%) = 505 (M^+, 1), 331 (79), 267 (35), 220 (46), 175 (32), 174 (100). HRMS (ESI): calcd for $C_{31}H_{25}N_3O_2$ (M+H) 506.1629, found 506.1627.

Acknowledgements

We gratefully acknowledge financial support from the Research Council of University of Qom.

References

1. Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. http://dx.doi.org/10.1021/cr050011g
2. Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. http://dx.doi.org/10.1021/cr040004c
3. Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. http://dx.doi.org/10.1021/cr970324e
4. Lashgari, N.; Ziarani, G. M. *Arkivoc* **2012**, (*i*), 277. http://dx.doi.org/10.3998/ark.5550190.0013.108
5. Rajesh, R.; Raghunathan R. *Tetrahedron Lett.* **2010**, *51*, 5845. http://dx.doi.org/10.1016/j.tetlet.2010.09.002
6. Ghandi, M.; Taheri, A.; Abbasi A. *Tetrahedron* **2010**, *66*, 6744. http://dx.doi.org/10.1016/j.tet.2010.06.078
7. Lakshmi, N. V.; Thirumurugan, P.; Jayakumar, C.; Perumal P. T. *Synlett* **2010**, *6*, 955.
8. Bergman, J. *Adv. Heterocycl. Chem.* **2015**, *117*, 1. http://dx.doi.org/10.1016/bs.aihch.2015.08.001
9. Edmondson, S. D.; Danishefsky, S. J. *Angew. Chem.* **1998**, *110*, 1190. http://dx.doi.org/10.1002/(SICI)1521-3757199804201110:8<1190::AID-ANGE1190>3.0.CO;2-S
10. Hussein, E. M.; Abdel-Monem, M. I. *Arkivoc* **2011**, (*x*), 85. http://dx.doi.org/10.3998/ark.5550190.0012.a07
11. Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. http://dx.doi.org/10.1002/anie.200701342
12. Trost, B.; Brennan, M. K. *Synthesis* **2009**, 3003.
13. Millemaggi, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2010**, 4527. http://dx.doi.org/10.1002/ejoc.201090064
14. Colegate, S. M.; Anderton, N.; Edgar, J.; Bourke, C. A.; Oram, R. N. *Aust. Vet. J.* **1999**, *77*, 537.
15. Kornet, M. J.; Thio, A. P. *J. Med. Chem.* **1976**, *19*, 892. http://dx.doi.org/10.1021/jm00229a007
16. Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2006**, *49*, 3432. http://dx.doi.org/10.1021/jm051122a
17. Yu, S.; Qin, D.; Shangary, S.; Chen, J.; Wang, G.; Ding, K.; McEachern, D.; Qiu, S.; Nikolovska-Coleska, Z.; Miller, R.; Kang, S.; Yang, D.; Wang, S. *J. Med. Chem.* **2009**, *52*, 7970. http://dx.doi.org/10.1021/jm901400z
18. Garnick, R. L.; LeQuesne, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4213. http://dx.doi.org/10.1021/ja00481a034
19. Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527. http://dx.doi.org/10.1021/jo00023a016

20. Dideberg, O.; Lamotte-Brasseur, J.; Dupont, L.; Campsteyn, H.; Vermeire, M.; Angenot, L.; *Acta Crystallogr. Sect. B* **1977**, *33*, 1796. http://dx.doi.org/10.1107/S0567740877007080
21. Abou-Gharbia, M. A.; Doukas, P. H. *Heterocycles* **1979**, *12*, 637.
22. Ziarani, G. M.; Moradi, R.; Lashgari, N. *Arkivoc* **2016**, (*i*), 1. http://dx.doi.org/10.3998/ark.5550190.p009.385
23. Liu, J.; Sun, H.; Liu, X.; Ouyang, L.; Kang, T.; Xie, Y.; Wang, X. *Tetrahedron Lett.* **2012**, *53*, 2336. http://dx.doi:10.1016/j.tetlet.2012.02.099
24. Velikorodov, A. V.; Poddubnyi, O. Yu.; Krivosheev, O. O.; Titova, O. L. *Russ. J. Org. Chem.* **2011**, *47*, 402. http://dx.doi:10.1134/S1070428011030122
25. Lakshmi, N. V.; Thirumurugan, P.; Perumal P. T. *Tetrahedron Lett.* **2010**, *51*, 1064. http://dx.doi:10.1016/j.tetlet.2009.12.079
26. Kandrthikeyan, K.; Saranya, N.; Kalaivani, A.; Perumal P. T. *Synlett* **2010**, *18*, 2751.
27. Babu, A. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 305. http://dx.doi:10.1016/j.tetlet.2006.11.012
28. Shanmugam, P.; Viswambharan, B.; Madhavan, S. *Org. Lett.* **2007**, *9*, 4095. http://dx.doi:10.1021/ol701533d
29. Shanmugam, P.; Viswambharan, B.; Selvakumar, K.; Madhavan, S. *Tetrahedron Lett.* **2008**, *49*, 2611. http://dx.doi:10.1016/j.tetlet.2008.02.104
30. Muthusamy, S.; Kumar, S. G. *Tetrahedron* **2016**, *72*, 2392. http://dx.doi.org/10.1016/j.tet.2016.03.046
31. Liu, Y.-Y.; Duan, S.-W.; Zhang, R.; Liu, Y.-H.; Chen, J.-R.; Xiao, W.-J. *Org. Biomol. Chem.* **2016**, *14*, 5224. http://dx.doi. 10.1039/C6OB00891G
32. Ziarani, G. M.; Moradi, R.; Lashgari, N. *Tetrahedron: Asymmetry* **2015**, *26*, 517. http://dx.doi.org/10.1016/j.tetasy.2015.04.011
33. Babu, A. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 6809. http://dx.doi:10.1016/j.tetlet.2007.07.085
34. Habibi, D.; Nasrollahzadeh, M.; Sahebekhtiari H.; Parish, R. V. *Tetrahedron* **2013**, *69*, 3082. http://dx.doi.org/10.1016/j.tet.2013.01.069
35. Bazgir, A.; Ahadi, S.; Ghahremanzadeh, R.; Khavasi, H. R.; Mirzaei, P. *Ultrason. Sonochem.* **2010**, *17*, 447. http://dx.doi.org/10.1016/j.ultsonch.2009.09.009
36. Jose, L.; Ruano, G.; Parra, A.; Marzo, L.; Yuste, F.; Mastranzo, V. M *Tetrahedron* **2011**, *67*, 2905. http://dx.doi.org/10.1016/j.tet.2011.02.060
37. Ruiz, E.; Rodriguez, H.; Coro, J.; Salfran, E.; Suarez, M.; Martinez-Alvarez, R.; Martin, N. *Ultrason. Sonochem*. **2011**, *18*, 32. http://dx.doi.org/10.1016/j.ultsonch.2010.04.009
38. Said, K.; Moussaoui, Y.; Kammoun, M.; Salem, R. B. *Ultrason. Sonochem*. **2011**, *18*, 23. http://dx.doi.org/10.1016/j.ultsonch.2010.04.007
39. Cella, R.; Stefani, H. A. *Tetrahedron* **2009**, *65*, 2619. http://dx.doi.org/10.1016/j.tet.2008.12.027
40. Fan, G.; Luo, S.; Wu, Q.; Fang, T.; Li, J.; Song, G. *RSC Adv.* **2015**, *5*, 56478. http://dx.doi.org/10.1039/C5RA07431B
41. Moghaddam, F. M.; Kiamehr, M.; Khodabakhshi, M. R.; Javan, M. J.; Fathi, S.; Villinger, A.; Iaroshenko, V. O.; Langer, P.; *Helv. Chim. Acta* **2013**, *96*, 2103.

42. Moghaddam, F. M.; Khodabakhshi, M. R.; Kiamehr, M.; Ghahremannejad, Z. *Tetrahedron Lett.* **2013**, 54, 2685.
http://dx.doi.org/10.1016/j.tetlet.2013.03.070
43. Kiamehr, M.; Moghaddam, F. M.; Gormay, P. V.; Semeniuchenko, V.; Villinger, A.; Langer, P.; Iaroshenko, V. O. *Tetrahedron* **2012**, *68*, 9685.
http://dx.doi.org/10.1016/j.tet.2012.09.059
44. Kiamehr, M.; Moghaddam, F. M. *Tetrahedron Lett.* **2009**, *50*, 6723.
http://dx.doi.org/10.1016/j.tetlet.2009.09.106
45. Moghaddam, F. M.; Kiamehr, M. *Monatsh Chem* **2010**, *141*, 1333.
http://dx.doi.org/10.1007/s00706-010-0406-1
46. Ziarani, G. M.; Gholamzadeh, P.; Lashgari, N. Hajiabbasi, P. *Arkivoc* **2013**, (*i*), 470.
http://dx.doi.org/10.3998/ark.5550190.p008.074
47. Sun, L.; Tran, N.; Tang, F.; App, H.; Hirth, P.; McMahon, G.; Tang, C. *J. Med. Chem.* **1998**, *41*, 2588.
http://dx.doi.org/10.1021/jm980123i
48. Andreani, A.; Burnelli, S.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.; Kunkel, M. W. *J. Med. Chem.* **2006**, *49*, 6922.
http://dx.doi.org/10.1021/jm0607808
49. Crystallographic data for **8i** have been deposited in the Cambridge Crystallographic Data Centre with the deposition number CCDC 827753. Copies of data can be obtained free of charge via www.ccdc.ca-m.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).
50. Amornraksa, K.; Grigg, R.; Gunaratna, H. Q. N.; Kemp, J.; Sridharan, V. *J. Chem. Soc., Perkin Trans.* **1987**, *1*, 2285.
http://dx.doi.org/10.1039/P19870002285

