Research on the Synthesis and Characterization of New 1,3,4-oxadiazoles with 5H-dibenzo[a,d][7]annulene Moiety

LAURA-ILEANA SOCEA[1], GABRIEL SARAMET[2], CONSTANTIN DRAGHICI[3], STEFANIA-FELICIA BARBUCEANU[1]*, DIANA CAROLINA ILIES[1], BOGDAN SOCEA[4]

[1]University of Medicine and Pharmacy "Carol Davila", Faculty of Pharmacy, Organic Chemistry Department, 6 Traian Vuia Str., 020956, Bucharest, Romania

[2]University of Medicine and Pharmacy "Carol Davila", Faculty of Pharmacy, Pharmaceutical Technology Department, 6 Traian Vuia Str., 020956, Bucharest, Romania

[3]Romanian Academy, Organic Chemistry Centre "Costin D. Nenitescu", 202B Splaiul Independenþei, 060023, Bucharest, Romania

[4]Faculty of General Medicine, University of Medicine and Pharmacy "Carol Davila", St. Pantelimon Emergency Hospital, 340-342 Soseaua Pantelimon Str., 021623, Bucharest, Romania

*A series of 2-amino-1,3,4-oxadiazoles **4a-f** with 5H-dibenzo[a,d][7]annulene moiety were synthesized by cyclization of 2- acylhydrazinecarbothioamides **3a-f** in the presence of mercury oxide. 2-Acylhidrazinecarbothioamide **3a-f** were synthesized by nucleophilic addition of 2-(5H-dibenzo[a,d][7]annulen-5-yl)acetohydrazide to different isothiocyanates. All the newly synthesized compounds were characterized by their spectral data (IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy) and elemental analysis.*

Keywords: 5H-dibenzo[a,d][7]annulene, 2-amino-1,3,4-oxadiazole, hydrazinecarbothioamide

The 1,3,4-oxadiazole derivatives have been found to exhibit diverse biological activities such as antimicrobial, antiviral, antitubercular, antimalarial, anti-inflammatory, anticonvulsant, antitumor, antioxidant, anti HIV, muscle relaxant, antimitotic, diuretic, hypnotic, sedative, etc [1-9].

Furthermore, the 5H-dibenzo[a,d][7]annulene ring is present in the structure of many compounds used in therapeutics as antibacterial agents, anticonvulsive agents, anticholinergic agents, miorelaxant agents, antihistaminic agents, antifungal agents, carbonic anhydrase inhibitors, but mostly they are used as antidepressant drugs [2,10-15].

These observations and our interest in the chemistry of heterocyclic compounds prompted us to synthesize a series of 2-amino-1,3,4-oxadiazoles which contain dibenzo [a,d][7]annulene ring.

Newly compounds were prepared by cyclization of acylhydrazinecarbothioamides in the presence of mercury oxide. 2-Acylhydrazinecarbothioamides previously described were prepared from corresponding acylhydrazides by treating with different isothiocianates [16].

Experimental part

All reagents were purchased from the Merck, Sigma-Aldrich and Fluka Companies. Melting points were determined on a Böetius apparatus and were uncorrected. The IR spectra were recorded in KBr pellets on a Vertex 70 Bruker spectrometer. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini 300BB spectrometer (300 MHz for H and 75 MHz for C), using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. The ^{1}H-NMR and ^{13}C-NMR spectral data are shown in tables 1 and 2. The

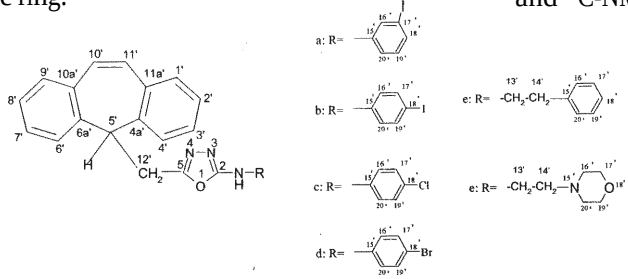


Table 1
^{1}H-NMR DATA for **4a-f** ($CDCl_3$, δ ppm, J Hz)

Comp.	H$^{1'-4'}$ H$^{6'-9'}$	H$^{5'}$	H$^{10'}$ H$^{11'}$	H$^{12'}$	H$^{13'}$	H$^{14'}$	H$^{16'}$	H$^{17'}$	H$^{18'}$	H$^{19'}$	H$^{20'}$	NH
4a	7.15-7.45	4.55 t (8.0)	7.06s	3.26 d (8.0)	-	-	7.61 t (1.9)	-	7.15-7.45 m	7.02 t (8.2)	7.15-7.45 m	8.90ls
4b	7.10-7.40 m	4.51 t (8.0)	7.02s	3.23 d (8.0)	-	-	6.91 d (8.5)	7.58 d (8.5)	-	7.58 d (8.5	6.91 d (8.5)	8.25ls
4c	7.20-7.40 m	4.52 t (8.0)	7.03s	3.25 d (8.0)	-	-	7.06 d (8.5)	7.25 d (8.5)	-	7.25 d (8.5)	7.06 d (8.5)	8.78ls
4d	7.20-7.40 m	4.52 t (8.0)	7.02s	3.24 d (8.0)	-	-	7.03 d (8.8)	7.40 d (8.8)	-	7.40 d (8.8)	7.03 d (8.8)	8.15ls
4e	7.10-7.40 m	4.49 t (8.0)	6.99s	3.13 d (8.0)	3.43 q (6.4)	2.81 t (6.4)	7.10-7.40m	7.10-7.40m	7.10-7.40m	7.10-7.40m	7.10-7.40 m	4.43ls
4f	7.10-7.35 m	4.59 t (7.3)	6.93s	3.02 d (7.3)	3.49 tl (3.9)	2.31 tl (3.9)	2.34 lt (4.9)	3.57 lt (4.9)	-	3.57 lt (4.9)	2.34 lt (4.9)	4.20ls

* email: sbarbuceanu@gmail.com; stefaniafelicia_barbuceanu@yahoo.com; Tel: 0722763428

Table 2

^{13}C-NMR DATA for 4a-f ($CDCl_3$, δ ppm, J Hz)

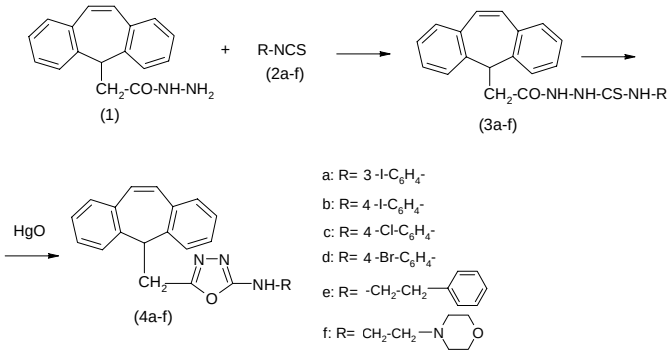
Comp.	C$^{5'}$	C$^{12'}$	C$^{10'}$ C$^{11'}$	C^{5}	C^{2}	C$^{9'a}$ C$^{11'a}$	C$^{4'a}$ C$^{6'a}$	C$^{13'}$	C$^{14'}$	C$^{1'}$- C$^{9'}$	C$^{15'}$	C$^{16'}$	C$^{17'}$	C$^{18'}$	C$^{19'}$	C$^{20'}$
4a	52.98	29.83	131.16	159.50	160.41	134.08	138.80	-	-	131.89; 130.21; 129.88; 129.62; 129.23	139.22	125.97	94.61	127.25	1125.97	119.49
4b	53.02	29.87	131.18	158.26	160.01	134.10	138.86	-	-	130.13; 129.64; 129.29; 127.27	139.00	119.49	138.26	85.51	138.26	116.94
4c	53.07	29.83	131.17	159.90	160.16	134.08	138.85	-	-	130.13; 129.61; 129.36; 128.83	136.64	118.76	127.25	128.17	129.27	118.76
4d	53.03	29.43	131.17	159,87	159.97	134.09	138.85	-	-	131.17; 130.14; 129.63; 127.26	137.04	119.10	132.32	127.13	132.32	119.10
4e	52.86	26.51	131.14	159.46	161.90	134.54	139.07	44.60	35.68	130.11; 129.67; 129.09; 128.97; 128.85; 126.84; 127.11						
4f	53.37	27.07	131.13	152.66	154.61	134.36	139.65	53.96	27.07	130.23; 129.99; 129.43; 127.15	-	57.75	66.76	-	66.76	57.75

content of C, H, and N was assayed using an ECS-40-10-Costeh microdosimeter.

Synthesis of compounds

The starting compound, 2-(5*H*-dibenzo[a,d][7]annulen-5-yl)acetohydrazide **1**, was synthesized according to the previously reported procedure [19]. 2-(5H-Dibenzo[a,d][7] annulen-5-ylacetyl)-N-arylhydrazinecarbothioamides **3a-f** were obtained by nucleophilic addition of 2-(5*H*-dibenzo[a,d][7]annulen-5-yl)acetohydrazide **1** to different isothiocyanates **2a-f**, according to the literature method [10,16,19].

The synthesis of 1,3,4-oxadiazoles **4a-f** was realized by cyclization of 2-acylhydrazinecarbothioamides **3a-f** in the presence of mercury oxide in methanol.



Scheme 1. Synthesis of the new compounds

a) *Synthesis of 5-[5H-dibenzo[a,d][7]annulen-5-ylmethyl]-N-(R)-1,3,4-oxadiazol-2 amines **4a-f***

To a solution of 2-acylhydrazinecarbothioamide **3** (1 mmol) in ethanol yellow mercuric oxide (2 mmol) was added. The mixture was refluxed for 5-8 h. The resulted product was filtered off in order to remove the HgS, and after cooling the solution, the corresponding 2-arylamino-1,3,4-oxadiazoles precipitates were obtained.

*5-[5H-Dibenzo[a,d][7]annulen-5-ylmethyl]-N-(3-iodophenyl)-1,3,4-oxadiazol-2-amines **4a***: m.p. 199-201°C; yield: 48.2%; elemental analysis: anal. calcd. for $C_{24}H_{18}IN_3O$ (491.32 g/mol): C, 58.67; H, 3.69; N, 8.55; found: C, 58.67; H, 3.67; N, 8.56; IR (KBr, cm^{-1}): 3337 (N–H stretching), 3051, 3024 (C–H stretching of aromatic ring), 2913, 2859 (CH_2 stretching), 1631, 1591, 1563, (C=C stretching, C=N stretching), 515 (C-I);

*5-[5H-Dibenzo[a,d][7]annulen-5-ylmethyl]-N-(4-iodophenyl)-1,3,4-oxadiazol-2-amines **4b***: m.p. 225-227°C; yield: 39.4%; elemental analysis: anal. calcd. for $C_{24}H_{18}IN_3O$ (491.32 g/mol): C, 58.67; H, 3.69; N, 8.55; C, 58.68; H, 3.68; N, 8.56; IR (KBr, cm^{-1}): 3326 (N–H stretching), 3054, 3018 (C–H stretching of aromatic ring), 2965, 2864 (CH_2 stretching), 1624, 1591, 1567 (C=C stretching, C=N stretching), 524 (C-I);

*5-[5H-Dibenzo[a,d][7]annulen-5-ylmethyl]-N-(4-chlorophenyl)-1,3,4-oxadiazol-2-amines **4c***: m.p. 235-236°C; yield: 55.1%; elemental analysis: anal. calcd. for $C_{24}H_{18}ClN_3O$ (399.87 g/mol): C, 72.09; H, 4.54; N, 10.51; found: C, 72.09; H, 4.52; N, 10.53; IR (KBr, cm^{-1}): 3253 (N–H stretching), 3064, 3026 (C–H stretching of aromatic ring), 2964, 2863 (CH_2 stretching), 1625, 1601, 1571 (C=C stretching, C=N stretching), 766 (C-Cl);

*5-[5H-Dibenzo[a,d][7]annulen-5-ylmethyl]-N-(4-bromophenyl)-1,3,4-oxadiazol-2-amines **4d*** m.p. 237-239°C; yield: 54.5%; elemental analysis: anal. calcd. for $C_{24}H_{18}BrN_3O$ (444.32 g/mol): C, 64.88; H, 4.08; N, 9.46; found: C, 64.88; H, 4.09; N, 9.44; IR (KBr, cm^{-1}): 3328 (N–H stretching), 3046, 3023 (C–H stretching of aromatic ring), 2918 (CH_2 stretching), 1623, 1596, 1568, 1534,(C=C stretching, C=N stretching) 614 (C-Br);

*5-[5H-Dibenzo[a,d][7]annulen-5-ylmethyl]-N-(phenylethyl)-1,3,4-oxadiazol-2-amines **4e*** m.p. 163-165°C; yield: 42.5%; elemental analysis: anal. calcd. for $C_{26}H_{23}N_3O$ (393.48 g/mol): C, 79.36; H, 5.89; N, 10.68; found: 79.35; H, 5.88; N, 10.69; IR (KBr, cm^{-1}): 3334 (N–H stretching), 3058, 3027 (C–H stretching of aromatic ring), 2962, 2926, 2865 (CH_2 stretching), 1632, 1580, 1515 (C=C stretching, C=N stretching);

*5-[5H-Dibenzo[a,d][7]annulen-5-ylmethyl]-N-(morpholinethyl)-1,3,4-oxadiazol-2-amines **4f***: m.p 146-148°C; yield: 67.2%; elemental analysis: anal. calcd. for $C_{24}H_{26}N_4O_2$ (402.48 g/mol): C, 71.62; H, 6.51; N, 13.92; found: C, 71.60; H, 6.52; N, 13.91; IR (KBr, cm^{-1}): 3395 (N–

H stretching), 3067, 3016 (C–H stretching of aromatic ring), 2959, 2854, 2815 (CH_2 stretching), 1630, 1598, 1513 (C=C stretching, C=N stretching); 1141, 1116 (C-O-C stretching).

Results and discussions

Chemistry

2-Acylhydrazinecarbothioamides **3a-f** were synthesized by refluxing of an equimolecular mixture formed by the 2-(5*H*-dibenzo[a,d][7]annulen-5-yl)acetohydrazide **1** and different isothiocyanate, in anhydrous ethanol.

Obtaining of 1,3,4-oxadiazoles **4a-f** by cyclo-desulfurization of hydrazinecarbothioamides with mercury oxide took place with low yields. 2-Amino-1,3,4-oxadiazoles are obtained in the form of a single isomer, axially opposed to the 2-acylhydrazinecarbothioamides which are obtained in the form of two isomers 5'-axial and 5'-equatorial in about 3:1 ratio [16,19].

The stretching band due to NH group from 2-amino-1,3,4-oxadiazoles **4** was present at 3253-3337 cm^{-1}. The appearance of a new band generated by the stretching vibration of a C=N group (1624-1631cm^{-1}) and the absence of carbonyl absorption in the IR spectra of the 1,3,4-oxadiazoles indicated that cyclization reaction occurred.

In the ^{1}H-NMR spectrum of the 1,3,4-oxadiazoles, the 5-H-dibenzo[a,d][7]annulene system is identified through a singlet at 6.93-7.06 ppm corresponding to $H^{10'}$ and $H^{11'}$ protons from trans annular double bond. The signals of the $H^{1'-4'}$ and $H^{6'-9'}$ protons appear as a multiplet between 7.10-7.45 ppm. The signal of the $H^{5'}$ proton appears as a triplet at 4.49-4.59 ppm, and the signal of the methylene protons ($H^{12'}$) appears as a doublet at 3.02-3.26 ppm. The 2-amino-1,3,4-oxadiazoles **4a-c** structure is confirmed by the presence in the ^{1}H-NMR spectrum of one singlet for the NH group at 4.20-8.90 ppm: 4.20 pm for 1,3,4-oxadiazoles **4f**, 4.43 ppm for **4e** and between 8.15-8.90 ppm for 1,3,4-oxadiazoles **4a-d**.

In the ^{13}C-NMR spectrum of the new compounds, the 5-H-dibenzo[a,d][7]annulene system is easy to recognize, the carbon signals being present at the corresponding chemical shift [19].

Cyclization of these 2-acylthiosemicarbazides **3a-f** to 2-amino-1,3,4-oxadiazoles **4a-f** was proved in the ^{13}C-NMR spectra by the presence of two new signals characteristic to C-2 1,3,4-oxadiazolic carbon (154.61-161.90 ppm) and to C-5 heterocyclic carbon (152.66-159.90 ppm).

Conclusions

This study reports the synthesis, characterization of six new compounds from 1,3,4-oxadiazoles class by cyclization of corresponding 2-acylhydrazine-carbothioamides with HgO. 2-Amino-1,3,4-oxadiazoles are obtained in the form of a single isomer, axially opposed to the 2-acylhydrazinecarbothioamides which are obtained in the form of two isomers 5'-axial and 5'-equatorial. The chemical structure was determined by elemental analysis and spectral methods.

Acknowledgements: This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/159/1.5/S/132395.

References

1.OLIVEIRA, C. S., LIRA, B. F., BARBOSA-FILHO, J.M., LORENZO, J.G.F., DE ATHAYDE-FILHO, P.F., Molecules, 17, 2012, p. 10192
2.SOCEA, L. I., SARAMET G., DINU-PRVU, C. E., DRAGHICI, C., SOCEA, B., Rev. Chim.(Bucharest), **65**, no. 3, 2014, p. 253
3.ABDEL-AAL, M.T., EL-SAYED, W.A., EL-KOSY, S.M., EL-ASHRY, E.S.H., Arch. Pharm. Chem. Life Sci., 341, 2008, p. 307
4.FARSHORI, N.N., BANDAY, M.R., AHMAD, A., KHAN, A.U., RAUF, A., Bioorg. Med. Chem. Lett., 20, 2010, p. 1933
5.KADI, A.A., EL-FROLLOSY, N.R., AL-DEEB, O.A., HABIB, E.E., IBRAHIM, T.M., EL-EMAM A.A., Eur. J. Med. Chem., 42, 2007, p. 235
6.SHARMA, R., MISRA, G.P., SAINY, J., CHATURVEDI, S.C., Med. Chem. Res., 20, 2011, p. 245
7.ALMASIRAD, A.; TABATABAI, S.A.; FAIZI, M.; KEBRIAEEZADEH, A.; MEHRABI, N.; DALVANDIA, A.; SHAFIEE, A., Bioorg. Med. Chem. Lett., 14, 2004, p. 6057
8.REN, J., WU, L., XIN, W.Q., CHEN, X., HU, K., Bioorg. Med. Chem. Lett., 22, 2012, p. 4778
9.BARBUCEANU, S. F., ILIES, D. C., RADULESCU, V., SOCEA, L. I., DRÎGHICI, C., SARAMET, G., Rev. Chim.(Bucharest), **65**, no. 10, 2014, p. 1172
10.SOCEA, L. I., APOSTOL, T. V., ªARAMET, G., BÃRBUCEANU, ª. F., DRÃGHICI, C., DINU, M., J. Serb. Chem. Soc., 77(11), 2012, p. 1541
11.ILIEª, M., BANCIU, M. D., SCOZZAFAVA, A., ILIEª, M. A., CÃPROIU, M. T., SUPURAN, C. T., Bioorg. Med. Chem., 11, 2003, p. 2227
12.MARINDALE, M., The Extra Pharmacopoeia, 30th ed., Pharmaceutical Press, London, 1993, p. 932
13.MUNOZ-BELLIDO, J. L., MUNOZ-CRIDO, S., GARCIA RODRIGUEZ, J. A., Int. J. Antimicrobial Agents, 14, 2000, p. 177
14.MIHALCEA, F., BARBUCEANU, S. F., SOCEA, L. I., SARAMET, G., CRISTEA, C., DRAGHICI, C., ENACHE-PREOTEASA, C., SARAMET, I., Rev. Chim.(Bucharest), **64**, no. 2, 2013, p. 127
15.SOCEA, L. I., SARAMET, G., MIHALCEA, F., APOSTOL, T. V., ANDREESCU, C., DRAGHICI, C., SOCEA, B., Rev. Chim. (Bucharest), **65**, no. 2, 2014, p. 156
16.SOCEA, L. I., SARAMET, G., DRAGHICI, C., SOCEA, B., CONSTANTIN, V. D., RADU-POPESCU, M. A., submitted to J. Serb. Chem. Soc.
17.SOCEA, L. I., SARAMET, G., SOCEA, B., DRAGHICI, C., Rev. Chim.(Bucharest), **57** , no. 12, 2006, p. 1242
18.SOCEA, L., SARAMET, I., SOCEA, B., DRAGHICI, C., Rev. Chim.(Bucharest), **58**, no. 3, 2007, p. 328
19.ªARAMET, I., BANCIU, A., SOCEA, L., DRÃGHICI, C., BANCIU, M. D., Heterocycl. Commun, 9(6), 2003, p. 653

Manuscript received: 20.05.2015