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A convenient regioselective synthesis of spirooxindolinopyrrolizidines incorporating the pyrene moiety through a [3 + 2]-cycloaddition reaction

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Abstract: A facile one-pot synthesis of spirooxindolinopyrrolizidines incorporating the pyrene moiety was accomplished in good yields through a 1,3-dipolar cycloaddition reaction of 3-aryl-1-(pyren-1-yl)prop-2-en-1-one derivatives with *in situ*-generated azomethine ylides.

Keywords: azomethine ylide; cycloaddition; oxindolinopyrrolizidines; pyrene; spiroheterocycles.

Introduction

The pyrene moiety is one of the most useful scaffolds for the construction of fluorogenic chemosensors for a diversity of important chemical species [1]. Multi-component 1,3-dipolar cycloaddition reactions are useful processes for building five-membered heterocyclic ring systems [2–8]. The azomethine ylides are reactive and versatile classes of 1,3-dipoles that can be readily trapped by many dipolarophiles [9–12] to construct pyrrolidine, pyrrolizine and pyrrolothiazole derivatives. Such compounds are important bioactive agents that have glucosidase inhibitory activity as well as potent anti-inflammatory, antibacterial, antiviral, antidiabetic, anticancer and antitubercular activities [13–17]. However, there is little published work regarding the synthesis of spiroheterocyclic compounds which incorporate the pyrene moiety. Herein, in continuation of our previous work on the synthesis of bioactive spiroheterocycles [17–23], we report for the first time a convenient protocol for the synthesis of novel pyrene-incorporated spirooxindolinopyrrolizidines **6a–j** via a 1,3-dipolar cycloaddition reaction involving the olefin segment of 3-aryl-1-(pyren-1-yl)prop-2-en-1-ones **3a–e** and azomethine ylides that are generated by the decarboxylative condensation of indoline-2,3-diones **4a,b** and proline (**5**). The generated azomethine ylides undergo the reaction with the dipolarophiles 3-aryl-1-(pyren-1-yl)prop-2-en-1-ones **3a–e** regioselectively.

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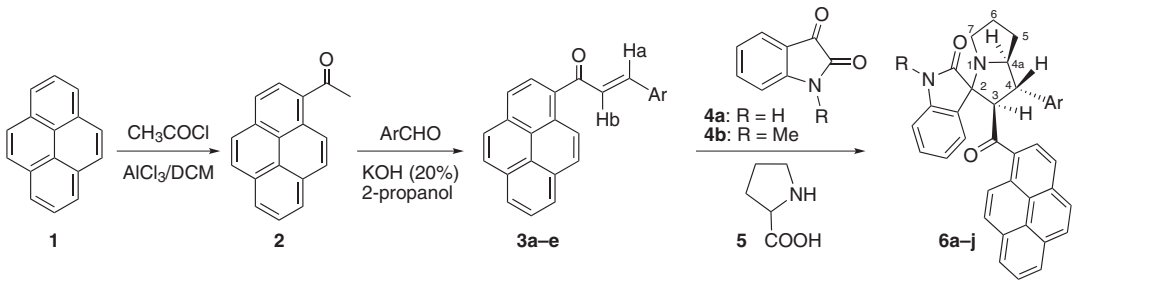
Results and discussion

The synthetic route to 3-aryl-1-(pyren-1-yl)prop-2-en-1-ones **3a–e** is presented in Scheme 1. Acetylpyrene (**2**) was synthesized from pyrene by the classical Friedel-Crafts reaction according to the previously reported procedure with some modifications [1]. The dipolarophiles (*E*)-3-aryl-1-(pyren-1-yl)prop-2-en-1-ones **3a–e** were obtained in good to excellent yields (75%–89%) through the Claisen-Schmidt condensation of acetylpyrene and aromatic aldehydes, namely benzaldehyde, 4-methoxybenzaldehyde, 4-(dimethylamino)-benzaldehyde, 4-chlorobenzaldehyde and 4-nitrobenzaldehyde in 2-propanol in the presence of potassium hydroxide as a catalyst. The chemical structures of compounds **3a–e** were confirmed using spectroscopic and analytical tools.

In the preliminary work, a three-component reaction of (*E*)-3-phenyl-1-(pyren-1-yl)prop-2-en-1-one (**3a**), 1*H*-indoline-2,3-dione (**4a**) and proline (**5**) in various solvents including acetonitrile, ethanol, methanol, 2-propanol, dioxane and toluene under reflux conditions was investigated. The desired product **6a** was obtained in good yields of up to 70% and 79% with a comparatively short reaction time (5 h) when the reaction was carried out in ethanol and methanol, respectively. Moderate yields of 61% and 66% were obtained when acetonitrile and 2-propanol were used, respectively. The yield decreased and a longer reaction time (7–8 h) was required for the reaction conducted in dioxane or toluene. This result is consistent with a polar transition state that is stabilized in polar solvents.



3a: Ar = Ph
3b: Ar = 4-MeO-C_6H_4
3c: Ar = 4-$(CH_3)_2NC_6H_4$
3d: Ar = 4-Cl-C_6H_4
3e: Ar = 4-O_2N-C_6H_4

6a: R = H; Ar = Ph (79%)
6b: R = H; Ar = 4-MeO-C_6H_4 (76%)
6c: R = H; Ar = 4-$(CH_3)_2N$-C_6H_4 (74%)
6d: R = H; Ar = 4-Cl-C_6H_4 (77%)
6e: R = H; Ar = 4-O_2N-C_6H_4 (84%)

6f: R = Me; Ar = Ph (79%)
6g: R = Me; Ar = 4-MeO-C_6H_4 (75%)
6h: R = Me; Ar = 4-$(CH_3)_2N$-C_6H_4 (70%)
6i: R = Me; Ar = 4-Cl-C_6H_4 (76%)
6j: R = Me; Ar = 4-O_2N-C_6H_4 (82%)

Scheme 1 Synthesis of compounds **6a–j**.

A series of novel pyrene-substituted spirooxindolinopyrrolizidines were synthesized by the reaction of various (*E*)-3-aryl-1-(pyren-1-yl)prop-2-en-1-ones **3a–e** with azomethine ylides generated from 1*H*-indoline-2,3-dione (**4a**) or *N*-methylindoline-2,3-dione (**4b**) and proline (**5**). Under optimized conditions, the reaction proceeds smoothly to afford spiro[2.3′]-oxindoline-4-aryl-3-(1-pyrenoyl)pyrrolizidine **6a–j** in good yields (74%–84%).

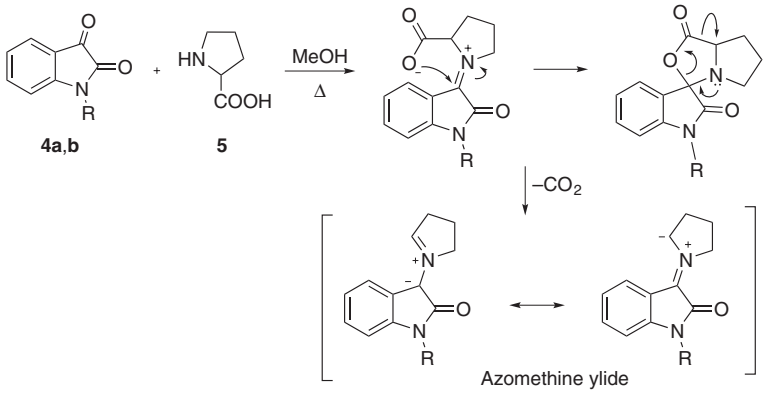
As suggested in Scheme 2, the reaction proceeds through the generation of an azomethine ylide via the decarboxylative condensation of indoline-2,3-diones **4a,b** with proline (**5**).

Although two diastereomers were obtained in each case, the reaction is regioselective, with the transition state suggested in Scheme 3. The regioselectivity in the product formation can be explained by considering a secondary interaction of the orbital of the carbonyl group of dipolarophile **3a–e** with those of the azomethine ylide as shown in Scheme 3 [24].

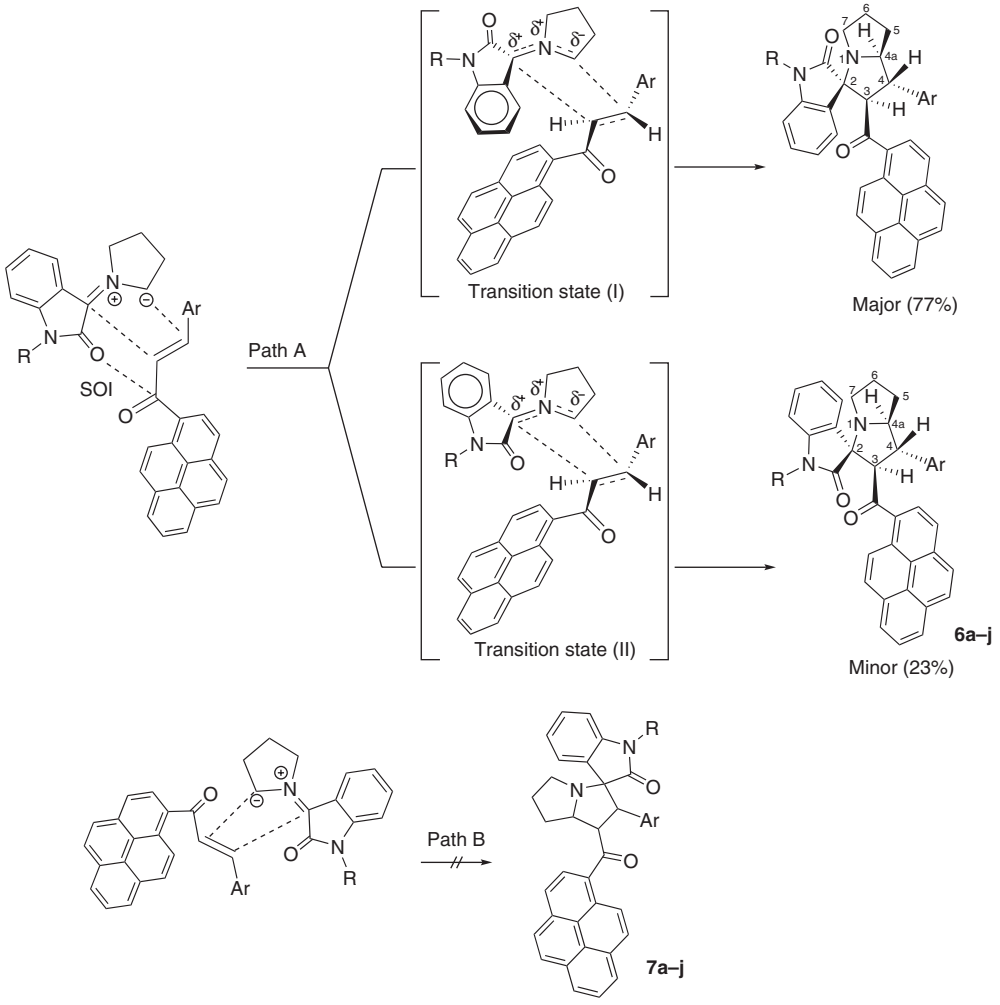
Accordingly, the observed regioisomer, spiro[2.3′]-oxindoline-4-(aryl)-3-pyrenoyl-pyrrolizidine **6a–j**, is formed via path A, the transition states I and II of which are more favorable than the alternative transition state that would lead to hypothetical product **7a–j**. In addition, favorable secondary orbital interactions can be suggested for path A, which are not possible in path B.

The formation of two diastereoisomeric products is consistent with the results of the theoretical studies using GAMESS interface v.11.0. (CambridgeSoft). The calculation showed that the major diasteromer (77%) with a lower total energy of –3.0552 kcal mol^{-1} and heat of formation of $\Delta H = 56.0714$ kcal mol^{-1} is formed through transition state I, in which two carbonyl groups linked to *C*-2 and *C*-3 are *anti* to each other. This arrangement is translated into *trans* stereochemistry in the cycloadduct **6**. By contrast, the two carbonyl groups are *syn* to each other in transition state II, leading to the minor diasteromer (23%) with higher total energy and heat of formation due to electrostatic repulsion between the *cis* carbonyl groups (Scheme 3) [25].

As indicated by the analysis of the ^{1}H NMR data, the products **6a–j** are mixtures of diastereomers in the ratio of 77:23 in each case. Some of the proton signals of the minor stereoisomers overlap with the NMR signals of the major diastereomers. Due to this spectral complexity,



Scheme 2 Formation of azomethine ylide.



Scheme 3 Transition states and stereochemistry of the cycloadducts **6a–j**.

the given NMR data are for the major isomers. Signals of the methine protons attached to the stereogenic centers proved helpful in assigning relative stereochemistry. In particular, the ^{1}H NMR and two-dimensional (2D) correlation studies (COSY, HSQC, HMBC) of **6b** enabled an accurate identification of the methine protons that resonate as a doublet at 5.23 ppm (J = 14.1 Hz) for the downfield 3-CH proton. The 4-CH proton exhibits a triplet at 4.00 ppm (J = 14.1 Hz), whereas the 4a-CH proton exhibits a broad multiplet in the region of 3.91–3.93 ppm. The observed coupling constant value between the vicinal methine protons clearly indicates a large dihedral angel due to vicinal *trans* protons. On the other hand, two multiplets in the regions of 1.73–1.88 ppm and 2.34–2.42 ppm for 6-CH_2, 5-CH_2 and 7-CH_2 protons can be observed. The methoxy group exhibits a singlet at 3.73 ppm. These data are consistent with the formation of a single regioisomer **6** in each case. The deshielding effect in the hypothetical regioisomer **7** would be expected to result in the formation of a doublet of doublets (dd) instead of the observed doublet for the downfield *C*-H proton of the pyrrolizidine moiety.

Analysis of the ^{13}C NMR spectrum of **6b** added conclusive support to the proposed structure. The spiro carbon resonates at 73.2 ppm. The indoline carbonyl carbon and the carbonyl carbon resonate at 179.0 and 200.1 ppm, respectively. The signals at 27.7, 30.8, 47.5, 49.1, 51.7, 55.4, and 65.9 ppm can be assigned to 6-CH_2, 5-CH_2, 7-CH_2, 4-CH, CH_3, 3-CH, 4a-CH and 3-CH carbons, respectively (see Supplementary Material).

Conclusions

Novel pyrene-bearing mono spirooxindolinopyrrolizidines were synthesized in good yields through the [3 + 2]-cycloaddition of azomethine ylides generated *in situ* via the decarboxylative condensation of indoline-2,3-dione derivatives and proline with l-pyrene dipolarophiles.

Experimental

Melting points are not corrected. FT-IR spectra were recorded on a Shimadzu IR-3600 spectrometer in KBr pellets. ^{1}H NMR spectra (500 MHz) and ^{13}C NMR spectra (125 MHz) were recorded on a Bruker Avance 500 spectrometer in chloroform-*d* or dimethyl sulfoxide–d_6. Elemental analyses (C, H, N and Cl) were performed on a Vario EL V2.3 analyzer.

Synthesis of the dipolarophiles 3-aryl-1-(pyren-1-yl)prop-2-en-1-ones 3a–e

A 50-mL round-bottom flask was charged with acetylpyrene (244 mg, 1.0 mmol), the appropriate aromatic aldehyde [benzaldehyde, 4-methoxybenzaldehyde, 4-(dimethylamino)-benzaldehyde, 4-chlorobenzaldehyde or 4-nitrobenzaldehyde, 1 mmol each], 2-propanol (10 mL) and aqueous KOH (20%). The mixture was stirred at room temperature for 1.5–3 h (monitored by TLC using CH_2Cl_2 as an eluent). The formed precipitate was filtered off, dried and crystallized from 2-propanol to afford chalcone **3a–e**.

3-Phenyl-1-(pyren-1-yl)prop-2-en-1-ones (3a) 80% yield of orange crystals; mp 215–217°C; IR: ύ 3030 (CH arom.), 1675 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.43–7.48 (m, 3H, Ph-H), 7.50 (d, 1H, H_b, J = 14.7 Hz), 7.60–7.64 (m, 2H, Ph-H), 7.68 (d, 1H, H_a, J = 14.7 Hz), 8.03–8.20 (m, 4H, pyrene-H), 8.22 (d, 1H, pyrene-H, J = 10.0 Hz), 8.24–8.30 (m, 3H, pyrene-H), 8.64 (d, 1H, pyrene-H, J = 10.0 Hz); ^{13}C NMR ($CDCl_3$): δ 120.6, 123.2, 124.4, 126.0, 126.2, 126.3, 126.8, 127.4, 127.5, 127.7, 128.5, 128.9, 129.1, 129.2, 129.4, 129.7, 130.3, 130.5, 130.7, 134.5, 146.5, 148.0, 196.0. Anal. Calcd. for $C_{25}H_{16}O$: C, 90.33; H, 4.85. Found: C, 90.45; H, 4.93.

3-(4-Methoxyphenyl)-1-(pyren-1-yl)prop-2-en-1-ones (3b) 89% yield of orange crystals; mp 196–198°C; IR: ύ 3037 (CH arom.), 1666 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.78 (s, 3H, CH_3), 6.96 (d, 2H, Ph-H, J = 10.1 Hz), 7.55–7.58 (m, 2H, H_b + pyrene-H), 7.73 (d, 2H, Ph-H, J = 10.1 Hz), 8.11 (d, 1H, H_a, J = 9.2 Hz), 8.22–8.27 (m, 3H, pyrene-H), 8.32–8.37 (m, 4H, pyrene-H), 8.56 (d, 1H, pyrene-H, J = 11.3 Hz); ^{13}C NMR ($CDCl_3$): δ 60.5, 118.8, 119.6, 129.6, 129.9, 131.1, 131.4, 131.6, 131.9, 132.4, 134.1, 134.2, 136.0, 150.6, 166.7, 199.5. Anal. Calcd. for $C_{26}H_{18}O_2$: C, 86.16; H, 5.01. Found: C, 86.30; H, 5.26.

3-(4-Dimethylaminophenyl)-1-(pyren-1-yl)prop-2-en-1-ones (3c) 75% yield of red crystals; mp 220–222°C; IR: ύ 3035 (CH arom.), 1670 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.04 (s, 6H, $2CH_3$), 6.70 (d, 2H, Ph-H, J = 10.0 Hz), 7.26 (d, 1H, H_b, J = 14.8 Hz), 7.49 (d, 2H, Ph-H, J = 10.0 Hz), 7.57 (d, 1H, H_a, J = 14.8 Hz), 8.01–8.28 (m, 8H, pyrene-H), 8.57 (d, 1H, pyrene-H, J = 11.3 Hz); ^{13}C NMR ($CDCl_3$): δ 40.2, 112.0, 122.9, 124.1, 124.5, 124.6, 124.9, 125.7, 125.8, 125.9, 126.2, 127.0, 127.2, 128.6, 129.2, 130.5, 130.8, 131.1, 132.2, 135.1, 147.5, 196.6. Anal. Calcd. for $C_{27}H_{21}NO$: C, 86.37; H, 5.64; N, 3.73. Found: C, 86.09; H, 5.70; N, 3.88.

3-(4-Chlorophenyl)-1-(pyren-1-yl)prop-2-en-1-ones (3d) 81% yield of yellow crystals; mp 200–202°C; IR: ύ 3038 (CH arom.), 1680 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.46 (d, 2H, Ph-H, J = 10.0 Hz), 8.04–8.40 (m, 9H, pyrene-H), 8.41 (d, 1H, H_b, J = 11.4 Hz), 8.64 (d, 2H, Ph-H, J = 11.1 Hz), 9.09 (d, 1H, H_b, J = 11.4 Hz); ^{13}C NMR ($CDCl_3$): δ 124.0, 124.5, 124.9, 125.0, 126.0, 126.1, 126.3, 126.4, 127.0, 127.1, 128.8, 129.1, 129.6, 130.5, 131.5, 131.9, 132.2, 133.8, 134.0, 141.9, 169.4, 202.9. Anal. Calcd. for $C_{25}H_{15}ClO$: C, 81.85; H, 4.12; Cl, 9.66. Found: C, 82.12; H, 4.40; Cl, 9.70.

3-(4-Nitrophenyl)-1-(pyren-1-yl)prop-2-en-1-ones (3e) 87% yield of pale brown crystals; mp 241–242°C; IR: ύ 3038 (CH arom.), 1685 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.52 (d, 2H, Ph-H, J = 10.0 Hz), 7.62 (d, 2H, Ph-H, J = 10.0 Hz), 7.66 (d, 1H, H_b, J = 11.4 Hz), 8.08–8.33 (m, 9H, pyrene-H), 8.71 (d, 1H, H_a, J = 11.4 Hz); ^{13}C NMR ($CDCl_3$): δ 123.6, 123.8, 124.1, 124.3, 124.4, 125.5, 126.2, 126.5, 126.7, 128.1, 128.9, 130.6, 130.9, 132.7, 142.6, 146.9, 148.6, 194.5. Anal. Calcd. for $C_{25}H_{15}NO_3$: C, 79.56; H, 4.01; N, 3.71. Found: C, 79.40; H, 4.20; N, 3.96.

General procedure for the synthesis of pyrene bearing monospiro-oxindolino- pyrrolizidines 6a–j

A mixture of the appropriate dipolarophile **3a–e** (1 mmol), **4a,b** (1.1 mmol), proline (126 mg, 1.1 mmol) and methanol (10 mL) was heated under reflux for 4–9 h. Upon completion of the reaction, as monitored by TLC using CH_2Cl_2 as the eluent, the mixture was cooled to room temperature. The resultant solid product was filtered off and crystallized from methanol.

Spiro[2.3′]oxoindoline-4-phenyl-3-(1-pyrenoyl)pyrrolizidine (6a) Pale yellow crystals; mp 180–182°C; IR: ύ 3209 (NH), 3026 (CH arom.), 2960 (CH aliph.), 1701 (C=O), 1697 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.40–2.00 (m, 4H, 6-CH_2, 5-CH_2), 2.25–2.45 (m, 2H, 7-CH_2), 3.35 (t, 1H, 4-CH, J = 11.3 Hz), 3.60–3.75 (m, 1H, 4a-CH), 5.25 (d, 1H, 3-CH, J = 11.3 Hz), 6.10–6.40 (m, 1H, Ar-H), 6.75–7.40 (m,9H, Ar-H), 7.50–7.75 (m, 2H, Ar-H), 8.00–8.50 (m, 6H, Ar-H), 10.25 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 20.5, 27.3, 30.4, 47.0, 52.0, 67.6, 72.7, 108.8, 109.3, 109.9, 120.8, 121.1, 123.5, 124.4, 125.9, 126.6, 127.2, 127.8, 128.7, 128.9, 129.0, 129.9, 130.6, 132.1, 133.0, 140.3, 142.3, 142.7, 178.5, 203.4. Anal. Calcd. for $C_{37}H_{28}N_2O_2$: C, 83.43; H, 5.30; N, 5.26. Found: C, 83.66; H, 5.45; N, 5.15.

Spiro[2.3′]oxoindoline-4-(4-methoxyphenyl)-3-(1-pyrenoyl) pyrrolizidine (6b) Orange crystals; mp 166–167°C; IR: ύ 3030 (CH arom.), 2945 (CH aliph), 1708 (C=O), 1676 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.73–1.88 (m, 4H, 5-CH_2, 6-CH_2), 2.34–2.42 (m, 2H, 7-CH_2), 3.73 (s, 3H, CH_3), 3.91–3.93 (m, 1H, 4a-CH), 4.00 (t, 1H, 4-CH, J = 14.1 Hz), 5.23 (d, 1H, 3-CH, J = 14.1 Hz), 6.97 (d, 2H, Ph-H, J = 10.0 Hz), 7.09–7.15 (m, 2H, indoline-H), 7.24 (d, 2H, Ph-H, J = 10.0 Hz), 7.59–7.81 (m, 2H, indoline-H), 8.07–8.32 (m, 9H, pyrene-H), 9.61 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 27.7, 30.8, 47.5, 49.1, 51.7, 55.4, 65.9, 73.2, 110.3, 114.5, 121.6, 124.1, 124.5, 126.3, 126.9, 127.0, 128.6, 129.2, 132.7, 133.5, 142.4, 158.5, 179.0, 200.1. Anal. Calcd. for $C_{38}H_{30}N_2O_3$: C, 81.12; H, 5.37; N, 4.98. Found: C, 81.00; H, 5.58; N, 4.70.

Spiro[2.3′]oxoindoline-4-(4-dimethylaminophenyl)-3-(1-pyrenoyl)pyrrolizidine (6c) Orange crystals; mp 174–176°C; IR: ύ 3206 (NH), 3035 (CH arom.), 2957 (aliph.), 1701 (C=O), 1697 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.25–2.05 (m, 4H, 6-CH_2, 5CH_2), 2.38–2.40 (m, 2H, 7-CH_2), 2.52 (t, 1H, 4-CH, J = 11.4 Hz), 3.52 (s, 6H, $2CH_3$), 3.75–3.95 (m, 1H, 4a-CH), 5.30 (d, 1H, 3-CH, J = 11.4 Hz), 7.04–7.96 (m, 8H, Ar-H), 8.00–8.41 (m, 9H, Ar-H), 10.24 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 27.6, 30.4, 47.4, 52.1, 65.6, 72.4, 73.3, 76.1, 110.3, 121.9, 124.1, 124.8, 126.3, 126.9, 127.1, 127.6, 127.7, 128.7, 129.9, 130.1, 130.9, 133.6, 134.2, 142.1, 146.8, 148.9, 149.3, 179.3, 199.8. Anal. Calcd. for $C_{39}H_{33}N_3O_2$: C, 81.37; H, 5.78; N, 7.30. Found: C, 81.45; H, 5.82; N, 7.61.

Spiro[2.3′]oxoindoline-4-(4-chlorophenyl)-3-(1-pyrenoyl)pyrrolizidine (6d) Pale yellow crystals; mp 170–171°C; IR: ύ 3225 (NH), 3097 (CH arom.), 2966 (CH aliph.), 1708 (C=O), 1684 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.25–2.00 (m,4H, 6-CH_2, 5-CH_2), 2.28–2.43 (m, 2H, 7-CH_2), 2.96 (t, 1H, 4-CH, J = 11.1 Hz), 3.43–3.62 (m, 1H, 4a-CH), 5.58 (d, 1H, 3-CH, J = 11.1 Hz), 6.40–6.80 (m, 4H, indoline-H), 6.90–7.20 (m, 4H, pyrene-H), 7.15 (d, 2H, Ph-H, J = 10.0 Hz), 7.30–7.40 (m, 1H, pyrene-H), 7.45 (d, 2H, Ph-H, J = 10.0 Hz), 7.50–7.60 (m, 3H, pyrene-H), 7.74–7.82 (m, 1H, pyrene-H), 9.90 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 27.5, 30.9, 45.9, 51.8, 56.5, 65.2, 72.5, 110.3, 112.2, 113.2, 121.6, 124.2, 124.9, 125.5, 126.4, 127.7, 127.8, 128.7, 129.5, 130.3, 131.1, 142.4, 147.3, 149.9, 160.9, 177.3, 196.5. Anal. Calcd. for $C_{37}H_{27}ClN_2O_2$: C, 78.37; H, 4.80; N, 4.94; Cl, 6.25. Found: C, 78.45; H, 5.00; N, 4.80; Cl, 6.40.

Spiro[2.3′]oxoindoline-4-(4-nitrophenyl)-3-(1-pyrenoyl)-pyrrolizidine (6e) Pale brown crystals; mp 189–190°C; IR: ύ 3201 (NH), 3035 (CH arom.), 2957 (CH aliph.), 1708 (C=O), 1684 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.25–2.01 (m,4H, 6-CH_2, 5-CH_2), 2.30–2.45 (m, 2H, 7-CH_2), 2.90 (t, 1H, 4-CH, J = 11.1 Hz), 3.46–3.66 (m, 1H, 4a-CH), 5.15 (d, 1H, 3-CH, J = 11.1 Hz), 6.44–6.85 (m, 4H, indoline-H), 6.90–7.19 (m, 4H, pyrene-H), 7.20 (d, 2H, Ph-H, J = 10.0 Hz), 7.25–7.40 (m, 1H, pyrene-H), 7.44 (d, 2H, Ph-H, J = 10.0 Hz), 7.50–7.61 (m, 3H, pyrene-H), 7.79–7.85 (m, 1H, pyrene-H), 9.59 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 27.7, 30.9, 47.5, 51.8, 56.5, 66.0, 72.5, 110.3, 112.2, 113.2, 121.6, 124.1, 124.9, 125.5, 126.4, 127.7, 127.8, 128.7, 129.5, 130.3, 131.1, 142.3, 147.3, 149.9, 169.9, 179.0, 200.2. Anal. Calcd. for $C_{37}H_{27}N_3O_4$: C, 76.93; H, 4.71; N, 7.27. Found: C, 77.15; H, 4.80; N, 7.40.

Spiro[2.3′]oxoindoline-1′-methyl-4-phenyl-3-(1-pyrenoyl)pyrrolizidine (6f) Pale yellow crystals; mp 161–163°C; IR: ύ 3043 (CH arom.), 2951 (CH aliph.), 1706 (C=O), 1665 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.40–2.00 (m, 4H, 6-CH_2, 5-CH_2), 2.25–2.45 (m, 2H, 7-CH_2), 3.35 (t, 1H, 4-CH, J = 14.1 Hz), 3.41 (s, 3H, CH_3), 3.60–3.75 (m, 1H, 4a-CH), 5.25 (d, 1H, 3-CH, J = 14.1 Hz), 6.10–6.40 (m, 1H, Ar-H), 6.75–7.40 (m, 9H, Ar-H), 7.50–7.75 (m, 2H, Ar-H), 8.00–8.50 (m, 6H, Ar-H); ^{13}C NMR (DMSO-d_6): δ = 20.5, 27.3, 30.4, 47.0, 52.0, 56.3, 58.3, 72.7, 108.8, 109.3, 109.9, 120.8, 121.1, 123.5, 124.4, 125.9, 126.6, 127.8, 128.7, 128.9, 129.9, 130.6, 132.1, 133.0, 140.3, 142.3, 142.7, 178.5, 203.4. Anal. Calcd. for $C_{38}H_{30}N_2O_2$: C, 83.49; H, 5.53; N, 5.12. Found: C, 83.70; H, 5.30; N, 5.41.

Spiro[2.3′]oxoindoline-1′-methyl-4-(4-methoxyphenyl)-3-(1-pyrenoyl)pyrrolizidine (6g) Orange crystals; mp 160–162°C; IR: ύ 3043 (CH arom.), 2947 (CH aliph.), 1705 (C=O), 1692 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.40–1.70 (m, 2H, 6-CH_2), 2.30–2.45 (m, 2H, 5-CH_2), 3.11–3.47 (m, 2H, 7-CH_2), 3.62 (t, 1H, 4-CH, J = 14.1 Hz), 3.69 (s, 3H, CH_3), 3.70–3.85 (m, 4H, 4a-CH, CH_3), 5.06 (d, 1H, 3-CH, J = 14.1 Hz), 6.23 (d, 2H, Ph-H, J = 9.0 Hz), 6.77 (d, 2H, Ph-H, J = 9.0 Hz), 6.95–7.25 (m, 4H, indoline-H), 7.57 (m, 1H, pyrene-H), 7.73–7.78 (m, 1H, pyrene-H), 8.02–8.19 (m, 7H, pyrene-H); ^{13}C NMR (DMSO-d_6): δ 27.7, 30.8, 36.5, 48.0, 51.7, 55.4, 66.0, 72.6, 73.1, 110.3, 113.8, 114.8, 114.9, 121.6, 124.7, 126.4, 127.6, 128.0, 129.2, 129.4, 129.8, 130.4, 131.8, 133.5, 134.0, 142.4, 146.0, 158.6, 177.6, 199.6, 202.9. Anal. Calcd. for $C_{39}H_{32}N_2O_3$: C, 81.23; H, 5.59; N, 4.86. Found: C, 81.45; H, 5.62; N, 5.00.

Spiro[2.3′]oxoindoline-1′-methyl-4-(4-dimethylaminophenyl)-3-(1-pyrenoyl)pyrrolizidine (6h) Orange crystals; mp 163–165°C; IR: ύ 3043 (CH arom.), 2969 (CH arom.), 1706 (C=O), 1690 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.26–2.15 (m, 4H, 6-CH_2, 5CH_2), 2.38–2.42 (m, 2H, 7-CH_2), 2.80 (t, 1H, 4-CH, J = 11.2 Hz), 3.51 (s, 6H, 2CH_3), 3.65–3.90 (m, 4H, 4a-CH, CH_3), 5.30 (d, 1H, 3-CH, J = 11.2 Hz), 7.15–7.95 (m, 8H, Ar-H), 8.00–8.45 (m, 9H, Ar-H); ^{13}C NMR (DMSO-d_6): δ 27.6, 30.4, 36.2, 47.2, 52.1, 65.7, 72.4, 73.3, 76.1, 110.2, 121.9, 123.7, 124.1, 124.9, 125.7, 126.9, 127.1, 127.6, 127.7, 128.7, 129.7, 129.8, 129.9, 130.1, 130.3, 130.9, 131.0, 133.6, 134.2, 142.1, 146.8, 148.9, 149.3, 179.5, 200.2. Anal. Calcd. for $C_{40}H_{35}N_3O_2$: C, 81.47; H, 5.98; N, 7.13. Found: C, 81.60; H, 6.21; N, 7.00.

Spiro[2.3′]oxoindoline-1′-methyl-4-(4-chlorophenyl)-3-(1-pyrenoyl)pyrrolizidine (6i) Yellow crystals; mp 159–160°C; IR: ύ 3035 (CH arom.), 2965 (CH arom.), 1702 (C=O), 1693 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.25–2.00 (m,4H, 6-CH_2, 5-CH_2), 2.25–2.40 (m, 2H, 7-CH_2), 2.74 (t, 1H, 4-CH, J = 11.2 Hz), 3.47–3.60 (m, 4H, 4a-CH, CH_3), 5.20 (d, 1H, 3-CH, J = 11.2 Hz), 6.42–6.81 (m, 4H, indoline-H), 6.90–7.20 (m, 4H, pyrene-H), 7.13 (d, 2H, Ph-H, J = 10.0 Hz), 7.30–7.40 (m, 1H, pyrene-H), 7.47 (d, 2H, Ph-H, J = 10.0 Hz), 7.50–7.60 (m, 3H, pyrene-H), 7.74–7.82 (m, 1H, pyrene-H); ^{13}C NMR (DMSO-d_6): δ 27.3, 30.9, 46.0, 51.8, 56.5, 65.2, 72.5, 73.2, 110.3, 112.2, 113.2, 120.6, 124.2, 124.9, 125.5, 126.4, 127.0, 127.8, 128.7, 129.2, 129.5, 130.3, 131.1, 142.4, 147.3, 149.9, 155.7, 179.3, 200.0. Anal. Calcd. for $C_{38}H_{29}ClN_2O_2$: C, 78.54; H, 5.03; N, 4.82; Cl, 6.10. Found: C, 78.36; H, 4.88; N, 4.56; Cl, 5.89.

Spiro[2.3′]oxoindoline-1′-methyl-4-(4-nitrophenyl)-3-(1-pyrenoyl)pyrrolizidine (6j) Pale brown crystals; mp 177–179°C; IR: ύ 3039 (CH arom.), 2963 (CH aliph.), 1702 (C=O), 1689 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.26–2.11 (m,4H, 6-CH_2, 5-CH_2), 2.30–2.45 (m, 2H, 7-CH_2), 3.15 (t, 1H, 4-CH, J = 11.1 Hz), 3.45–3.65 (m, 4H, 4a-CH, CH_3), 5.25 (d, 1H, 3-CH, J = 11.1 Hz), 6.45–6.85 (m, 4H, indoline-H), 6.90–7.20 (m, 4H, pyrene-H), 7.27 (d, 2H, Ph-H, J = 10.0 Hz), 7.29–7.38 (m, 1H, pyrene-H), 7.42 (d, 2H, Ph-H, J = 10.0 Hz), 7.50–7.61 (m, 3H, pyrene-H), 7.76–7.91 (m, 1H, pyrene-H); ^{13}C NMR (DMSO-d_6): δ 27.7, 30.9, 35.8, 47.4, 51.8, 56.5, 66.0, 73.2, 110.3, 112.2, 113.1, 121.6, 124.0, 124.9, 125.5, 126.4, 127.7, 128.7, 129.2, 129.5, 130.3, 131.0, 142.3, 147.3, 149.9, 167.9, 179.7, 201.5. Anal. Calcd. for $C_{38}H_{29}N_3O_4$: C, 77.14; H, 4.94; N, 7.10. Found: C, 76.90; H, 5.10; N, 6.88.

References

[1] Weng, J.; Mei, Q.; Ling, Q. Q.; Fan, Q.; Huang, W. A new colorimetric and fluorescent ratiometric sensor for Hg2+ based on 4-pyren-1-yl-pyrimidine. *Tetrahedron* **2012**, *68*, 3129–3134.

[2] Tsuge, O.; Kanemasa, S. Recent Advances in Azomethine Ylide Chemistry. In *Advances in Heterocyclic Chemistry*. Katritzky, A. R., Ed. Academic: San Diego, 1989; Vol. 45, pp 231–252.

[3] Grigg, R. Prototropic routes to 1,3- and 1,5-dipoles and 1,2-ylides: applications to the synthesis of heterocyclic compounds. *Chem. Soc. Rev.* **1987**, *16*, 89–121.

[4] Shi, F.; Mancuso, R.; Larock, R. C. 1,3-Dipolar cycloaddition of arynes with azomethine imines: synthesis of 1,2-dihydropyrazolo[1,2-a]indazol-3(9H)-ones. *Tetrahedron Lett.* **2009**, *50*, 4067–4070.

[5] Shi, F.; Zhu, R.; Liang, X.; Tu, S. Catalytic asymmetric 1,3-dipolar cycloadditions of alkynes with isatin-derived azomethine ylides: enantioselective synthesis of spiro[indoline-3,2′-pyrrole] derivatives. *Adv. Synth. Catal.* **2013**, *355*, 2447–2458.

[6] Wang, C.; Zhu, R.; Zheng, J.; Shi, F.; Tu, S. Enantioselective construction of spiro[indoline-3,2′-pyrrole] framework via catalytic asymmetric 1,3-dipolar cycloadditions using allenes as equivalents of alkynes. *J. Org. Chem.* **2015**, *80*, 512–520.

[7] Dai, W.; Jiang, X.; Wu, Q.; Shi, F.; Tu, S. Diastereo- and enantioselective construction of 3,3′-pyrrolidinyldispirooxindole framework via catalytic asymmetric 1,3-dipolar cycloadditions. *J. Org. Chem.* **2015**, *80*, 5737–5744.
[8] Wang, Y.; Zhang, H.; Li, C.; Fan, T.; Shi, F. Catalytic asymmetric chemoselective 1,3-dipolar cycloadditions of azomethine ylide with isatin derived imines: diastereo- and enantioselective construction of spiro[imidazolidine-2,3′-oxindole] framework. *Chem. Commun.* **2016**, *52*, 1804–1807.
[9] Nair, V.; Suja, T. D. Intramolecular 1,3-dipolar cycloaddition reactions in targeted syntheses. *Tetrahedron* **2007**, *63*, 12247–12275.
[10] Ghandi, M.; Yari, A.; Rezaei, S. J. T.; Taheri, A. Synthesis of novel spiropyrrolidine/pyrrolizine-oxindole scaffolds through 1,3-dipolar cycloadditions. *Tetrahedron Lett.* **2009**, *50*, 4724–4726.
[11] Ahrendt, K. A.; Williams, R. M. A concise asymmetric synthesis of the ADE fragment of nakadomarin A. *Org Lett.* **2004**, *6*, 4539–4541.
[12] Karthikeyan, S. V.; Bala, B. D.; Raja, V. P. A.; Perumal, S.; Yogeeswari, P.; Sriram, D. A highly atom economic, chemo-, regio- and stereoselective synthesis and evaluation of spiropyrrolothiazoles as antitubercular agents. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 350–353.
[13] Murugan, S. R.; Anbazhagan, S.; Narayanan, S. Synthesis and in vivo antidiabetic activity of novel dispiropyrrolidines through [3 + 2] cycloaddition reactions with thiazolidinedione and rhodanine derivatives. *Eur. J. Med. Chem.* **2009**, *44*, 3272–3279.
[14] Karthikeyan, K.; Kumar, R. S.; Muralidharan, D.; Perumal, P. T. Diastereoselective synthesis of pyrrolidines via 1,3-dipolar cycloaddition of a chiral azomethine ylide. *Tetrahedron Lett.* **2009**, *50*, 7175–7179.
[15] Girgis, A. S. Regioselective synthesis of dispiro[1*H*-indene-2,3′-pyrrolidine-2′,3″-[3*H*]indole]-1,2″(1″*H*)-diones of potential anti-tumor properties. *Eur. J. Med. Chem.* **2009**, *44*, 91–100.
[16] Kumar, R. R.; Manju, S. P. S. C.; Bhatt, P.; Yogeeswari, P.; Sriram, D. An atom economic synthesis and antitubercular evaluation of novel spiro-cyclohexanones. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3461–3465.
[17] Hussein, E. M.; Abdel-Monem, M. I. Regioselective synthesis and anti-inflammatory activity of novel dispiro [pyrazolidine-4,3′-pyrrolidine-2′,3″-indoline]-2″,3,5-triones. *Arkivoc* **2011**, *10*, 85–98.
[18] Hussein, E. M.; El-Khawaga, A. M. Simple and clean procedure for three-component syntheses of spiro{pyrido[2,1-b] benzothiazole-3,3′-indolines} and spiro{thiazolo[3,2-a] pyridine-7,3′-indolines} in aqueous medium. *J. Heterocycl. Chem.* **2012**, *49*, 1296–1301.
[19] Abdel-Mohsen, S. A.; Hussein, E. M. A green synthetic approach to the synthesis of Schiff bases from 4-amino-2-thioxo-1,3-diazaspiro[5.5]undec-4-ene-5-carbonitrile as potential anti-inflammatory agents. *Russ. J. Bioorg. Chem.* **2014**, *40*, 343–349.
[20] Hussein, E. M.; Masaret, G. S.; Khairou, K. S. Efficient synthesis and antimicrobial evaluation of some Mannich bases from 2-arylidine-1-thia-4-azaspiro[4.5] decan-3-ones. *Chem. Cent. J.* **2015**, *9*, 25.
[21] Hussein, E. M.; Al-Shareef, H. F.; Aboellil, A. H.; Elhady, H. A. Synthesis of some novel 6′-(4-chlorophenyl)-3,4′-bipyridine-3′-carbonitriles: assessment of their antimicrobial and cytotoxic activity. *Z. Naturforsch. B.* **2015**, *70*, 783–795.
[22] Al-Shareef, H. F.; Aboellil, A. H.; Elhady, H. A.; Hussein, E. M. Ammonium chloride catalyzed synthesis of novel Schiff bases from spiro[indoline-3,4′-pyran]-3′-carbonitriles and evaluation of their antimicrobial and anti-breast cancer activities. *SpringerPlus.* **2016**, *5*, 887.
[23] Abdel-Rahman, M. A.; Hussein, E. M.; Hussein, M. A. Synthesis and characterization of novel anti-inflammatory poly(spirothiazolidinone)s. *Des. Monomers Polym.* **2016**, *19*, 650–660.
[24] Pardasani, R. T.; Pardasani, P.; Chaturvedi, V.; Yadav, S. K.; Saxena, A.; Sharma, I. Theoretical and synthetic approach to novel spiroheterocycles derived from isatin derivatives and L-proline via 1,3-dipolar cycloaddition. *Heteroat. Chem.* **2003**, *14*, 36–41.
[25] Kumar, R. R.; Perumala, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D. A facile synthesis and antimycobacterial evaluation of novel spiro-pyrido-pyrrolizines and pyrrolidines. *Eur. J. Med. Chem.* **2009**, *44*, 3821–3829.

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