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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 8207–8211

Cyclopropanation of 3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-diones

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Received 22 August 2005; revised 13 September 2005; accepted 16 September 2005
Available online 11 October 2005

Abstract—A two step parallel synthesis protocol for the preparation of 1*N*-substituted spirobenzodiazepineones is described. Treatment of 4-methyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione with a series of alkyl halides using a microwave-assisted heating protocol provided *N*-derivatized compounds, which were transformed to the corresponding cyclopropylamines employing modified Kulinkovich-type reaction conditions. X-ray structural analysis gave conclusive evidence of the newly created spiro centre and revealed a significant flattening of the seven-membered ring system compared with the benzodiazepinedione system providing a characteristically different pattern of bond exit vectors. The physicochemical parameters $\log D$, pK_a, solubility and membrane permeability of both cyclopropanated and precursor compounds were assessed.

The cyclopropyl group has gained considerable interest in medicinal chemistry over recent years due to its interesting bond characteristics,[1] the ability to orient vectors in a unique three dimensional fashion,[2] the potential to control local conformation by restricting the number of rotational degrees of freedom and the possibility to fine-tune physicochemical properties. There has also been a continuing interest in the cyclopropyl group as an important synthetic intermediate especially for the synthesis of condensed structures and molecules of higher complexity.[3] A recent literature survey revealed more than 200 patents of pharmaceutically active compounds that contain a cylopropylamine moiety demonstrating this class to be of outstanding interest to the medicinal chemist.[4]

Over the last decades, benzodiazepinones have emerged as a particularly fascinating class of scaffolds in medicinal chemistry and have been viewed repeatedly as the prototype of a 'privileged structure' as they hit various classes of pharmacologically relevant targets such as GPCRs, ion channels and enzymes.[5] Prominent examples include the $GABA_A$ agonists *Diazepam*[6] (sedative) or *Zolpidem*[7] (nonaddictive hypnotic), the antitumour antibiotic *Chicamycin-A*[8] or the cholecystokinin antagonist *Asperlicin*,[9] respectively. The number of publications on benzodiazepines in general and the recurrent interest in novel synthetic routes towards benzodiazepine backbones underlines the continuing interest in this enduring compound class.[10] Herein, we describe the merger of these two structurally appealing compound classes into one single molecule, namely cyclopropanated benzodiazepineones, and the exploration of their potentially interesting physicochemical properties.

In 1996 de Meijere et al. described the extension of the classical Kulinkovich reaction[11] transforming alkyl esters into cyclopropanols to amides using stoichiometric amounts of titanium reagent allowing corresponding cyclopropylamines to be synthesized in a convenient one-step procedure.[12] Not surprisingly, it was reported that this reaction does not work on primary and secondary amides as well as on α,β-unsaturated systems.[13] We thus speculated that the Kulinkovich-type reaction applied to benzodiazepinediones would occur in a regioselective fashion exclusively at the acetamide moiety, leaving the benzamide group unaffected due to its α,β-unsaturated character.

Condensation of isatoic acid anhydride (**1**) and glycine (**2**) or sarcosine (*N*-methylglycine, **3**) at 120 °C in a 1:1 mixture of acetic acid and DMF afforded the unprotected benzodiazepinedione **4** or the *N*-methylbenzamide derivative **5**, respectively, which were used as the first

Keywords: Benzodiazepineone; Kulinkovich reaction; Combinatorial chemistry; Medicinal chemistry.
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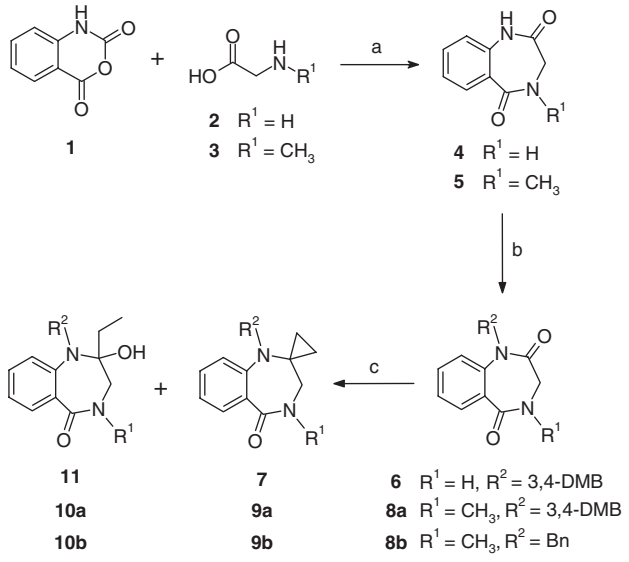
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.09.096

substrates to investigate the cyclopropanation reaction (Scheme 1). As expected, using starting material, $Ti(OiPr)_4$ and CH_3CH_2MgBr in a ratio of 1:1:2 did not show any signs of conversion to the desired products of both the doubly unprotected compound **4** and the benzamide methylated derivative **5** according to analytical HPLC, which can be attributed to the presence of acidic amide protons. Interestingly, the acetamide protected compound **6** containing a free benzamide moiety did provide the corresponding cyclopropanated reaction product **7**, albeit in very poor yields of only 10%.[14] However, most of the starting material was recovered. Conducting the reaction with the doubly alkylated compound **8a**, which can be obtained by either benzylation of acetamide **5** or methylation of benzamide **6**, $Ti(OiPr)_4$ and CH_3CH_2MgBr in a ratio of 1:1:2 resulted in a significant increase of the desired cyclopropanated product **9a** to 35% isolated yield. However, the main product obtained was Grignard-adduct **10a**.

Systematic variation of the reaction conditions including time, temperature and sequence of reagent addition and ratio had only a minor influence on the yield of the cyclopropanated product **9a** yielding still considerable amounts of undesired addition product **10a** in all cases.

A considerable improvement in terms of product to starting material ratio was observed when the reaction was conducted with $CH_3Ti(OiPr)_3$ instead of $Ti(OiPr)_4$, consistent with previous observations.[15] Increasing the ratio of titanium versus Grignard reagent improves product ratios in favour of the cyclopropanated product (Table 1).[16] For instance, changing the ratio of benzylated compound **8b**/$CH_3Ti(OiPr)_3$/CH_3CH_2MgBr from 1:1:1 to 1:2:1 resulted in a significant increase of the ratio of desired product **9b** relative to Grignard adduct **10b** from 0.76 to 25, although the ratio of combined products **9b** + **10b** to starting material **8b** dropped slightly from 0.79 to 0.58 (Table 1, entries 1 and 3). Most importantly, the use of $CH_3Ti(OiPr)_3$ enabled both the complex formation as well as the cyclopropanation reaction to be carried out at rt rather than −78 °C, simplifying considerably the synthetic protocol and making it amenable to parallel synthesis. In contrast, performing the reaction with $Ti(OiPr)_4$ at rt resulted in decomposition of the entire starting material.

In order to elucidate the structural impact of the cyclopropyl group on the benzodiazepine scaffold we conducted single crystal X-ray analysis studies on both starting material **8c** and the corresponding cyclopropanated product **9c** (Fig. 1).[17,18]



Scheme 1. Synthesis of cyclopropanated benzodiazepinones. Reagents and conditions: (a) CH_3COOH/DMF (1:1), 120 °C, 18 h, **4**: 82%, **5**: 84%; (b) R_2Cl/R_2Br, K_2CO_3, DMF, MW 140 °C, 20 min, **8a**: 65%, **8b**: 83%; (c) (i) $Ti(OiPr)_4$, CH_3CH_2MgBr, THF, −78 °C → rt, 16 h, **7**: 10%, **9a**: 35%; (ii) $CH_3Ti(OiPr)_3$, CH_3CH_2MgBr, THF, rt, 16 h, **9b**: 75%. DMB = 3,4-di-methoxybenzyl; Bn = benzyl.

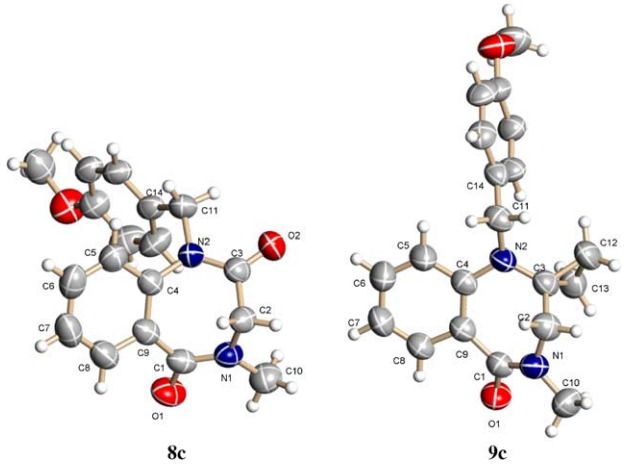


Figure 1. Single crystal X-ray diffraction analysis of parent and cyclopropanated benzodiazepinones **8 c** and **9c**, respectively. The ORTEP drawing depicts thermal ellipsoides at a 30% probability level.

Table 1. Reaction conditions, yields and ratios obtained for the optimization of the cyclopropanation reaction of benzodiazepinedione **8b**

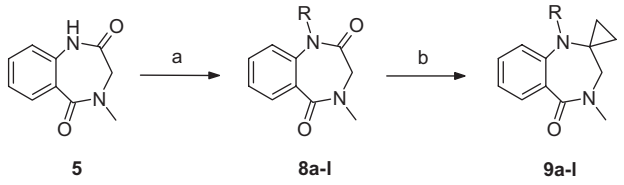
Entry	Starting material (SM)	SM/$CH_3Ti(OiPr)_3$/CH_3CH_2MgBr[a]	Ratio (**9b**+**10b**)/**8b**[b]	Ratio **9b**/**10b**[c]
1	**8b**	1:1:1	0.79	0.76
2	**8b**	1:1:2	0.68	0.54
3	**8b**	1:2:1	0.58	25
4	**8b**	1:2:2	0.66	2.3

[a] Complex formation 1 h at rt, reaction at rt.
[b] Ratio determined by analyt. HPLC.
[c] Estimated by quantitative TLC spot analysis.

As anticipated the benzodiazepinedione **8c** structure shows a perfect boat-like conformation of the seven-membered ring system. In contrast, the cyclopropanated compound **9c** does not exhibit a twist-like conformation as observed for benzazepinone derivatives, indicating that conjugation of the anilinic nitrogen with the aromatic system is strong enough to maintain coplanarity about the endocyclic C^4–N^2 bond with the aryl system.[19] The exocyclic C^{11}–N^2 bond deviates somewhat from planarity causing a slight pyrimidalization at the aniline nitrogen atom. The stronger conjugation of this nitrogen atom with the phenyl group in **9c** is also evidenced by a significant shortening of the C^4–N^2 bond lengths from 1.44 to 1.39 Å, typical for alkyl-substituted aniline derivatives, accompanied by a concomitant lengthening of the N^2–C^3 bond from 1.37 Å in **8c** to 1.44 Å in structure **9c**, respectively. The resulting conformation might best be described as an 'envelope-type' conformation with five atoms in plane and two atoms (N^1, C^2) forming a twisted flap. This flattening of the seven-membered ring system upon cyclopropanation is interesting from a structural and medicinal chemistry point of view as it gives access to a characteristically distinct pattern of bond exit vectors emanating from the benzoyl lactam nitrogen (N^1) and the methylene carbon (C^2).

The preparation of a cyclopropanated benzodiazepinone compound library using the optimized Kulinkovich-type reaction protocol is outlined in Scheme 2.

Alkylation of building block **5** with a series of different alkyl and benzyl halides using K_2CO_3 as a base in DMF under microwave-assisted heating to 140 °C for 20 min provided benzodiazepinediones **8a–l** in good to excellent yields after purification by preparative HPLC.[20] Treatment of library **8a–l** with a 2.5-fold excess of a preformed 2:1 complex of $CH_3Ti(OiPr)_3$ and CH_3CH_2MgBr at rt for 16 h provided the expected compounds **9a–l** after isolation by preparative HPLC in moderate yields (Table 2). The cyclic methylene group in benzodiazepinediones **8a–l** display two diastereotopic protons giving rise to a classical AB system in the ^1H NMR spectra. Interestingly, these two distinctly different protons merge to a singlet for all products **9a–l**, indicating an increased conformational flexibility of the cyclopropanated framework compared to the more rigid benzodiazepinediones **8a–l**. Similarly, the exocyclic methylene groups present in compounds **8a–f**, which also display a pair of doublets, merge to a single signal for the cyclopropanated analogues **9a–f**.



Scheme 2. Parallel synthesis of cyclopropanated benzodiazepinones. Reagents and conditions: (a) RCl/RBr, K_2CO_3, DMF, MW 140 °C, 20 min; (b) $CH_3Ti(OiPr)_3$, CH_3CH_2MgBr, THF, rt, 16 h.

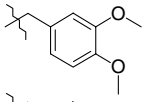
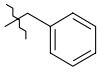
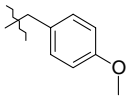
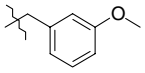
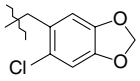
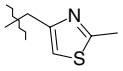
The physicochemical data of compound library **8a–l** and **9a–l** including aniline basicity (pK_a), solubility (Lysa), passive membrane permeation (Pampa)[21] and distribution coefficients ($\log D$) are summarized in Table 2. The cyclopropanated compounds **9a–l** display pK_a values between 3.0 and 3.9. Compared with amide counterparts **8a–l**, the solubility of all cyclopropanated compounds investigated decreases considerably, with the only exception being compound pair **8f/9f** where nearly identical solubilities for both starting material and product were obtained.

Interestingly, permeabilities increase from amide to cyclopropanated compounds with short alkyl substituents **8g–i/9g–i** whereas in compound pairs with aromatic and more bulky alkyl substituents such as **8a–e/9a–e** and **8j–l/9j–l** a trend towards lower permeability values is observed. Again the thiazole pair **8f/9f** is an exception, following the trend of the shorter alkyl substituents rather than the aromatic side chains, showing a higher permeability of the cylopropanated compound **9f** compared with the corresponding amide **8f**. The conversion of amides to the corresponding cyclopropanated amines on average increases the lipophilicity $\log D$ by about 1.2 units. However, for thiazole compound pair **8f/9f** only a minor increase of 0.2 units and for isopropyl counterparts **8i/9i**, a significant higher than average increase of 1.7 units is observed. The exception of compounds **8f/9f** from the general trend with respect to Lysa, Pampa or $\log D$ indicates that the thiazole side chain dominates the overall physicochemical properties of the molecule.

In summary, a convenient protocol for the regioselective cyclopropanation of benzodiazepinediones was developed using a modified Kulinkovich-type reaction protocol. The use of $CH_3Ti(OiPr)_3$ allowed the cyclopropanation to be carried out at rt, which greatly facilitated the rapid assembly of a compound library in a parallel fashion. The successful incorporation of a cyclopropyl group exclusively at the acetamide moiety was confirmed by ^1H NMR, ^{13}C NMR, HRMS as well as single crystal X-ray diffraction analysis. Assessment of the physicochemical properties of **9a–l** revealed interesting trends with respect to solubility and lipophilicity in comparison to their amide precursors **8a–l**. The spirocyclic benzodiazepinone backbone represents an interesting novel template that offers several possibilities for further modification, which may result in new biological activity.

General procedure: Compound library **8a–l**: To a solution of building block **5** (0.095 g, 0.5 mmol, 1.0 equiv) in DMA (1.0 mL) was added Cs_2CO_3 (0.65 g, 2.5 mmol, 5.0 equiv) and the corresponding alkylbromide/chloride (0.75 mmol, 1.5 equiv). After microwave-assisted heating to 140 °C for 20 min (Emrys Optimizer, Personal Chemistry) the reaction mixture was concentrated under reduced pressure, a solution of satd $NaHCO_3$ (1 mL) added and the mixture extracted with ethyl acetate (3 × 1 mL). The organic phases were combined and the organic solvent removed under reduced pressure, the residues dissolved

Table 2. Isolated yields and physicochemical data of both starting materials **8a–l** and cyclopropanated analogues **9a–l**

Compound	R	Yield[a] (%)	pK_a[b]	Lysa[c] (μg/mL)	Pampa Pe[d] (10^{-6} cm/s)	log D[e]
8a		31	—	53	7.7	1.8
9a		8	3.2	14	2.9	3.1
8b		23	—	>326	9.3	1.9
9b		43	3.1	23	4.1	2.9
8c[22]		41	—	208	7.6	1.4
9c[23]		20	3.0	49	5.7	2.6
8d		42	—	326	8.5	1.5
9d		15	3.2	71	4.2	2.6
8e		31	—	53	7.7	1.8
9e		8	3.2	14	2.9	3.1
8f		22	—	>378	5.4	1.9
9f		24	3.4	>352	6.4	2.1
8g		30	—	208	2.4	0.1
9g		16	3.1	123	6.0	1.4
8h		31	—	>290	3.9	0.5
9h		15	3.4	121	9.3	1.9
8i		44	—	>262	6.1	0.9
9i		25	3.4	71	8.3	2.6
8j		74	—	>255	5.3	0.7
9j		32	3.9	76	3.1	2.1
8k		33	—	>292	7.4	0.9
9k		20	3.4	168	6.2	2.3
8l		53	—	>307	9.0	1.4
9l		33	3.4	122	7.3	2.7

[a] After preparative HPLC purification.
[b] pK_a values were determined spectrophotometrically on a ProfilerSGA instrument in a SGA buffer system containing 10% (v/v) methanol at an ionic strength of 150 mM.
[c] Lyophilization solubility assay. Solubility was measured from lyophilized DMSO stock solutions spectrophotometrically at pH = 6.5 in a 50 mM phosphate buffer.
[d] Parallel Artificial Membrane Permeation Assay: low: Pe < 0.1, medium: 0.1 < Pe < 1.0, high: Pe > 1.0.
[e] log D values were measured spectrophotometrically at pH = 7.4 in a 1-octanol/50 mM TAPSO buffer system containing 5% (v/v) DMSO.

in DMSO, filtered and purified by preparative HPLC affording compounds **8a–l**. Compound library **9a–l**: To 12 solutions of $CH_3Ti(OiPr)_3$ (0.12 g, 0.5 mmol, 5.0 equiv) in dry THF (2 mL) at 0 °C was added in parallel slowly a solution of 1.0 M CH_3CH_2MgBr in THF (0.25 mL, 0.25 mmol, 2.5 equiv), which immediately resulted in the formation of a dark brown suspension. After stirring for 1 h, compounds **8a–l** (0.1 mmol, 1.0 equiv), dissolved in dry THF (2 mL), were added and the reaction mixtures shaked at rt for 16 h. Addition of a solution of 1.0 M NH_4Cl (1 mL), extraction with diethyl ether (3 × 1 mL) and combination of the organic phases provided after removal of the organic solvent under reduced pressure the crude reaction products. Dissolution in DMSO, filtration and purification by preparative HPLC gave compounds **9a–l**.

Acknowledgements

We are very much indebted to Professor Klaus Müller and Dr. Mark Rogers-Evans for seeding the ideas of this study as well as to Drs. Konrad Bleicher and Luke Green for many helpful discussions. We are also grateful to the Analytical Services and the Molecular Properties Group for providing spectroscopic and physicochemical data, respectively, as well as to Mr. André Alker for solving the single crystal X-ray structures.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.096.

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14. Compound **6** was prepared in 75% yield by reaction of 3,4-dimethoxy-benzyl-protected isatoic acid anhydride with glycine at 125 °C for 3 h followed by stirring at rt overnight in concd acetic acid.
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16. To guide the optimization process, the ratio of products **9b** and **10b** to starting material **8b** was assessed by analyt. HPLC. Due to the inability to resolve the reaction products **9b** and **10b** by HPLC they were quantified via TLC spot analysis conducted by a Camag Reprostar 3 UV cabinet using the UV image processing software Video-Scan TLC/HPTLC 1.0.01 and Video Store 2.25© from Synoptics Ltd, Camag.
17. Single crystals of **8c** and **9c** were obtained by slow evaporation of dichloromethane from a mixture of dichloromethane and heptane (1:1).
18. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 272207 and 272208. These data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
19. A search in the CSD database (CSD Version 5.26, November 2004, holding over 325'000 crystal structures of organic and metallorganic compounds) revealed two structurally close analogues. In the first structure the benzodiazepinone is annelated by a tetrahydropyrane ring (ref. code ITEPIG, Abrous, L.; Jokiel, P. A.; Friedrich, S. R.; Hynes, J., Jr.; Smith, A. B., III; Hirschmann, R. *J. Org. Chem.* **2004**, *69*, 280–302) showing a similar 'boat-like envelope' conformation as the cyclopropanated compound **9c**. In contrast, the second structure, a closely related benzazepinone (ref. code ISIFIZ, Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T.; private communication to the CSD), lacking the spirocyclopropane moiety of **9c**, displays a twist-like conformation as typically observed for many benzodiazepinone derivatives.
20. Compounds were purified by preparative HPLC on an Xterra® PrepMSC18, 5 μm, 19 × 50 mm column equipped with a Gilson Liquid Handler 215 autosampler, two Rainin Dynamax® SD-300 pumps a Sedex ELSD 75 lightscatter and a Dionex UVD 340S UV detector.
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22. Spectroscopic data for compound **8c**: ^{1}H NMR (300 MHz, DMSO): δ 3.14 (s, 3H), 3.68 (s, 3H), 3.76 (d, $J = 14.8$ Hz, 1H), 4.15 (d, $J = 14.8$ Hz, 1H), 4.90 (d, $J = 15.7$ Hz, 1H), 5.25 (d, $J = 15.7$ Hz, 1H), 6.80 (d, $J = 8.7$ Hz, 2H), 7.01 (d, $J = 8.7$ Hz, 2H), 7.24–7.65 (m, 4H). ^{13}C NMR (75 MHz, DMSO): δ 35.16, 48.16, 52.33, 54.94, 113.87, 121.98, 125.40, 128.07, 128.91, 129.52, 129.94, 131.68, 139.29, 158.26, 166.32, 167.97. FTIR (ATR, cm^{-1}): 2934 (w), 2839 (w), 1672 (s), 1632 (s), 1601 (s), 1512 (s), 1466 (m), 1397 (m), 1240 (s), 1213 (m), 1174 (m). HRMS (EI POS) *m/z* calculated for $C_{18}H_{18}N_2O_3$ $(M)^+$: 310.1317, found: 310.1317.
23. Spectroscopic data for compound **9c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.65 (t, $J = 6.6$ Hz, 2H), 0.92 (t, $J = 6.6$ Hz, 2H), 3.08 (s, 3H), 3.31 (s, 2H), 3.70 (s, 3H), 4.40 (s, 2H), 6.65 (d, $J = 8.0$ Hz, 1H), 6.75 (d, $J = 8.6$ Hz, 2H), 6.89 (t, $J = 7.9$ Hz, 1H), 7.01 (d, $J = 8.6$ Hz, 2H), 7.14 (td, $J = 8.0$ Hz, $J = 1.7$ Hz, 1H), 8.11 (dd, $J = 7.9$ Hz, $J = 1.7$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.01, 37.91, 45.66, 55.24, 56.58, 58.98, 113.97, 120.66, 120.86, 126.42, 127.67, 131.46, 131.74, 133.14, 148.62, 158.68, 169.28. FTIR (ATR, cm^{-1}): 2923 (w), 2853 (w), 1621 (s), 1595 (s), 1587 (m), 1507 (s), 1482 (s), 1455 (m), 1389 (m), 1284 (m), 1241 (s), 1212 (s), 1167 (s). HRMS (EI POS) *m/z* calculated for $C_{20}H_{22}N_2O_2$ $(M)^+$: 322.1681, found: 322.1681.