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**Diastereoselective Synthesis of 3,4-Dıbenzoil-3,4-Dihydro-1H-Spiro [Benzo[cd]Indol-5,3'-Indoline]-2,2’(2aH)-Diones**

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**Abstract**

Diastereoselective syntheses of 3,4-dibenzoyl-3,4-dihydro-1H-spiro[benzo[cd]indole-5,3'-indoline]-2,2'(2aH)-dionesin boiling DMF have been carried out starting with 3-(2-phenyl-2-oxoethylidene)indolin-2-ones via a Diels-Alder addition reaction. Theoretical and practical investigations of structure-activity relationships in the group of synthesizedspirooxindoleshave been performed.

**Keywords:** Oxindoles, spirooxindoles, dimerisation, Diels-Alder reaction.

**Introduction**

A successful development of the spiro-compounds’chemistry in recent years has beencaused by numerous studies of their syntheses, as well asby the search for new biologically active entities among them (Macaev et al., 2011; Millemaggi and Taylor 2010). The work carried out in this direction led to the creation of new effective drugs that have become part of the therapy of a number of pathologies (Hansch et al., 1990). In this regard, investigation of new effective synthetic methods for the selective synthesis of polyfunctionalizedspirooxindolesis an actual task and is of practical interest with the view to the study of the structure-bioactivity relationship.

**Results and Discussion**

In this article, the synthesis of derivatives containing in its structure a residue of lysergic acid 1 and velvitindolinolinone2 (Figure 1) is reported, with the latter belonging to the group of alkaloids extracted from blue-green algae.

**Figure 1:** The structure of lysergic acid **1** and velvitindolinone**2**

We have previously reported that compounds **3a** can be obtained in two-step synthesis from the corresponding isatins (Radul, 1983). However, it was not possible to obtain the N-acetyl-5-bromo derivative **3b** via this syntheticpathway. Therefore, we attempted to synthesizecompound **3b** by direct acetylation of **3a** according to the Scheme 1.

 **Scheme 1:** Synthesis of theacetyl derivative **3b** and thediastereomers**4**.

It wasrevealed that the yield of the target product **3b** consist only 7%. The remaining part was a chromatographically inseparable mixture of four diastereomers with a predominant content of one of the isomers **4**. After a series of manipulations, the major diastereomerwas isolated in an individual form and characterized by various physicochemical methods of analysis. It turned out that under the conditions of acylation and the Diels-Alder reaction,synthesis results in the formation of the corresponding dimers **4**. It was established that the separated compound contains in its structure lysergic acid and velvitinindolinone residues. Sincethere are four asymmetric carbon atoms in the structure of this molecule, the formation of eight pairs of diastereomers is possible.

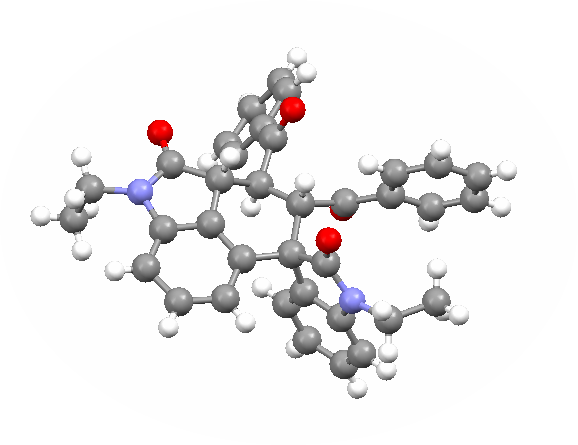
Taking into consideration that derivatives of the lysergic acid are psychotropic substances, and velvitindolinone possess antibacterial and antifungal activities, we set out to choose the conditions for diastereoselective synthesis of derivatives **4**.

After a number of studies, it was established that refluxing in DMF leads to formation of only one diastereomer**5a** from the enone**3c** (Scheme 2). As a result, it was isolated and characterized.



**Scheme2:** Diastereoselective synthesis of the compounds **5a-d**.

In order to confirm the structure of the synthesized compound **5a**, a single crystal was grown and an X-ray structural analysis was carried out (Sucman et al., 2010), the result of which is shown in the Figure 2.

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**Figure 2:** Structure of the compound **5a.**

The same synthetic pathway only starting with the isatins **3c-f,** resulted in theformation of products **5b-d** that were obtained individually in good yields.

We have previously shown that the presence of a 2,4-dichlorophenyl fragment in a molecule can lead to the appearanceof biological activity or to increase it (Macaev et al., 2011; Macaev et al., 2005; Geronikaki et al., 2004a; Geronikaki 2004b). Different oxindoles with the 2,4-dichlorophenyl fragment were synthesized from the corresponding isatins. However, under dimerization conditions, these substrates did not lead to the desired dimers. N-decyl derivative **3f** became an exception and was subjected to the Diels-Alder reaction with formation of the target product in a moderate yield.

It should be mentioned that unsubstituted enones**3g**,**h** lead to the condensed derivatives **6a, b**(Sch. 3).



**Scheme 3:** Synthesis of the compounds **6a, b.**

***Bioactivity assessment***

Initially, bioactivity calculations were performed using the computerized prediction system “PASS” (Research Institute of Biomedical Chemistry RAMS) using the method (Geronikaki et al., 2004a; Geronikaki 2004b). , which showed that dimers **5** with 98.5% probability can posed cerebrovascular and cardiovascular activity in the presence of three new descriptors . These data indicate the promise of research in this direction for the creation of substances with high biological activity.

The next step was a virtual screening, which was carried out on the MolTechLeadFinder software on the HP Z800 workstation at the Scientific Research Laboratory“Molecular Pharmacology” of the Federal State Educational Institution of Higher Professional Education at the St. Petersburg State Institute of Technology. The inhibitors were searched for the following protein targets: 1) MDM2 - p53 binding domain and 2) MDMX (MDM4) - p53 binding domain. Targets, associated with the process of programmed cell death, apoptosis, were considered. Evidence has been obtained that inhibition of E3 of ubiquitin-ligase specific to p53 with the participation of phenanthridine-5(4H)-ones **6a, b** as well as spiro[benzindole-5,3'-indoline]-2,2'-diones **4**, **5a-d**, leads to the stabilization of these proteins and suppresses the growth of tumor cells.

Further, the antifungal activity of the obtained derivatives was evaluated *in vitro*. It turned out that all of the tested compounds have significant antifungal activity, the most active compound being**5d**. *In vitro* biological studies were carried out by the group of Prof. Geronikaki from the Aristotle University of Thessaloniki, Greece.

**Experimental Methods**

All used solvents were of reagent quality, and all commercial reagents were used without additional purification. Removal of all solvents was carried out under reduced pressure. Analytical TLC plates were Silufol® UV-254. IR spectra were recorded on a Spectrum 100 FT-IR spectrophotometer (Perkin–Elmer) using the universal ATR sampling accessory. 1H and 13C NMR spectra have been recorded in2% solution in CDCl3 with a Bruker -Avance III NMR spectrometer (400.13 and 100.61 MHz). Melting points were determined with a Boëtius apparatus.

Isatins**3a,c-f** were prepared using the previously described methods [10].

*General procedure for the synthesis of 3,4-dibenzoyl-3,4-dihydro-1H-piro[benzo[cd]indole-5,3'-indoline]-2,2'(2aH)-diones***5.**

The solution of compound **3**(0.001 mol) in DMFA(5 mL) was refluxed for 2.5 hours. The mixture was cooled, dissolved by water and extracted with dichloromethane. Organic layer was dried and evaporated under reduced pressure. The residue was chromatographically separated on silica gel. The mixture of dichloromethane and methanol was used as mobile phase.

**5a:** M.p. 221-2230С. 1H-NMR: 8.07 (d, 2H, J=7.2, Ar); 7.60 (t, 1H, J=7.6, Ar); 7.49 (t, 2H, J=7.6, Ar); 7.43 (t, 1H, J=7.6, Ar); 7.24 (t, 2H, J=7.6, Ar); 7.15 (m, 3H, Ar); 7.00 (m, 3H, Ar); 6.76 (d, 1H, J=8.0, Ar); 6.60 (d, 1H, J=7.6, Ar); 5.95 (d, 1H, J=8.0, Ar); 5.03 (d, 1H, J=8.0, C*H*CON); 4.44 (t, 1H, J=8.0, C*H*CO); 3.94 (d, 1H, J=7.6, C*H*CCO); 3.80 (hx, 2H, C*H2*); 3.50 (dhx, 2H, *CH2*); 1.25 (t, 3H, C*H3*); 0.86 (t, 3H, C*H3*). 13C-NMR: 201.84, 199.75, 176.99, 174.46, 142.61, 142.55, 138.20, 137.60, 133.19, 132.91, 131.63, 129.18, 129.14, 128.90, 128.23, 128.09, 126.73, 126.51, 122.82, 118.48, 108.14, 106.55, 56.45, 54.43, 54.37, 46.67, 41.51, 34.82, 34.77, 30.78, 13.11, 12.27.

**5b:** M.p.>2550 C. 1H-NMR:8.08 (d, 2H, J=8.4, Ar); 7.60 (t, 1H, J=7.6, Ar)7.49 (t, 2H, J=7.6, Ar); 7.42 (t, 1H, J=7.6, Ar); 7.25 (t, 2H, J=7.6, Ar); 7.16-7.13 (m, 3H, Ar); 7.00 (m, 3H, Ar); 6.73 (d, 1H, J=7.6, Ar); 6.54 (d, 1H, J=8.0, Ar); 5.98 (d, 1H, J=8.0, Ar); 5.05 (d, 1H, J=7.2, C*H*CON); 4. 39 (t, 1H, J=8.0, C*H*CO); 3.99 (d, 1H, J=7.6, C*H*CCO); 3.75 (m, 1H, C*H2*N); 3.41 (m, 2H, C*H2*N); 2.82 (m, 1H, C*H2*N); 1.71 (hx, 2H, C*H2*CH3); 1.41 (hx, 2H, C*H2*CH3); 0.99 (t, 3H, *CH3*); 0.86 (t, 3H, *CH3*). 13C-NMR: 201.54, 199.58, 177.37, 174.75, 169.58, 143.15, 142.95, 138.30, 137.57, 133.23, 132.74, 132.55, 131.57, 129.16, 129.03, 128.77, 128.13, 127.93, 126.64, 126.61, 122.76, 118.50, 108.07, 106.49, 56.66, 54.41, 46.50, 41.67, 41.62, 41.56, 21.08, 20.67, 11.63, 11.52

**5c:** M.p.>2550 C.1H-NMR: 1H-NMR: 8.08 (d, 2H, J=8.0, Ar); 7.59 (t, 1H, Ar); 7.49 (t, 2H, Ar); 7.41 (t, 1H, Ar); 7.22 (t, 2H, Ar); 7.15-7.12 (m, 3H, Ar); 7.07 (t, 1H, Ar); 6.96-6.92 (m, 2H, Ar); 6.72 (d, 1H, J=7.6, Ar); 6.52 (d, 1H, J=7.6, Ar); 5.96 (d, 1H, J=8.0, Ar); 5.04 (d, 1H, J=10.8, C*H*CON); 4.38 (t, 1H, J=11.2, C*H*CO); 3.97 (d, 1H, J=11.6, C*H*CCO); 3.82-3.75 (m, 1H, C*H2*N); 3.45-3.42 (m, 2H, C*H2*N); 2.89-2.85 (m, 1H, C*H2*N); 1.66-1.61 (m, 2H, C*H2*C*H2*); 1.44-1.26 (m, 6H, C*H2*C*H2*); 0.99 (t, 3H, *CH3*); 0.91 (t, 3H, *CH3*).13C-NMR: 201.54, 199.60, 177.22, 174.68, 143.01, 142.88, 138.23, 137.54, 136.89, 133.17, 132.78, 132.59, 131.59, 129.16, 129.02, 128.77, 128.14, 127.95, 126.66, 126.60, 122.78, 118.50, 108.01, 106.43, 56.57, 54.36, 46.49, 41.59, 40.78, 39.64, 29.81, 29.30, 20.12, 20.04, 13.95, 13.93

**5d:** M.p.>2550 C.1H-NMR: 8.19 (d, 1H, J=8.4, Ar); 7.49 (d, 1H, J=2.0, Ar); 7.42 (dd, 1H, J1=2.0,J2=8.4, Ar); 7.31-7.21 (m, 5H, Ar); 7.01-6.95 (m, 3H, Ar); 6.75 (d, 1H, J=8.3, Ar); 6.66 (d, 1H, J=7.6, Ar); 5.93 (d, 1H, J=8.4, CH); 5.10 (d, 1H, J=11.04, CH); 4.30 (t, 1H, J=11.4, CH);3.78-3.69 (m, 1H, C*H2*N); 3.43-3.40 (m, 2H, C*H2*N); 2.81-2.78 (m, 1H, C*H2*N); 1.65-1.15 (m, 32H, C*H2*); 1.02 (t, 3H, *CH3*); 0.96 (t, 3H, *CH3*). 13C-NMR: 202.11, 199.49, 177.33, 173.99, 142.89, 142.76, 138.35, 137.46, 136.56, 132.87, 132.63, 132.56, 131.62, 129.00, 128.95, 128.65, 128.22, 127.88, 126.52, 126.47, 122.78, 118.56, 108.22, 106.21, 56.68, 54.33, 46.41, 41.01, 40.15, 38.64, 29.81, 29.30, 28.03, 27.58, 26.53, 26.22, 24.03, 23.89, 23.56, 23.01, 22.58, 22.31, 21.62, 21.24, 20.12, 20.04, 13.95, 13.93.

*General procedure for the synthesis of 6-benzoyl-7-phenylindolo[3,4-jk]phenanthridin-5(4H)-ones* **6**.

The solution of compound **3** (0.001 mol) in DMFA (5 mL) was refluxed for 2.5 hours. The mixture was cooled,then dissolved by water. The resulting precipitate was filtered, washed with water and ethanol.

**6a:** .p. >2550 C. 1H-NMR: 11.06 (s, 1H, N*H*); 9.28 (d, 1H, J=8.4, Ar); 8.72 (d, 1H, J=8.4, Ar); 8.20 (d, 1H, J=8.4, Ar); 7.99-7.91 (m, 2H, Ar); 7.85 (t, 1H, J=7.84, Ar); 7.69 (, 1H, J=8.4, Ar); 7.48 (s, 1H, Ar); 7.32 (d, 1H, J=8.4, Ar); 7.27 (d, 1H, J=8.4, Ar); 7.23-6.78 (s br, 3H, Ar). 13C-NMR: 209.31; 166.83, 156.71, 145.44, 140.08, 138.99, 137.81, 136.45,135.87, 135.34, 135.01, 131.50, 131.31, 130.53, 130.17, 128.67, 128.60, 128.36, 127.02, 126.39, 126.02, 125.58, 124.82, 124.32, 124.02, 120.75, 108.92.

**6b:** M.p. 211-2130С. 1H-NMR: 11.16 с (s, 1H, N*H*); 9.28 (d, 1H, J=8.1, Ar); 8.75 (d, 1H, J=8.8, Ar); 8.24 (d, 1H, J=7.8, Ar); 8.05-7.96 (m, 3H, Ar); 7.89 (t, 1H, J=7.6, Ar); 7.70 (, 1H, J=8.5, Ar); 7.64 (s; 1H, Ar); 7.38 (s, 2H, Ar); 7.31 (d, 1H, J=7.3, Ar); 7.26 (d, 1H, J=7.2, Ar).

13C-NMR: 210.91, 166.92, 156.95, 145.27, 139.76, 139.02,137.88, 137.69, 136.54, 135.55, 135.36,135.17, 134.72, 132.21, 131.50, 131.31, 130.07,129.94, 129.63, 129.13, 128.65, 127.69, 126.39,126.05, 125.96, 125.45, 124.64, 124.02, 123.94, 121.29, 109.47.

**Conclusion**

A number of compounds with potentially high biological activity were obtained as a result of simple synthesis using commercial available and cheap reagents.

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