Tetrahedron 68 (2012) 851–856

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Novel indole syntheses by ring transformation of β-lactam-condensed 1,3-benzothiazines into indolo[2,3-*b*][1,4]benzothiazepines and indolo[3,2-*c*]isoquinolines

Lajos Fodor [a,b,c,*], Péter Csomós [a,b,c], Antal Csámpai [d], Pál Sohár [d,*]

[a] *Institute of Health Care and Environmental Sanitation Studies, Szent István University, H-5700 Gyula, Szent István st. 17–19, Hungary*
[b] *Central Laboratory, County Hospital, H-5701 Gyula, POB 46, Hungary*
[c] *Institute of Pharmaceutical Chemistry, University of Szeged, and Research Group of Stereochemistry of the Hungarian Academy of Sciences, H-6720, Szeged, Eötvös u. 6, Hungary*
[d] *Institute of Chemistry, Eötvös Loránd University, H-1518 Budapest, POB 32, Hungary*

ARTICLE INFO

*Article history:*
Received 13 September 2011
Received in revised form 24 October 2011
Accepted 14 November 2011
Available online 19 November 2011

*Keywords:*
Indole synthesis
β-Lactam
1,3-Benzothiazine
Ring transformation
Indolo-1,4-benzothiazepine
Indolo[3,2-*c*]isoquinoline
IR, $^{1}$H and $^{13}$C NMR

ABSTRACT

*ortho*-Nitrophenyl-substituted condensed 1,3-benzothiazines proved to be a useful core unit in indole syntheses under non-reductive conditions. Thus, the treatment of *ortho*-nitro-2-aryl-2a-chloro-4*H*-azeto[2,1-*b*][1,3]benzothiazin-1-ones with sodium methoxide in methanol provided indolo-1,4-benzothiazepines via a novel rearrangement. Through the sulfur extrusion reaction of indolo[2,3-*b*][1,4]benzothiazepines, further alkaloid-type indole derivatives, indolo[3,2-*c*]isoquinolines, were obtained. The structures of the new ring systems were determined by means of NMR spectroscopy.

© 2011 Elsevier Ltd. All rights reserved.

## 1. Introduction

Because of their privileged role in nature and medicine, indole compounds are of continuously increasing research interest.[1] Although basic synthetic pathways for the preparation of indoles have long been known,[2] several modifications of named indole syntheses have been published to provide a variety of substitution pattern and more efficient reactions, which occur under mild conditions.[1] On the other hand, new indole synthetic strategies, such as the C–H amination of azides,[3] Pd-catalysed C–H functionalization,[4] Nb-promoted C–F functionalization[5] and rearrangement reactions,[6] have also been developed.

Among the most widely used practical methods of indole synthesis, such as those of Bartoli[7] and Cadogan-Sundberg,[8] reductive N-heterocyclization utilizes the *ortho*-nitro group of a phenyl moiety for the construction of an indole nitrogen. In contrast, there are only rare examples (not even mentioned in main indole reviews) in which an *ortho*-nitroaryl compound under basic conditions furnishes an *N*-hydroxy-indole ring without the addition of any reducing agent. Reactions of this type were investigated by Wrobel et al.,[9] and some earlier examples can also be found in the literature.[10] By means of these methods, *N*-hydroxyindoles have been obtained.[9,10]

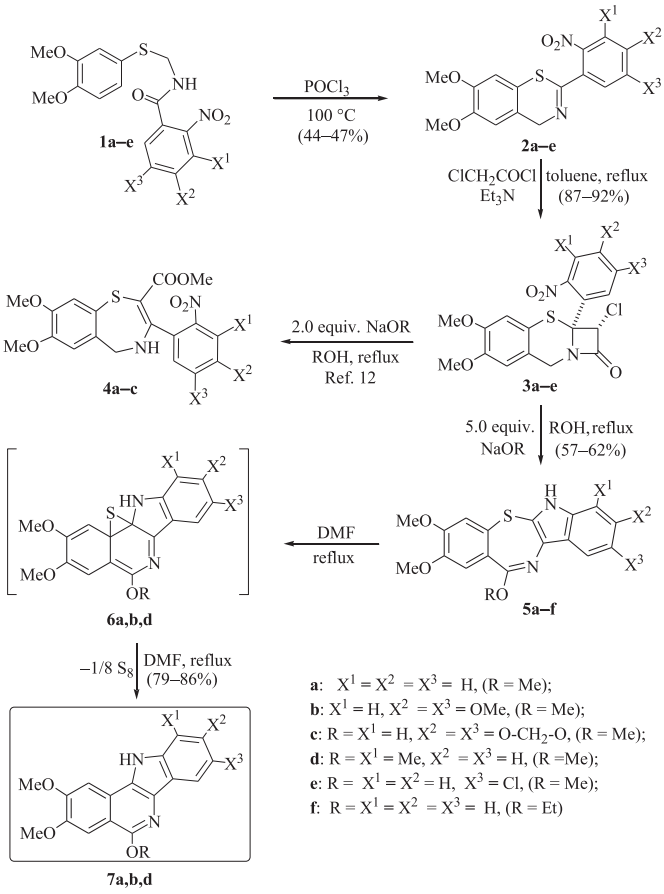
During our recent investigations of the ring-enlargement reactions of 2-aryl-2a-chloro-4*H*-azeto[2,1-*b*][1,3]benzothiazin-1-ones to 1,4-benzothiazepines,[11] we observed that the reaction of *ortho*-nitro-2-phenyl-substituted β-lactam with sodium methoxide in methanol gave an indole compound.[12] Somewhat surprisingly, treatment with a large excess of sodium methoxide led to the formation of indolo-1,4-benzothiazepines via a novel rearrangement.[12] As a continuation of that work, we set out to extend this novel indole synthesis to different derivatives and to investigate the substituent-reactivity pattern. On the other hand, these compounds in our view promise the possibility of rearrangement to indenoisoquinolines, which have been described as pharmacologically interesting compounds.[13]

## 2. Results and discussion

The starting 4*H*-1,3-benzothiazines were obtained from aroylamide thioethers **1a**–**e** through an acid-catalysed intermolecular rearrangement with phosphorus oxychloride (Scheme 1).[14]

* Corresponding authors. Tel.: +36 66 463763; fax: +36 66 526539 (L.F.); tel.: +36 1 3722911; fax: +36 1 3722592 (P.S.); e-mail addresses: fodor@pandy.hu (L. Fodor), sohar@chem.elte.hu (P. Sohár).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.11.036




**Scheme 1.**

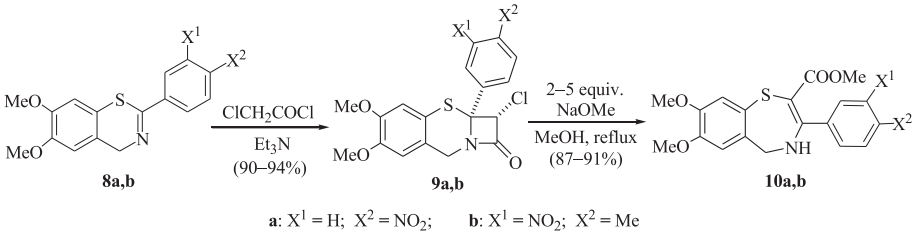
concerns the exploration of the role of the nitro group in the rearrangement reaction, *meta*- and *para*-substituted monochloro-β-lactams **9a**,**b** were also synthesized from the corresponding benzothiazines **8a**,**b** (Scheme 2). The treatment of **9a**,**b** with sodium methoxide (2–5 equiv) gave only benzothiazepines **10a**,**b**. In the reactions of **9a**,**b**, no other rearrangement was observed in which the nitro group could have been involved.

Sulfur extrusion reactions are attractive synthetic processes. If these reactions could be achieved by extrusion of either a sulfur atom or a sulfur monoxide moiety, various heterocycles,[15] including alkaloids,[16] could be obtained by ring contraction. In our case indolothiazepines **5** seemed to be suitable starting materials for the preparation of δ-carboline[17] analogue indolo[3,2-*c*]isoquinolines **7** (Scheme 1).

There are only a few examples for the preparation of this indole ring system;[13] such compounds were recently developed as poly(ADP-ribose)polymerase-1 (PARP-1) inhibitors.[13d] The treatment of **5a**,**b**,**d** in refluxing dimethylformamide afforded **7a**,**b**,**d** in good yields. The reaction most probably takes places through **6**. It is generally considered, that episulfides, such as **6** are intermediates in the extrusion pathway of thiepines, benzothiepines and benzothiazepines.[15a–c] Elimination of sulfur from **5** with the formation of indoloisoquinoline is energetically a very favourable process. The free enthalpy changes calculated by the B3LYP/6-31 G(d) method for the conversion of **5a**,**c** to **7a**,**c** are presented in Scheme 3.

A possible mechanistic pathway of the novel indole formation reaction is depicted in Scheme 4.

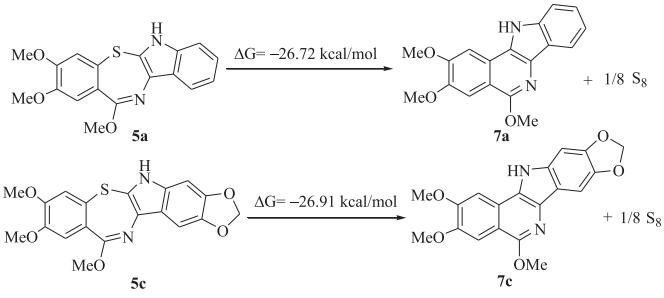
The key intermediates are 1,4-benzothiazepines, as proved earlier in the preparation of a derivative of **5**.[12] The next step most probably involves the formation of *N*-hydroxyindole derivatives **11** through reaction with sodium methoxide (Scheme 4).[9] Addition of methanol to **11** provides **12**. The formation of **5** can be further explained through **13**, followed by a 1,5-proton shift (Scheme 4).




**Scheme 2.**

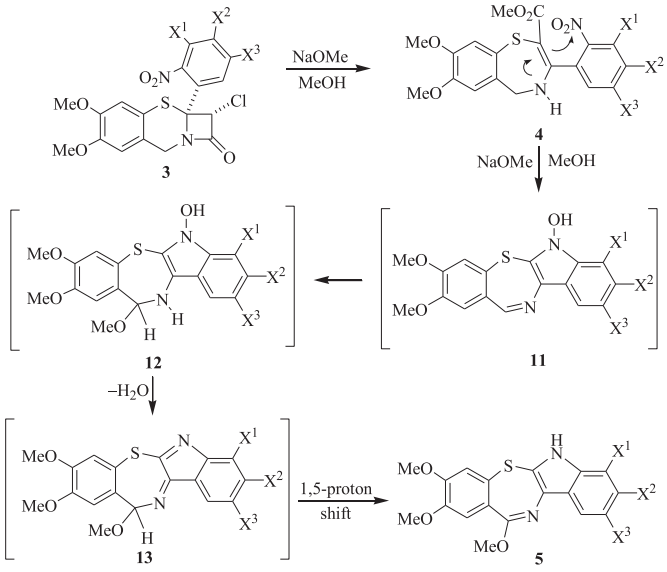
The key intermediate azetobenzothiazine derivatives **3a**–**e** were obtained in excellent yields through the reaction of 1,3-benzothiazines **2a**–**e**[14] and chloroacetyl chloride in the presence of base in refluxing toluene (Scheme 1).

These reactions resulted only in the formation of that diastereomer of **3a**–**e** in which the orientation of the chloro atom and the aryl group is cis.[11] The reactions of monochloro-β-lactam derivatives **3a**–**e** with 2 equiv of sodium methoxide in dry methanol at reflux afforded the enamine forms of 4,5-dihydro-1,4-benzothiazepines **4a**–**c** (Scheme 1).[12] In these latter reactions, the first step is most probably alcoholysis of the β-lactam ring, resulting in α-chloro esters, which lead to the products through episulfonium salts after the elimination of HCl. On the other hand, by the treatment of monochloro-β-lactams **3a**–**e** with 5 equiv of sodium alkoxide, we could extend the preparation of variously substituted indolo-1,4-benzothiazepines **5a**–**f** via the novel rearrangement (Scheme 1). The reactions proceeded well either in methanol (**5a**–**d**) or ethanol (**5f**) with the appropriate sodium alkoxides. As




**Scheme 3.**

In summary, we have developed a general procedure for the synthesis of the indolo[2,3-*b*][1,4]benzothiazepine ring system **5a**–**f** from *ortho*-nitro-2-aryl-2a-chloro-4*H*-azeto[2,1-*b*][1,3]benzothiazin-1-ones **3a**–**e**, using 5 equiv of sodium methoxide in



Scheme 4.

methanol under reflux. In the further transformations of indolobenzothiazepines by sulfur extrusion, alkaloid-type indolo[3,2-*c*]isoquinolines **7a**,**b**,**d** were obtained in good yields. The structures of the novel ring expansion products were proved by means of NMR spectroscopy.

## 3. Structure

The postulated structures of the molecules investigated are unambiguously confirmed by the spectral data (Tables 1 and 2). Only the following remarks are necessary.

The benzothiazine skeleton in the compounds of types **2** and **8** is confirmed by the chemical equivalence of the methylene H's with a singlet signal of 2H intensity. The downfield-lying carbon line of the S–C(Ar)=N group (158.7–161 ppm) provides further evidence of this structure.

The difference in the chemical shifts of the methylene H's in **2d**,**e** (~4.6 ppm) and in **8a**,**b** (~4.8 ppm) can be explained by the different conformations in these molecules. The electron-attracting nitrophenyl substituent is coplanar with the molecular skeleton in **2d**,**e**, whereas in **8a**,**b** it must lie perpendicular to that plane because of the steric hindrance between the nitro group and the skeleton. Consequently, the *–I* effect resulting in a downfield shift of the $CH_2$ signal can act only in **8a**,**b**.

The presence of the condensed azetidinone ring in the compounds of types **3** and **9** follows straightforwardly from the very high *ν*C=O IR frequency (1781–1794 $cm^{-1}$), in accordance with the literature data.[18a] The asymmetric structure of these molecules follows from the chemical non-equivalence of the methylene H's, with two doublets split by 16.0–16.9 Hz. The $^{13}C$ NMR chemical shifts of the carbon atoms in the four-membered ring ($C_{quat.}$: 70.4±0.2 ppm, CH: 68.8±0.8 ppm and C=O: 164.6±0.2 ppm) suggest the *trans* position of the H in this ring with the aryl substituent. These values are very similar to those for compounds with analogous structures measured earlier[11,19] (71.5±0.5, 68.8±0.5 and 164.9±0.3 ppm[11]).

It is noteworthy that the unusual high shift differences (~0.6 ppm) of the methylene H's in **3d**,**e** and **9a**,**b** arise from the anisotropic effect[20a] of the aryl substituents lying near to the quasi-axial H's.

Similarly, the $^1H$ NMR chemical shifts of the CH groups in the azetidinone ring are practically identical: here 5.12–5.36 ppm, while the corresponding chemical shifts for the compounds in Ref. 11 were 5.09–5.14 ppm.

**Table 1**
Characteristic IR frequencies[a] and $^1H$ NMR data[b] on compounds **2d**,**e**, **3d**,**e**, **5d**,**e**,**f**, **7a**,**b**,**d**, **8a**,**b**, **9a**,**b** and **10a**,**b**[c]

| Compound | *ν*NH band | *ν*C=O band | $\gamma C_{Ar}H$ band[d] | $CH_3$ (3H) | $OCH_3$ (Pos. 6, 7)[e] | $NCH_2$ s, d or dd[f] | CH s (1H) | H-5 s (1H) | H-8 s (1H) | H-2′ | H-6′ | H-3′ | H-5′ | H-4′ | NH broad |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Ar group attached to the heteroring[g] | | | | | |
| **2d** | — | — | 854 | 2.31 | 3.81, 3.80 | 4.60 | — | 6.72 | 6.74 | — | 7.59 | — | 7.35 | 7.30 | — |
| **2e** | — | | 840 | — | 3.83, 3.80 | 4.63 | — | 6.76 | 6.72 | — | 7.52 | 7.85 | — | 7.45 | — |
| **3d** | — | 1788 | 813 | 2.34 | 3.74, 3.69 | 4.34, 4.90 | 5.13 | 6.55 | 6.48 | — | 7.16 | — | 7.28 | 7.22 | — |
| **3e** | — | 1781 | 831 | — | 3.79, 3.70 | 4.44, 4.98 | 5.36 | 6.62 | 6.43 | — | 7.20 | 8.10 | — | 7.39 | — |
| **5d** | 3390 | — | 872 | 2.38 | 3.73, 3.78 | — | — | 7.14 | 6.91 | — | — | 6.86 | 7.30 | 6.89 | 11.1 |
| **5e** | 3320 | — | 872 | — | 3.76, 3.80 | — | — | 7.16 | 6.95 | — | 7.49 | 7.27 | — | 7.09 | 11.5 |
| **5f** | 3350 | — | 863 | 1.45[h] | 3.76, 3.79 | 4.47[i] | — | 7.15 | 6.94 | — | 7.47 | 7.25 | 6.99 | 7.09 | 11.2 |
| **7a** | 3250–2800 | — | 825 | — | 3.85, 3.93 | — | — | 7.52 | 7.82 | — | 7.94 | 7.50 | 720 | 7.27 | 11.7 |
| **7b** | ~ 3160 | — | 834 | — | 3.91, 3.99 | — | — | 7.56 | 7.80 | — | 7.44 | 7.08 | — | — | 11.5 |
| **7d** | ~ 3190 | — | 856 | 2.65 | 3.92, 4.03 | — | — | 7.59 | 8.06 | — | 7.86 | — | 7.09 | 7.15 | 11.4 |
| **8a** | — | — | 850 | — | 3.92, 3.91 | 4.81 | — | 6.87 | 6.89 | 8.17[k] | | 8.29[k] | | — | — |
| **8b** | — | — | 846 | 2.65 | 3.91, 3.90 | 4.76 | — | 6.85 | 6.88 | 8.61 | 8.13 | — | 7.41 | — | — |
| **9a** | — | 1794 | 851 | — | 3.85, 3.81 | 4.35, 4.95 | 5.15 | 6.70 | 6.66 | 7.61[k] | | 8.23[k] | | — | — |
| **9b** | — | 1784 | 853 | 2.60 | 3.84, 3.82 | 4.34, 4.94 | 5.12 | 6.68 | 6.67 | 8.08 | 7.36 | — | 7.58 | — | — |
| **10a** | 3380 | 1682 | 858 | — | 3.88, 3.90 | 4.94 | — | 6.75 | 7.15 | 7.35[k] | | 8.14[k] | | — | 4.51[l] |
| **10b** | 3392 | 1671 | 843 | 2.49 | 3.76, 3.77 | 4.80 | — | 6.97 | 7.05 | 7.63 | 7.33 | — | 7.40 | — | 7.27[l] |

[a] In KBr discs ($cm^{-1}$). Further bands, $\nu_{as}NO_2$ and $\nu_sNO_2$ (**2**, **3**, **8**–**10**): 1531–1501 and 1336–1366; *ν*C–O: 1257–1265 and 1044–1056 (**2**, **3**, **8**), 1255±4 (**5**), 1175±2 (**5**) and 1045±(**5d**,**e**) and 1023 (**5f**), respectively, 1212±3 and 1007±3 (**7a**,**d**), 1258, 1209, 1190, 1038 and 1004 (**7b**), 1211 and 1049±4 (**9**), 1228±3 and 1062±6 (**10**); $\gamma C_{Ar}H$ (*p*-disubstituted Ar group): 811 (**8a**, **10a**), 821 (**9a**).

[b] In $CDCl_3$ (**2**, **3**, **8**, **9** and **10a**) or DMSO-$d_6$ (**5**, **7** and **10b**) solution at 500 MHz. Chemical shifts in ppm ($\delta_{TMS}$=0 ppm), coupling constants in Hz. Further signals: $OCH_3$ on the thiazepine at 3.98 (**5d**) and 4.01 (**5e**) or on the pyridine ring at 4.08(**7a**) and 4.15 (**7b**,**d**) or in the ester group at 3.45 (**10a**) and 3.27 (**10b**).

[c] Assignments were supported by 2D-HMQC and 2D-HMBC measurements.

[d] Condensed benzene ring.

[e] For **9b** reversed assignment is also possible.

[f] *s* (**2**, **8**), 2×*d*, *J*: 16.8(**3d**,**e**), 16.0 (**9a**), 16.5 (**9b**), *d*, *J*: 6.0 (**10a**), 5.1 (**10b**).

[g] Benzene ring condensed to the pyrrole.

[h] OEt group, *t* (3H), *J*: 7.1.

[i] OEt group, *qa* (2H), *J*: 7.1.

[k] AA′BB′-type spectrum, ~*d* (2H), *J*: 8.8 (**8a**, **9a**, **10a**).

[l] *t*.

**Table 2**
$^{13}$C NMR chemical shifts[a] of compounds **2d**,**e**, **3d**,**e**, **5d**,**e**,**f**, **7a**,**b**,**d**, **8a**,**b**, **9a**,**b** and **10a**,**b**[b]

| Compound | $CH_3$ | C=O or C=N[c] | $OCH_3$ | $NCH_2$ | C-4a | C-5 | C-6 | C-7 | C-8 | C-8a | C-1′ | C-2′ | C-6′ | C-3′ | C-5′ | C-4′ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Benzothiazine (**2**, **3**, **8**, **9**), benzothiazepine (**5**, **10**) or isoquinoline (**7**) part | | | | | | | | Aryl group (**2**, **3**, **8**–**10**) or benzene ring of indole (**5**, **7**) | | | | | |
| **2d** | 18.2 | 159.2 | 56.6[d] | 56.8 | 122.2 | 110.7 | 149.7 | 149.3 | 109.7 | 121.1 | 130.9 | ~150 | 128.3 | 131.6 | 130.5 | 133.9 |
| **2e** | — | 158.7 | 56.6, 56.6[g] | 57.2 | 122.4 | 110.8 | 149.7 | 149.4 | 109.6 | 121.3 | 139.8 | 146.9 | 131.2 | 126.4 | 135.7 | 130.9 |
| **3d** | 19.6 | 164.8 | 56.5, 56.4[g] | 43.0 | 119.2 | 111.2 | 148.8 | 149.2 | 112.7 | 119.9 | 132.0 | 148.6 | 126.8 | | 130.9 | 133.7 |
| **3e** | — | 164.5 | 56. 6, 56.4 | 43.4 | 119.0 | 111.0 | 148.9 | 149.4 | 112.4 | 119.9 | 136.9 | 145.0 | 128.9 | 128.4 | 140.9 | 130.3 |
| **5d** | 17.4 | 159.8 | 56.6, 56.7 | — | 128.4 | 113.8 | 149.5 | 152.4 | 114.6 | 129.0 | 136.2 | 121.7 | 124.1 | 123.5 | 115.7 | 120.2 |
| **5e** | — | 160.2 | 56.6, 56.7 | — | 128.2 | 113.9 | 149.6 | 152.5 | 114.8 | 128.4 | 135.0 | 114.8 | 125.5 | 123.5 | 117.2 | 125.2 |
| **5f** | 15.1 | 159.4 | 56.6, 56.7 | — | 128.5 | 113.9 | 149.5 | 152.4 | 114.6 | 129.0 | 136.6 | 112.3 | 124.4 | 123.0 | 118.1 | 120.0 |
| **7a** | — | 155.3 | 56.4, 56.7 | — | 113.2 | 105.3 | 149.4 | 153.2 | 102.4 | 122.8 | 128.9 | 112.4 | 138.8 | 112.4 | 119.5 | 119.8 |
| **7b** | — | 155.0 | 56.6, 56.7[g] | — | 112.1 | 105.3 | 148.8 | 153.2 | 101.9 | 122.9 | 133.6 | 96.1 | 115.6 | 149.4 | 101.8 | 145.2 |
| **7d** | 17.9 | 155.3 | 56.4, 56.8 | — | 113.1 | 105.2 | 149.3 | 153.2 | 102.7 | 123.0[e,g] | 138.2 | 123.0[e,g] | 121.5 | 125.6 | 117.1 | 119.9 |
| **8a** | — | 160.5 | 56.6, 56.6[g] | 57.3 | 123.0 | 110.6 | 149.7[f] | 149.4 | 110.0 | 121.1 | 142.9 | 128.9 | | 124.1 | | 149.7[f] |
| **8b** | 20.9 | ~161 | 56.6[d] | 56.6[d] | 123.0 | 110.6 | 149.7 | 149.3 | 110.0 | 121.0 | 136.3 | 124.4 | 132.0 | 149.7[f] | 133.5 | 136.9 |
| **9a** | — | 164.4 | 56.5[d] | 43.8 | 121.9 | 111.7 | 149.0 | 149.4 | 113.0 | 119.5 | 144.4 | 128.5 | | 124.0 | | 148.5 |
| **9b** | 20.8 | 164.3 | 56.5[d] | 43.5 | 121.5 | 111.6 | 148.9 | 149.3 | 113.0 | 119.6 | 136.9 | 123.9 | 133.5 | 149.4 | 131.9 | 135.0 |
| **10a** | — | 167.4 | 56.6, 56.6[g] | 49.4 | 135.4 | 111.7 | 149.7 | 149.5 | 116.2 | 129.0[d] | 147.9[f] | 129.0[d] | | 123.9 | | 148.1[f] |
| **10b** | 20.1 | 167.5 | 56.5[d] | 48.3 | 136.3 | 113.4 | 149.7 | 149.2[e] | 116.1 | 129.2 | 140.3 | 124.2 | 133.5[f] | 149.3[e] | 133.1 | 133.5[f] |

[a] In ppm ($\delta_{TMS}$ 0 ppm) at 125.7 MHz. Solvent: $CDCl_3$ (**2**, **3**, **8**, **9** and **10a**) or DMSO-$d_6$ (**5**, **7** and **10b**). Further signals, $OCH_3$ (ester group): 52.1 (**10a**), 51.7 (**10b**); $OCH_3$ [on the thiazepine (**5**) or pyridine (**7**) ring]: 54.4 (**5d**), 54.6 (**5e**), 54.1 (**7a**), 54.0 (**7b**,**d**); $OCH_3$ (on the indole ring in **7b**): 56.4 (Pos. 3), 56.9 (Pos. 4); $OCH_2$ (**5e**): 62.5; CH (azetidinone ring): 69.7 (**3d**), 69.5 (**3e**), 68. 0 (**9a**,**b**); $C_{quat.}$ (azetidinone ring): 70.2 (**3d**), 70.3 (**3e**), 70.6 (**9a**,**b**); S–C($sp^2$), heteroring: 92.3 (**10a**), 87.8 (**10b**); NH–C($sp^2$), heteroring: 115.9 (**5d**), 118.2 (**5e**), 116.0 (**5f**), 125.3 (**7a**), 124.4 (**7b**), 125.2 (**7d**), 155.1 (**10a**), 156.7 (**10b**); N($sp^2$)–C, pyrrole ring: 126.4 (**5d**), 124.8 (**5e**), 126.0 (**5f**), 138.8 (**7a**), 129.4 (**7b**,**d**).
[b] Assignments were supported by DEPT (except for **2d** and **8b**), 2D-HMQC and 2D-HMBC measurements.
[c] X=N (**2**, **5**,**7**,**8**).
[d] Two (three in **8b**) overlapping lines.
[e] Reversed assignment is also possible.
[f] Two (three in **8b**) overlapping lines.
[g] Two lines with a distance<0.1 ppm.

The structures of molecules of type **5** were earlier proved by using single-crystal diffraction and IR, $^1$H and $^{13}$C NMR spectroscopy.[12] The measured data on compounds **5d**–**f** characteristic of the presumed four-membered ring-condensed skeleton are very similar to those observed for the above-mentioned analogues, and thus the structures of the new molecules in question can be considered proven. As examples, C(OMe)=N: 160.3[12] and 159.8±0.4 ppm (**5d**–**f**), N($sp^2$)–C(pyrrole): 127.38±0.2[12] and 125.6±0.8 ppm (**5d**–**f**), OMe ($^1$H and $^{13}$C NMR shifts): 4.12±0.01[12] and 3.98 ppm (**5d**) and 4.01 (**5e**), respectively, and 54.3[12] and 54.5 (**5d**,**e**).

Desulfuration led to structures **7a**,**b**,**d**. This follows straightforwardly from the presence of the practically unchanged signals of the NH and 4-OMe groups and the two condensed benzene rings, respectively, and the upfield shifts of the C-4a and C-8a signals as compared with those of molecules of type **5**: C-4a: 128.4±0.2 ppm (**5d**–**f**) versus 112.6±0.5 ppm (**7a**,**b**,**d**), and C-8a: 128.7±0.3 ppm (**5d**–**f**) versus 122.9 ppm (**7a**,**b**,**d**).

In the IR spectrum of **10a**,**b**, instead of the high frequency of β-lactams, the ester bands appear: $\nu$C=O (β-enamino esters[21]): 1682 and 1671 cm$^{-1}$, $\nu_{as}$C–O: 1225 and 1230 cm$^{-1}$ and $\nu_s$C–O: 1055 and 1068 cm$^{-1}$, as expected.[18b]

The ring expansion is proved by the presence of the $CH_2$–NH–C=C(COOMe) moiety. Due to the vicinal coupling, the methylene and NH signals in the $^1$H NMR spectra are split to a doublet and a triplet, respectively. The chemical equivalence of the methylene H's indicates fast inversion of the azepine ring in **10a**,**b**.

The carbon signals of the enone group (β and α to the carbonyl) display very different chemical shifts: C(NH): 155.1 and 156.7 ppm, C(S): 92.3 and 87.8 ppm, in accordance with the literature.[20b] The polarization of the enone moiety is restrained by the electron-withdrawing effect of the *para*-nitrophenyl substituent in **10a**, due to the coplanar arrangement of this group and the enone moiety. Because of the steric interaction arising from the *ortho*-nitro group in **10b**, the aryl group is forced into an orientation perpendicular to the enone moiety and its *–I* effect cannot act in this arrangement. Consequently, the difference in the β- and α-carbon shifts mentioned above is significantly smaller in **10a** (62.8 ppm) than in **10b** (68.9 ppm).

## 4. Experimental

### 4.1. General

Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Elemental analyses were performed with a Perkin–Elmer 2400 CHNS elemental analyser. Merck Kieselgel 60$F_{254}$ plates were used for TLC, and Merck Silica gel 60 (0.063–0.100) for column chromatography. The $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature, on a Bruker DRX 500 spectrometer at 500 ($^1$H) and 126 ($^{13}$C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The standard Bruker micro program NOEMULT.AU to generate NOE was used with a selective preirradiation time. DEPT spectra were run in a standard manner, using only the $\Theta$=135° pulse to separate CH/$CH_3$ and $CH_2$ lines phased 'up' and 'down', respectively. The 2D-HSC and 2D-HMBC spectra were obtained by using the standard Bruker pulse programs. 1,3-Benzothiazines[14] (**2a**–**c**) and compounds **3a**–**c**, **4a**–**c** and **5a**–**c** were prepared by earlier methods.[12]

### 4.2. General procedure for the preparation of 4*H*-1,3-benzothiazine derivatives 2d,e and 8a,b

The appropriately substituted *N*-(3,4-dimethoxyphenylthiomethyl)-aroylamides (33.0 mmol) were heated with phosphorus oxychloride (10 mL) on a boiling water bath for 1 h. After cooling, the reaction mixture was decomposed with ice, neutralized with $Na_2CO_3$ and extracted with toluene. The toluene solution was dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. The residue was dissolved in hot ethanol (6 mL) and crystallized.

*4.2.1. 2-(3-Methyl-2-nitrophenyl)-6,7-dimethoxy-4H-1,3-benzothiazine (**2d**).* A pale-yellow crystalline powder, mp: 141–143 °C, yield

47%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.24. Anal. Calcd for $C_{17}H_{16}N_2O_4S$ (344.39): C, 59.29; H, 4.68; N, 8.13; S, 9.31. Found: C, 59.03; H, 4.92; N, 7.91; S, 9.60.

*4.2.2. 2-(5-Chloro-2-nitrophenyl)-6,7-dimethoxy-4H-1,3-benzothiazine (**2e**).* A pale-yellow crystalline powder, mp: 167–169 °C, yield 44%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.22. Anal. Calcd for $C_{16}H_{13}ClN_2O_4S$ (364.80): C, 52.68; H, 3.59; N, 7.68; S, 8.79. Found: C, 52.44; H, 3.81; N, 7.70; S, 8.88.

*4.2.3. 2-(4-Nitrophenyl)-6,7-dimethoxy-4H-1,3-benzothiazine (**8a**).* A pale-yellow crystalline powder, mp: 187–189 °C, yield 49%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.26. Anal. Calcd for $C_{16}H_{14}N_2O_4S$ (330.36): C, 58.17; H, 4.27; N, 8.48; S, 9.71. Found: C, 58.44; H, 3.98; N, 8.75; S, 9.95.

*4.2.4. 2-(4-Methyl-3-nitrophenyl)-6,7-dimethoxy-4H-1,3-benzothiazine (**8b**).* A pale-yellow crystalline powder, mp: 143–144 °C, yield 46%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.25. Anal. Calcd for $C_{17}H_{16}N_2O_4S$ (344.39): C, 59.29; H, 4.68; N, 8.13; S, 9.31. Found: C, 59.l2; H, 4.82; N, 7.82; S, 9.52.

### 4.3. General procedure for azetobenzothiazines 3d,e and 9a,b

To a stirred solution of the appropriately substituted 4*H*-1,3-benzothiazine derivative (**2 or 8**) (2.00 mmol) in anhydrous toluene (10 mL), monochloroacetyl chloride (3.00 mmol) was added. The solution was heated to reflux, and triethylamine (0.40 mL, 3.00 mmol) in anhydrous toluene (20 mL) was added dropwise during 4 h under reflux. The reaction mixture was then cooled and filtered, and the remaining triethylammonium chloride was washed with toluene. The organic layer was extracted with brine (20 mL) and dried with $Na_2SO_4$. After evaporation, the oily residue crystallized on trituration with ethanol.

*4.3.1. trans-2-Chloro-2a-(3-methyl-2-nitrophenyl)-2,2a-dihydro-5,6-dimethoxy-1H,8H-azeto[2,1-b][1,3]benzothiazin-1-one (**3d**).* A pale-yellow crystalline powder, mp: 222–224 °C, yield 87%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.58. Anal. Calcd for $C_{19}H_{17}ClN_2O_5S$ (420.87): C, 54.22; H, 4.07; N, 6.66; S, 7.62. Found: C, 54.51; H, 3.89; N, 6.82; S, 7.90.

*4.3.2. trans-2-Chloro-2a-(5-chloro-2-nitrophenyl)-2,2a-dihydro-5,6-dimethoxy-1H,8H-azeto[2,1-b][1,3]benzothiazin-1-one (**3e**).* A pale-yellow crystalline powder, mp: 230–234 °C, yield 92%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.60. Anal. Calcd for $C_{18}H_{14}Cl_2N_2O_5S$ (441.29): C, 48.99; H, 3.20; N, 6.35; S, 7.27. Found: C, 50.21; H, 3.35; N, 6.08; S, 7.48.

*4.3.3. trans-2-Chloro-2a-(4-nitrophenyl)-2,2a-dihydro-5,6-dimethoxy-1H,8H-azeto[2,1-b][1,3]benzothiazin-1-one (**9a**).* A pale-yellow crystalline powder, mp: 157–159 °C, yield 90%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.60. Anal. Calcd for $C_{18}H_{15}ClN_2O_5S$ (406.84): C, 53.14; H, 3.72; N, 6.89; S, 7.88. Found: C, 53.08; H, 4.01; N, 6.95; S, 8.12.

*4.3.4. trans-2-Chloro-2a-(4-methyl-3-nitrophenyl)-2,2a-dihydro-5,6-dimethoxy-1H,8H-azeto[2,1-b][1,3]benzothiazin-1-one (**9b**).* A pale-yellow crystalline powder, mp: 159–160 °C, yield 94%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.56. Anal. Calcd for $C_{19}H_{17}ClN_2O_5S$ (420.87): C, 54.22; H, 4.07; N, 6.66; S, 7.62. Found: C, 54.48; H, 4.24; N, 6.38; S, 7.79.

### 4.4. General procedure for indolo[2,3-*b*][1,4] benzothiazepines 5d–f from azetobenzothiazines 3d,e,a

Azeto-1,3-thiazine **3d**,**e**,**a** (0.66 mmol) was dissolved in dry methanol or in ethanol (40 mL). To the stirred solution, the appropriate sodium alkoxide (3.30 mmol) was added. The reaction mixture was stirred under reflux for 3 h. After evaporation, the residue was dissolved in dichloromethane (20 mL). The organic phase was extracted with water (10 mL), dried ($Na_2SO_4$) and evaporated.

*4.4.1. 6H-2,3,12-Trimethoxy-7-methylindolo[2,3-b][1,4]benzothiazepine (**5d**).* A pale-yellow powder, mp: 127–130 °C, yield 62%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.78. Anal. Calcd for $C_{19}H_{18}N_2O_3S$ (354.42): C, 64.39; H, 5.12; N, 7.90; S, 9.05. Found: C, 64.28; H, 5.30; N, 7.82; S, 9.23.

*4.4.2. 6H-2,3,12-Trimethoxy-9-chloroindolo[2,3-b][1,4]benzothiazepine (**5e**).* A pale-yellow powder, mp: 164–166 °C, yield 64%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.80. Anal. Calcd for $C_{18}H_{15}ClN_2O_3S$ (374.84): C, 57.68; H, 4.03; N, 7.47; S, 8.55. Found: C, 57.49; H, 4.33; N, 7.69; S, 8.82.

*4.4.3. 6H-2,3-Dimethoxy-12-ethoxyindolo[2,3-b][1,4]benzothiazepine (**5f**).* A pale-yellow powder, mp: >350 °C, yield 57%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.78. Anal. Calcd for $C_{19}H_{18}N_2O_3S$ (354.42): C, 64.39; H, 5.12; N, 7.90; S, 9.05. Found: C, 64.69; H, 5.34; N, 7.61; S, 8.80.

### 4.5. General procedure for indolo[3,2-*c*]isoquinolines 7a,b,d

Indolo[2,3-*b*][1,4]benzothiazepine **5a**,**b**,**d** (0.30 mmol) was dissolved in dimethylformamide and the solution was heated at reflux for 3 h. After evaporation, the oily residue crystallized on trituration with ethanol.

*4.5.1. 11H-2,3,5-Trimethoxyindolo[3,2-c]isoquinoline (**7a**).* A pale-yellow powder, mp: 260–263 °C, yield 86%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.45. Anal. Calcd for $C_{18}H_{16}N_2O_3$ (308.33): C, 70.11; H, 5.23; N, 9.09. Found: C, 70.32; H, 4.99; N, 9.21.

*4.5.2. 11H-2,3,5,8,9-Pentamethoxyindolo[3,2-c]isoquinoline (**7b**).* A pale-yellow powder, mp: 271–273 °C, yield 81%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.48. Anal. Calcd for $C_{20}H_{20}N_2O_5$ (368.38): C, 65.21; H, 5.47; N, 7.60. Found: C, 64.95; H, 5.67; N, 7.48.

*4.5.3. 11H-10-Methyl-2,3,5-trimethoxyindolo[3,2-c]isoquinoline (**7d**).* A pale-yellow powder, mp: 280–283 °C, yield 79%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.50. Anal. Calcd for $C_{19}H_{18}N_2O_3$ (322.36): C, 70.79; H, 5.63; N, 8.69. Found: C, 70.68; H, 5.90; N, 8.81.

### 4.6. General procedure for 4,5-dihydro-1,4-benzothiazepines 10a,b

Azeto-1,3-thiazine **9a**,**b** (0.66 mmol) was dissolved in dry methanol (40 mL). To the stirred solution, sodium methoxide (70 mg, 1.32 mmol) was added, and stirring was continued under reflux for 1 h. After evaporation, the residue was dissolved in dichloromethane (20 mL). The organic phase was extracted with water (10 mL), dried ($Na_2SO_4$) and evaporated.

*4.6.1. Methyl 3-(4-nitrophenyl)-4,5-dihydro-7,8-dimethoxy-1,4-benzothiazepine-2-carboxylate (**10a**).* An orange-yellow crystalline powder, mp: 200–202 °C, yield 87%; $R_f$ (*n*-hexane/EtOAc 4:1) 0.41. Anal. Calcd for $C_{19}H_{18}N_2O_6S$ (402.42): C, 56.71; H, 4.51; N, 6.96; S 7.97. Found: C, 56.49; H, 4.66; N, 7.20; S, 8.01.

*4.6.2. Methyl 3-(4-methyl-3-nitrophenyl)-4,5-dihydro-7,8-dimethoxy-1,4-benzothiazepine-2-carboxylate (**10b**).* An orange-yellow crystalline powder, mp: 179–185 °C, yield 91%; $R_f$ (*n*-

hexane/EtOAc 4:1) 0.43. Anal. Calcd for $C_{20}H_{20}N_2O_6S$ (416.45): C, 57.68; H, 4.84; N, 6.73; S, 7.70. Found: C, 57.82; H, 5.19; N, 6.98; S, 7.82.

## Acknowledgements

The authors express their thanks to the Hungarian Scientific Research Foundation (OTKA 101548 and K-68887) for financial support. The European Union and the European Social Fund also provided financial support for the project under grant agreement no. TÁMOP 4.2.1/B-09/KMR-2010-0003.

## References and notes

1. (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045; (b) Gribble, G. W. *Pure Appl. Chem.* **2003**, *75*, 1417; (c) Patil, S.; Boulamwini, J. K. *Curr. Org. Synth.* **2006**, *3*, 477; (d) Patil, S. A.; Patil, R.; Miller, D. D. *Curr. Med. Chem.* **2009**, *16*, 2531; (e) Russel, J. S. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier Ltd: Oxford, 2009; Vol. 21, p 145; (f) Song, J. J.; Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Arkivoc* **2010**, *i*, 390; (g) Patil, S. A.; Patil, R.; Miller, D. *Curr. Med. Chem.* **2011**, *18*, 615; (h) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. Biomol. Chem.* **2011**, *9*, 641; (i) Palmisano, G.; Penoni, A.; Sisti, M.; Tibiletti, F.; Tollari, S.; Nicholas, K. M. *Curr. Org. Chem.* **2010**, *14*, 2409; (j) Barluenga, J.; Rodriguez, F.; Fananas, F. J. *Chem.—Asian J.* **2009**, *4*, 1036; (k) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195.
2. *Name Reactions*; Li, J. J., Ed.; Springer: Berlin, Heidelberg, 2009.
3. (a) Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500; (b) Driver, T. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5056.
4. Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572.
5. Akiyama, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 8070.
6. (a) Liu, K. G.; Robichaud, A. J.; Lo, J. R.; Mattes, J. F.; Cai, Y. *Org. Lett.* **2006**, *8*, 5769; (b) Pei, T.; Chen, C.-Y.; Dormer, P. G.; Davies, I. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4231; (c) Ding, F.; Zhang, Y.; Qu, B.; Li, G.; Farina, V.; Lu, B. Z.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1067; (d) Leogane, O.; Lebel, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 350.
7. Dalpozzo, R.; Bartoli, G. *Curr. Org. Chem.* **2005**, *9*, 163.
8. Creencia, E. C.; Kosaka, M.; Muramatsu, T.; Kobayashi, M.; Iizuka, T.; Horaguchi, T. *J. Heterocycl. Chem.* **2009**, *46*, 1309.
9. (a) Wróbel, Z.; Makosza, M. *Tetrahedron* **1993**, *49*, 5315; (b) Makosza, M. *Pure Appl. Chem.* **1997**, *69*, 59; (c) Bobin, M.; Kwast, A.; Wróbel, Z. *Tetrahedron* **2007**, *63*, 11048.
10. (a) Preston, P. M.; Tennant, G. *Chem. Rev.* **1972**, *72*, 627; (b) Acheson, R. M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Elsevier Ltd.: Oxford, 1990; Vol. 51, p 106.
11. Fodor, L.; Csomós, P.; Csámpai, A.; Sohár, P. *Synthesis* **2010**, 2943.
12. Fodor, L.; Csomós, P.; Holczbauer, T.; Kálmán, A.; Csámpai, A.; Sohár, P. *Tetrahedron Lett.* **2011**, *52*, 224.
13. (a) Béres, M.; Timári, G.; Hajós, G. *Tetrahedron Lett.* **2002**, *43*, 6035; (b) Hiremath, S. P.; Saundane, A. R.; Mruthyunjayashwamy, B. H. M. *J. Heterocycl. Chem.* **1993**, *30*, 603; (c) Jagtap, P. G.; Baloglu, E.; Southan, G.; Williams, W.; Roy, A.; Nivorozhkin, A.; Landrau, N.; Kevin Desisto, K.; Andrew, L.; Salzman, A. L.; Szabó, C. *Org. Lett.* **2005**, *7*, 1753; (d) Jagtap, P.; Williams, W.; Szabó, C. WO. Patent, 082079, 2005; *Chem. Abstr.* **2005**, *143*, 279446; (e) Van Baelen, G.; Meyers, C.; Lemière, G. L. F.; Hostin, S.; Dommisse, R.; Maes, L.; Augustins, K.; Haemers, A.; Pieters, L.; Maes, B. U. W. *Tetrahedron* **2008**, *64*, 11802; (f) Qu, J.; Kumar, N.; Alamgir, M.; Black, D. StC. *Tetrahedron Lett.* **2009**, *50*, 5628.
14. Szabó, J.; Bani-Akoto, E.; Dombi, G.; Bernáth, G.; Fodor, L.; Sohár, P. *J. Heterocycl. Chem.* **1992**, *29*, 1513.
15. (a) Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 277; (b) Gleiter, R.; Krennrich, G.; Cremer, D.; Yamamoto, K.; Murata, I. *J. Am. Chem. Soc.* **1985**, *107*, 6874; (c) Fodor, L.; MacLean, D. B. *Can. J. Chem.* **1987**, *65*, 18; (d) Williams, C. R.; Harpp, D. H. *Sulfur Rep.* **1990**, *10*, 103; (e) Bole, M.; Liebscher, J. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Elsevier Ltd.: Oxford, 1996; Vol. 65, p 40; (f) Kassaee, M. Z.; Musavi, S. M.; Majdi, M.; Cheshmehkani, A.; Motamedi, E.; Aghaee, A. *J. Mol. Struct.: THEOCHEM* **2008**, *848*, 67; (g) Fu, R.; Xu, X.; Dang, Q.; Chen, F.; Bai, X. *Org. Lett.* **2007**, *9*, 571.
16. (a) Leonard, J.; Hague, A. B.; Jones, M. F. *Tetrahedron Lett.* **1997**, *38*, 3071; (b) Marques, M. M. B.; Santos, M. M. M.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **2000**, *41*, 9835; (c) Lobo, A. M.; Prabhakar, S. *J. Heterocycl. Chem.* **2002**, *39*, 429.
17. (a) Querioz, M.-J. R. P.; Castanheira, E. M. S.; Pinto, A. M. R.; Ferreira, I. C. F. R.; Begouin, A.; Kirsch, G. *J. Photochem. Photobiol., A* **2006**, *181*, 290; (b) Ishiyama, H.; Ohsita, K.; Abe, T.; Nakata, H.; Kobayashi, J. *Bioorg. Med. Chem.* **2008**, *16*, 3825; (c) Franck, P.; Hostyn, S.; Dajka-Halász, B.; Polonka-Bálint, Á; Monsieurs, K.; Mátyus, P.; Maes, B. U. W. *Tetrahedron* **2008**, *64*, 6030; (d) Eick, A.; Xiao, Z.; Langer, P.; Weisz, K. *Bioorg. Med. Chem.* **2008**, *16*, 9106.
18. Holly, S.; Sohár, P. In *Theoretical and Technical Introduction to the Series Absorption Spectra in the Infrared Region*; Láng, L., Prichard, W. H., Eds.; Akadémiai Kiadó: Budapest, 1975; (a) p 113; (b) p 101.
19. Fodor, L.; Szabó, J.; Sohár, P. *Tetrahedron* **1981**, *37*, 963.
20. Sohár, P. In *Nuclear Magnetic Resonance Spectroscopy*; CRC: Boca Raton, Florida, 1983; (a) Vol. 1, pp 35–38; (b) Vol. 2, p 181.
21. Wamhoff, H.; Dürbeck, H. W.; Sohár, P. *Tetrahedron* **1971**, *27*, 5873.