Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Synthesis of novel aza-heterocyclic derivatives from diester and diacid chlorides having the dibenzobarrelene skeleton

İrfan Çapan & Süleyman Servi

To cite this article: İrfan Çapan & Süleyman Servi (2018): Synthesis of novel aza-heterocyclic derivatives from diester and diacid chlorides having the dibenzobarrelene skeleton, Synthetic Communications, DOI: 10.1080/00397911.2018.1437449

To link to this article: https://doi.org/10.1080/00397911.2018.1437449

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2018.1437449

Taylor & Francis
Taylor & Francis Group

Synthesis of novel aza-heterocyclic derivatives from diester and diacid chlorides having the dibenzobarrelene skeleton

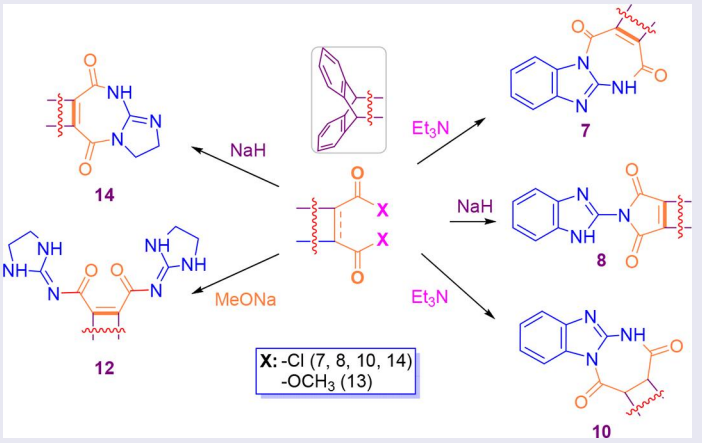
İrfan Çapan[a] and Süleyman Servi[b]

[a]Department of Polymer Technology, Technical Sciences Vocational College, Gazi University, Ankara, Turkey; [b]Department of Chemistry, Faculty of Science, Fırat University, Elazığ, Turkey

ABSTRACT

When attempting to synthesize the symmetric aza-heterocyclic-substituted dibenzobarrelene derivatives from the 2-aminobenzimidazole (or 2-aminoimidazoline) with diacid chlorides and diester in the presence of various organic bases, different products were isolated in high yield. NMR spectroscopic analysis proved these products to be dibenzobarrelene-substituted fused benzimidazodiazepine, imidazolinediazepine, and dicarboxamides derivatives. Cyclic or noncyclic dicarboxamides with the dibenzobarrelene skeleton have been synthesized for the first time using these methods.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 10 December 2017

KEYWORDS
Benzimidazolediazepine; dibenzobarrelene; dicarboxamides; guanidine; imidazolinediazepine

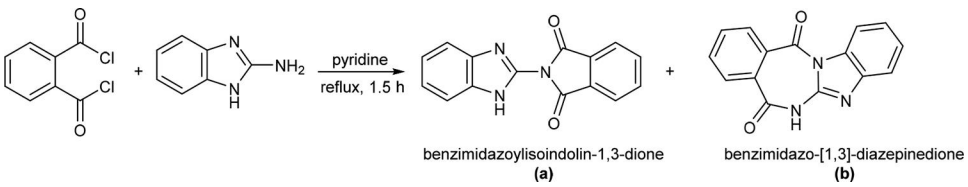
Introduction

Benzimidazole and imidazolines of natural or synthetic origin are found in the molecular structure of many drugs. Since these compounds have a wide range of chemotherapeutic applications, they are widely used in the medicine design strategy.[1–6] There are different methods for the synthesis of 2-substituted benzimidazole and imidazoline compounds in

CONTACT Süleyman Servi sservi@firat.edu.tr Department of Chemistry, Faculty of Science, Fırat University, Elazığ, 23169 Turkey.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.

Supplemental data (experimental procedures and supplementary data associated with the synthesized compounds; data include experimental and the spectra (^{1}H-, ^{13}C-, and HETCOR-NMR) of the aza-heterocyclic derivatives (compounds **7, 8, 10, 12**, and **14**) having the dibenzobarrelene skeleton) can be accessed on the publisher's website.



Scheme 1. The phthaloylation reaction of 2-aminobenzimidazole with phthaloyl chloride.

the literature.[7–11] In the synthesis of these compounds, in addition to classical synthesis methods, solid support, solvent-free, ionic liquids and microwave-assisted synthesis methods are also used.[7]

Diazepine core is considered as a privileged structure to access active compounds displaying a wide range of pharmacological activities. In particular, polyfused diazepine derivatives led to the discovery of compounds with anticancer potency.[12] Moreover, heterocycles containing the imidazo[4,5-*e*][1,3]diazepine ring system have shown potent *in vitro* activity at low micromolar concentrations against lung, breast, ovarian, and prostate cancer cell lines.[13,14] As chemical structures of these drugs are investigated more closely, it is understood that the carboxamide functional group is the major component of five-, six-, or seven-membered heterocyclic ring structures.[14]

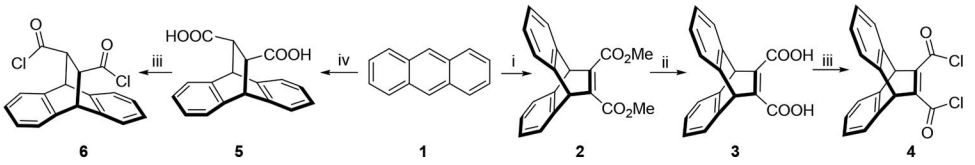
In the literature, the reaction of phthaloyl chloride with different 2-aminobenzimidazoles has been mechanistically investigated to conclude a discussion that began in previous years.[15] The reaction of these compounds resulted in either benzimidazoylisoindolin-1,3-dione (**a**) or the benzimidazo-[1,3]-diazepinedione (**b**) (Scheme 1). The structures of the obtained products with the phthaloylation reaction were clarified using ^{1}H-NMR spectroscopy. The benzimidazo-[1,3]-diazepinedione (**b**) is stable at room temperature but can easily be converted into the thermodynamic more stable benzimidazoylisoindolin-1,3-dione (**a**).[15] This conversion is dependent on the substituents on the 2-aminobenzimidazole, the solvent used, the base, and type of the guanidine nucleophiles.[15,16]

Unlike heteroaromatic-substituted benzene dicarboxamides, benzimidazole or imidazoline derivatives which contain diazepine, imide, and dicarboxamides fused to the dibenzobarrelene skeleton are not known in the literature. In this work, we aimed at the synthesis of imidazoline and benzimidazole-substituted novel dibenzobarrelene derivatives.

Results and discussion

The aza-heterocyclic derivatives incorporated into the dibenzobarrelene skeleton were synthesized from diacid chlorides (or diester) with the 2-aminobenzimidazole (**9**) or 2-aminoimidazoline *p*-toluenesulfonate (**11**) in the presence of various bases. The compounds **7, 8, 10**, and **14** were synthesized using new methods (**Methods A** and **B**), while compound **13** was synthesized by modifying the known **Method C**.[17] The synthetic routes for the preparation of different aza-heterocyclic derivatives are outlined in Schemes 2–6.

Diels–Alder cycloaddition reaction was used to synthesize the starting reactants from the different dienophiles and anthracene. Diacid chlorides **4** and **6**, and the diester-**2**, which have the dibenzobarrelene skeleton, were used as the starting reagents. The diacid chloride-**4** was synthesized from the reaction of $SOCl_2$ with the diacid, which obtained from the hydrolysis of the diester-**2** in the basic medium. Similarly, the diacid chloride-**6** was synthesized from the reaction $SOCl_2$ with the diacid, which was obtained from the

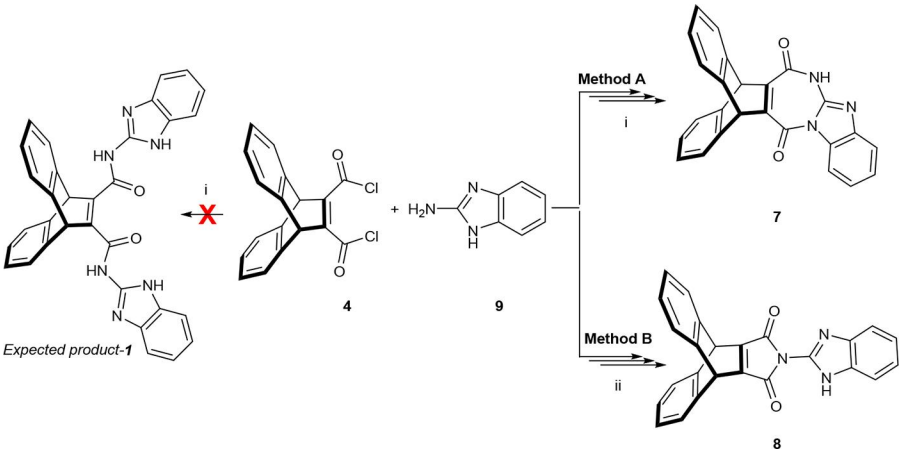


Scheme 2. Synthesis of diacid chlorides (**4, 6**) and diester (**2**) compounds used as the starting reagents. Reagents and conditions: (i) DMAD, argon atmosphere, 170–180 °C; (ii) NaOH; (iii) $SOCl_2$, benzene, 3-h reflux; (iv) fumaric acid, 1,4-dioxane, 72-h reflux.

reaction of anthracene and fumaric acid (Scheme 2). Starting compounds **2, 4**, and **6** were described in the literature.[18]

To synthesize the *Expected product-1* by the nucleophilic addition–elimination reaction on acyl carbon, the reaction was performed under the argon atmosphere at 0 °C in THF. In this reaction, when the diacid chloride-**4**/**9**/Et_3N reagents were used in the molar ratio of 1/2/2, the benzimidazolediazepine **7** was obtained in 82.8% yield instead of *Expected product-1* (**Method A**). NaH was used as the base instead of the Et_3N in THF in **Method B**. When the acid chloride-**4**/**9**/NaH molar ratio of 1/1/2 was used, compound **8** was isolated in 74.3% yield.

The methods for the synthesis of compounds **7** and **8** are given in Scheme 3. In the FT-IR spectrum of the isolated product, the observation of amide carbonyl at 1634 cm^{-1} suggested that *Expected product-1* was formed. However, a detailed NMR evaluation (^{1}H-, ^{13}C-, and COSY) revealed that the isolated product was compound **7**. In the ^{1}H-NMR spectrum, while in the *Expected product-1* structure required 16 protons in the aromatic region, there were 12 protons in this region. The bridgehead proton signals (H-1 and H-4) were observed at 6.13 and 5.99 ppm as two different signals. In the ^{13}C-APT-NMR spectrum of compound **7**, the presence of two different amide carbonyl (C-9 and C-10) signals at 167.95 and 164.64 ppm proved that the molecular structure of



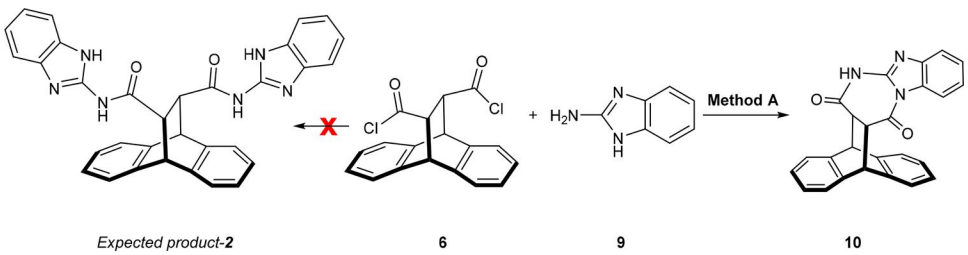
Scheme 3. Synthesis of compounds **7** and **8** from the reaction of compound **4** with **9**. Reagents and conditions: (i) Et_3N, anhyd. THF, 0 °C, argon atmosphere; (ii) NaH, anhyd. THF, 0 °C, argon atmosphere. The molar ratio of **Method A**: comp. **4** (1 equiv.), comp. **9** (2 equiv.), Et_3N (2 equiv.); **Method B**: comp. **4** (1 equiv.), comp. **9** (1 equiv.), NaH (2 equiv.).

the benzimidazolediazepine was not symmetric. In the FT-IR spectrum of compound **8**, only one stretching vibration was observed belonging to the amide carbonyl at 1633 cm^{-1}. In the ^{1}H-NMR spectrum, the H-1 and H-4 bridgehead protons resonated as 2H singlet at the same chemical shift. The ^{13}C-APT-NMR spectrum proved that the molecular structure is the symmetrical imide, since the C-1 and C-4 bridgehead carbons observed at 53.53 ppm were equivalent. (Details of the NMR analysis of compounds **7, 8, 10, 12**, and **14** can be found in the Supporting Information section.)

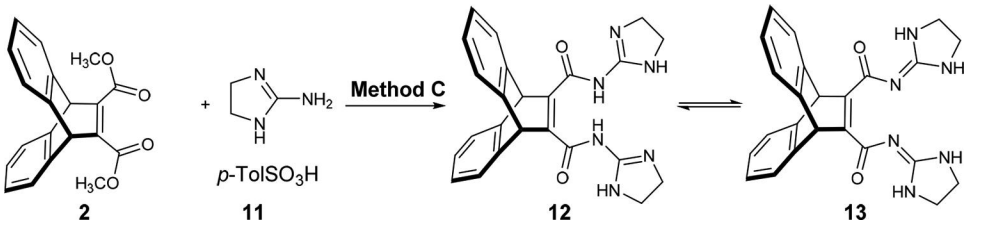
The *trans*-diacid chloride-**6** was used in the next stage of this work; instead of benzimidazolediazepine **10**, it was thought that the *Expected product-2* compound could be easily obtained. However, compound **10** was isolated in 71.9% yield instead of *Expected product-2* at the same reagent molar ratios used in the **Method A** (Scheme 4) for the synthesis of compound **7**. In the NMR spectra of compound **10**, findings similar to compound **7** were obtained. In addition to this similar data in the ^{1}H-NMR spectrum, the signals for the H-7 and H-8 protons were observed between 3.45 and 3.35 ppm. The mass spectrum data supported this structure.

In the literature, there is the method for the synthesis of 2-imidazoline derivatives from the reaction of the ester compounds with the 2-aminoimidazoline *p*-toluenesulfonate.[17] In this method, *N*-substituted (imidazolidin-2-ylidene) amides have been synthesized in yields between 40 and 75% in methanol in the presence of sodium methoxide as the base. In our study, this method was used by modifying to synthesize compound **12** (Scheme 5, **Method C**). This compound was obtained in 39.1% yield from the reaction of the diester-**2** with compound **11**, which was synthesized according to the cited reference.[17]

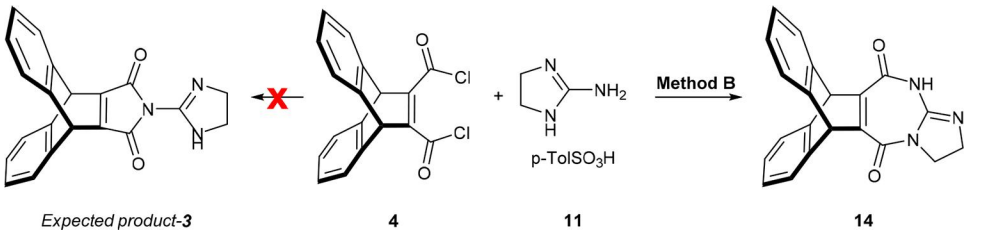
In the ^{1}H-NMR spectrum taken in DMSO-d_6, the imidazoline methylene protons were not observed clearly because they coincided with the signals of the proton residues of the DMSO-d_6. For this reason, the spectrum was taken up in $CDCl_3$ by adding two drops of acetic acid. In symmetrical imidazoline compounds, the CH_2 proton signals are observed as the singlet, while in other unsymmetrical 2-imidazoline compounds, these protons are observed as the triplet. The imine–enamine dynamic tautomerization makes the CH_2 protons equivalent. At the same time, this effect causes lowering of the order of the spectra ($\Delta\upsilon/J = 0$).[19] When the spectrum data were analyzed, the signal of the methylene protons on the imidazoline ring appeared equivalent with a 8H singlet observed at 3.65 ppm. The bridgehead proton signals observed 2H singlet at 6.01 ppm. In the ^{13}C-APT-NMR spectrum, the imidazoline methylene carbon signals were observed at 42.95 ppm, while the bridgehead carbon signal was observed at 53.57 ppm. In the HETCOR spectrum, the



Scheme 4. Synthesis of compound **10** from the reaction of compound **6** with **9**. Reagents and conditions: Et_3N, anhyd. THF, 0 °C, argon atmosphere. The molar ratio of **Method A**: comp. **6** (1 equiv.), comp. **9** (2 equiv.), Et_3N (2 equiv.).



Scheme 5. Synthesis of compound **12** from the reaction of compound **2** with **11**. Reagents and conditions: metallic Na, CH_3OH, and room temperature. The molar ratio of **Method C**: comp. **2** (1 equiv.), comp. **11** (2.6 equiv.), and metallic Na (2.8 equiv.).



Scheme 6. Synthesis of compound **14** from the reaction of compound **4** with **11**. Reagents and conditions: NaH, anhyd. THF, argon atmosphere. The molar ratio for **Method B**: comp. **4** (1 equiv.), comp. **11** (1 equiv.), and NaH (2 equiv.).

CH_2 proton signals at 3.65 ppm coincided with the CH_2 carbon signals at 42.95 ppm and the bridgehead proton signal at 6.01 ppm coincided with the carbon signal at 53.57 ppm.

We aimed to synthesize the 2-imidazoline derivative of diacid chloride-**4** after compound **8** has been isolated and characterized. Under the same molar ratios and the experimental condition for the synthesis of compound **8**, compound **14** was obtained in 68.9% yield instead of the targeted *Expected product-3* (**Method B**, Scheme 6). In the ^{13}C-APT-NMR spectrum, the observation of two different amide carbonyl signals, bridgehead methine carbons, and imidazoline methylene carbon signals confirmed that the molecule was unsymmetrical. When the ^{1}H-NMR spectrum of compound **14** was analyzed, it was understood that the chemical structure contained 1-mol ethyl acetate. Therefore, the signals belonging to ethyl acetate were observed in the NMR spectra of this compound.

Experimental section

The synthetic routes for the preparation of compounds are outlined in Schemes 2–6. The preparation of these compounds is briefly described as follows.

General synthesis of 8,13-dihydro-6H-8,13-[1,2]benzenobenzo [4,5]imidazo [1,2-a] naphtho [2,3-e][1,3]diazepin-7,14-dione (7) and 7a, 8,13,13a-tetrahydro-6H-8,13[1,2]benzenobenzo[4,5] imidazo[1,2-a]naphtho[2,3-e][1,3]diazepin-7,14-dione (10) (Method A)

A total of 0.810 g of compound **9** (6.08 mmol) was dissolved in anhydrous THF (50 mL) and cooled at 0 °C in an ice bath under an argon atmosphere. Then, 0.615 g (0.86 mL,

6.08 mmol) of triethylamine and 3.04 mmol of compound **4** (or compound **6**) were added consecutively to the cold solution. The reaction mixture turned light yellow. The solution was stirred at 0 °C for 1 h. The mixture was allowed to warm to room temperature and stirred under an argon atmosphere for 24 h. The resulting white solid was filtered and the solvent was evaporated under reduced pressure. The crude product was dissolved in 10 mL of methanol and precipitated by dropwise addition of methanol solution to 200 mL of water. The obtained solid was filtered, dried, and then crystallized from benzene (methanol for compound **10**).

8,13-Dihydro-6H-8,13-[1,2]benzenobenzo[4,5]imidazo[1,2-a]naphtho[2,3-e][1,3] diazepin-7,14-dione (7)

Yield 82.8%, yellow powder, mp: 238–240 °C; IR (ATR, cm^{-1}): 3376, 3061, 3026, 2923, 2851, 1634, 1546, 1457, 1370, 1274, 744; ^{1}H NMR: (400 MHz, DMSO-d_6) δ 12.16 (1H, br), 7.51–7.31 (6H, m), 7.07 (2H, dd, $J = 5.4$ and 2.9 Hz), 7.02 (4H, dd, $J = 5.1$ and 3.2 Hz), 6.13 (1H, s), 5.99 (1H, s); ^{13}C NMR: (100 MHz, DMSO-d_6) δ (ppm): 167.95–164.64 (C=O), 154.57 (C_{ipso}-benzimidazole), 148.04–143.86 (C_{ipso}-benzimidazole), 145.68–145.51 (C_{ipso}-DBB), 125.21, 124.11, 123.78, 122.37, 121.53, 111.99 (CH-aromatic), 55.41–51.67 (CH-bridgehead), 46.24–9.11 (triethylamine salt); Anal. calc. for $C_{25}H_{15}N_3O_2$ (389,41): C, 77.11; H, 3.88, N, 10.79; found C, 77.29; H, 3.96; N, 11.03.

General synthesis of 13-(1H-benzimidazol-2-yl)-9,10-dihydro-9,10-[3,4] epipyrroloanthracene-12,14-dione (8) (Method B)

A total of 0.405 g of compound **9** 3.04 mmol of compound **9** (0.405 g) was dissolved in anhydrous THF (50 mL) and cooled at 0 °C in an ice bath under an argon atmosphere. Then, 0.243 g of NaH (60%, 6.08 mmol) and 3.04 mmol of compound **4** were added to the cold solution, respectively. The color of the reaction mixture turned red. The solution was stirred for 1 h at 0 °C. The mixture was allowed to warm to room temperature and stirred under the argon atmosphere for 24 h. The mixture was filtered and the solvent was evaporated under reduced pressure. The crude product was dissolved in 10 mL of methanol. The crude product was precipitated by dropwise addition of methanol solution to 200 mL of water. The crude product was dried, filtered, and then crystallized from methanol.

13-(1H-benzimidazol-2-yl)-9,10-dihydro-9,10-[3,4]epipyrroloanthracene-12,14-dione (8)

Yield 74.3%, colorless powder, mp: 281–282 °C; IR (ATR, cm^{-1}): 3316, 3066, 2951, 2922, 2851, 1683, 1633, 1537, 1456, 1362, 1272, 742; ^{1}H NMR: (400 MHz, DMSO-d_6) δ 12.36 (1H, br), 7.38 (4H, dd, $J = 5.3$ and 3.2 Hz), 7.34 (2H, dd, $J = 5.9$ and 3.2 Hz), 7.20 (2H, dd, $J = 5.9$ and 3.2 Hz), 6.98 (4H, dd, $J = 5.3$ and 3.1 Hz), 5.97 (2H, s); ^{13}C NMR: (100 MHz, DMSO-d_6) δ 166.08 (C=O), 151.31 (C_{ipso}-benzimidazole), 150.00 (C=C), 145.55 (C_{ipso}-DBB), 130.94 (C=C, Ar-benzimidazole), 125.11–123.96 (CH-DBB), 123.18–111.82 (CH-benzimidazole), 53.53 (CH-bridgehead). Anal. calc. for $C_{25}H_{15}N_3O_2$ (389,41): C, 77.11; H, 3.88, N, 10.79; found C, 77.44; H, 3.89; N, 10.84.

Synthesis of N^{11},N^{12}-di(imidazolidin-2-ylidene)-9,10-dihydro-9, 10-ethenoanthracene-11,12-dicarboxamide (12) (Method C)

A total of 0.100 g Na (4.35 mmol) was dissolved in anhydrous methanol (10 mL) and the mixture was stirred at room temperature for 10 min. To the resulting sodium methoxide

solution, 2-aminoimidazoline *p*-toluenesulfonate (1.029 g, 4.00 mmol) was added as solid in one portion. The reaction mixture was stirred for 10 min followed by the addition of compound **2** (0.50 g, 1.56 mmol). The mixture was stirred at room temperature for 4 days, and then the solvent was evaporated under reduced pressure. The yellow crude product was crystallized from water. After 2 days, the solid was decanted off and recrystallized from methanol.

N^{11},N^{12}-Di(imidazolidin-2-ylidene)-9,10-dihydro-9,10-ethenoanthracene-11, 12-dicarboxamide (12)

Yield 39.1%, colorless powder, mp: 293–294.93 °C. From the DSC and TGA analysis, it was understood that this compound held 1-mol water in its chemical structure. IR (ATR, cm^{-1}): 3509, 3338, 3127, 3024, 2975, 2898, 1689, 1676, 1595, 1544, 1456, 1374; ^{1}H NMR: (400 MHz, $CDCl_3$ + 2 drop CH_3COOH) δ 11.60 (acetic acid), 7.82–7.50 (4H, br.), 7.42–7.41 (4H, d, $J = 3.4$ Hz), 7.0–6.99 (4H, d, $J = 3.4$ Hz), 6.01 (2H, s), 3.65 (8H, s), 2.09 (acetic acid); ^{13}C NMR: (100 MHz, $CDCl_3$-d + 2 drop CH_3COOH) δ (ppm) 177.85 (acetic acid), 168.75 (C=O), 160.76 (C=N), 150.83, 144.28 ($ArC\text{-}_{ipso}$), 125.12, 123.82 (CH-aromatic), 53.57 (CH), 42.95 (CH_2). Anal. Calc. for $C_{24}H_{22}N_6O_2$, (426.48): C, 64.85; H, 5.44; N, 18.91; found C, 65.59; H, 5.72; N, 19.43.

Conclusion

In this study, attempts to obtain the symmetrical dibenzobarrelene-substituted imidazoline and benzimidazole derivatives (*Expected product-1–3*) were unsuccessful and instead obtained some novel products resulted from intramolecular cyclization. As a result, we have synthesized different and completely new imidazoline and benzimidazole derivatives, which have the dibenzobarrelene skeleton using simple synthetic methods. In these synthesis methods, we obtained unexpected products by changing the nature of the base and the reagent ratios. The synthesized compounds are dicarboxamide derivatives which contain together 1.3-diazepine and guanidine main structures. The coexistence of two functional groups in one molecule may potentially contribute positively to the biological activity of these compounds. Based on chemical structures, new compounds **8, 12** and dibenzobarrelene-substituted benzimidazole and imidazoline fused with 1.3-diazepinedione ring derivatives (**7, 10**, and **14**) appear to be ideal candidates for medicinal investigations.

Funding

We are indebted to the Firat University Research Project Coordination Unit (Project Number FF.16.10 and FF.13.04) for financial support of this work.

ORCID

İrfan Çapan http://orcid.org/0000-0002-9555-1555
Süleyman Servi http://orcid.org/0000-0003-0827-8624

References

[1] Liu, H.; Du, D. M. *Adv. Synth. Catal.* **2009**, *351*, 489–519. DOI: 10.1002/adsc.200800797.
[2] Hong, S. S.; Bavadekar, S. A.; Lee, S. I.; Patil, P. N.; Lalchandani, S. G.; Feller, D. R.; Miller, D. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4691–4695. DOI: 10.1016/j.bmcl.2005.07.083.

[3] Clarke, R. W.; Harris, J. *CNS Drug Rev.* **2002**, *8*, 177–192. DOI: 10.1111/j.1527-3458.2002.tb00222.x.
[4] Nikolic, K.; Agbaba, D. *Cardiovasc. Ther.* **2012**, *30*, 209–216. DOI: 10.1111/j.1755-5922.2011.00269.x.
[5] Delang, L.; Froeyen, M.; Herdewijn, P.; Neyts, J. *Antiviral Res.* **2012**, *93*, 30–38. DOI: 10.1007/978-3-642-27340-7_12.
[6] Shi, W.; Siemann, D. W. *Anticancer Res.* **2005**, *25*, 3899–3904.
[7] Crouch, R. D. *Tetrahedron* **2009**, *65*, 2387–2397. DOI: 10.1016/j.tet.2008.12.022.
[8] Fujioka, H.; Murai, K.; Ohba, Y.; Hiramatsu, A.; Kita, Y. *Tetrahedron Lett.* **2005**, *46*, 2197–2199. DOI: 10.1016/j.tetlet.2005.02.025.
[9] Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. *Tetrahedron* **2007**, *63*, 638–643. DOI: 10.1016/j.tet.2006.11.007.
[10] Gogoi, P.; Konwar, D. *Tetrahedron Lett.* **2006**, *47*, 79–82. DOI: 10.1016/j.tetlet.2005.10.134.
[11] Ishihara, M.; Togo, H. *Tetrahedron* **2007**, *63*, 1474–1480. DOI: 10.1016/j.tet.2006.11.077.
[12] Danneberg, P.; Weber, K. *Br. J. Clin. Pharmacol.* **1983**, *16*, 231S–244S. DOI: 10.1111/j.1365-2125.1983.tb02295.x.
[13] Wittine, K.; Poljak, K.; Kovač, M.; Makuc, D.; Plavec, J.; Balzarini, J.; Martinović, T.; Pavelić, S. K.; Pavelić, K.; Mintas, M. *Molecules* **2013**, *18*, 13385–13397. DOI: 10.3390/molecules181113385.
[14] Gallud, A.; Vaillant, O.; Maillard, L. T.; Arama, D. P.; Dubois, J.; Maynadier, M.; Lisowski, V.; Garcia, M.; Martinez, J.; Masurier, N. *Eur. J. Med. Chem.* **2014**, *75*, 382–390. DOI: 10.1016/j.ejmech.2014.01.044.
[15] Katritzky, A. R.; Yates, F. J. *Chem. Soc., Perkin Trans. 1* **1976**, 309–312. DOI: 10.1039/P19760000309.
[16] Gondi, S. R.; Son, Y. D. *Synth. Commun.* **2004**, *34*, 3061–3072. DOI: 10.1081/SCC-200028517.
[17] Smejkal, T.; Gribkov D.; Geier, J.; Keller, M.; Breit, B. *Chem. Eur. J.* **2010**, *16*, 2470–2478. DOI: 10.1002/chem.200902553.
[18] Alibert, S.; Santelli, R. C.; Pradines, B.; Houdoin, C.; Parzy, D.; Karolak, W. J.; Barbe, J. *J. Med. Chem.* **2002**, *45*, 3195–3209. DOI: 10.1021/jm011046l.
[19] Servi, S.; Genc, M.; Gür, S.; Koca, M. *Eur. J. Med. Chem.* **2005**, *40*, 687–693. DOI: 10.1016/j.ejmech.2005.02.002.