New Heterocyclic Compounds from 1,2,4-triazoles and 1,3,4-Oxadiazoles Class Containing 5H-dibenzo[a,d][7]Annulene Moiety

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In this paper we present the synthesis of the new heterocyclic compounds with 5H-dibenzo[a,d][7]annulene moiety obtained by cyclization of 2-acylhydrazinecarbothioamides (2a,b). The acylhydrazinecarbothioamides were obtained by treating 2-(5H-dibenzo[a,d][7]annulen-5-yl)acetohydrazide (1) with 2,5-difluorophenyl or 3-bromophenyl isothiocyanates. 2-Amino-1,3,4-oxadiazoles (3a,b) were synthesized by cyclization of 2-acylhydrazinecarbothioamides in the presence of mercury oxide. The new 1,2,4-triazole-3-thioles (4a,b) were synthesized by cyclization, in alkaline media, of the corresponding acylhydrazinecarbothioamide. The structures of the new compounds synthesized were investigated by ^{1}H-NMR, ^{13}C-NMR, IR and elemental analysis.

Keywords: acylhydrazinecarbothioamide, 1,2,4-triazol-3-thiole, 2-amino-1,3,4-oxadiazole, dibenzo[a,d] [7]annulene

The synthesis of 1,2,4-triazoles and investigation of their chemical and biological behavior have gained more importance for the drug discovery process. 1,2,4-Triazole and 1,2,4-triazole-3-thioles are known to exhibit a broad spectrum of biological activities like as tuberculostatic, analgesic, antioxidant, antiviral, antitumor, antibacterial, anti-inflammatory, carbonic anhydrase inhibitors [1-11, 34].

Several compounds containing 1,2,4-triazole moiety, for example Fluconazole, Posaconazole and Itraconazole have been used for the treatment of fungal infection disease [12,13].

A few other drugs containing 1,2,4-triazole ring have been used in therapy Vorozole (antineoplastic and imunnomodulatory) [14], Loreclezole (anticonvulsant) [15], Ribavirin (antiviral) [16] Rizatriptan (for the treatment of migraine headaches) [17] Alprazolam (anxiolytic) [18].

In the last years research was focused on obtaining biological active products because there is a continuous need for the development of new drugs as the currently available drugs are becoming ineffective due to the drug resistance developed by pathogens [19,20].

The 1,3,4-oxadiazole derivatives have been found to exhibit diverse biological activities such as antimicrobial, antimitotic, antiviral, anti HIV, antitubercular, antimalarial, anti-inflammatory, anticonvulsant, antitumor, antioxidant, muscle relaxant, diuretic, hypnotic, sedative, etc [21-29].

Moreover, life threatening infections caused by pathogenic fungi and bacteria are increasingly becoming very common 1,2,4-triazole and 1,3,4-oxadiazole compounds have shown a great efficacy against antifungal and antibacterial infections. In this situation, discovery of new 1,2,4-triazole and 1,3,4-oxadiazole derivatives with both a pharmaceutical profile and therapeutic safety are of a great interest among researches.

Bacterial sortases are cysteine transpeptidases that regulate the covalent linkage of several surface protein virulence factors in Gram-positive bacteria. Virulence factors play significant roles in the adhesion, invasion of host tissues, biofilm formation and immune evasion, mediating the bacterial pathogenesis and infectivity. Therefore, sortases are emerging as important targets for the design of new anti-infective agents [30].

For those reasons, we have started a complex study by designing 1,2,4-triazoles or 1,3,4-oxadiazole derivatives that contained the dibenzo[a,d][7]annulene fragment, possible sortase inhibitors. The synthesis of the newly 1,2,4-triazoles or 1,3,4-oxadiazole compounds was realized in order to discover new potent SrtA inhibitors, potential anti-virulence agents targeted against Gram-positive bacteria, including multiresistant strains.

Newly compounds were prepared starting from of 2-(5H-dibenzo[a,d][7]annulen-5-yl)acetohydrazide (1) according with scheme 1.

Experiemental part

Materials and methods

All reactants and solvents were obtained commercially with the highest purity and were used without further purification. Melting points were determined on a Boetius apparatus and are uncorrected. The UV-Vis spectra were recorded on a SPECORD 40 Analytik Jena spectrometer, in methanol ($2.5x10^{-5}$ M) in the wavelength range 200–600 nm. IR spectra were recorded on a FT-IR-100 Perkin Elmer spectrometer, in solid phase by ATR and frequencies are expressed in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra are recorded on Varian Gemini 300 BB spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) using DMSO-d_6 as solvent for hydrazinecarbothioamides and $CDCl_3$ for 1,2,4-triazole and 1,3,4-oxadiazole compounds, chemical shifts are given in ppm relative to TMS as internal standard. Complementary spectra: 2D-NMR and decoupling. Coupling constants, *J*, are expressed in Hertz (Hz). The content of C, H, and N was assayed using an ECS-40-10-Costeh microdosimeter.

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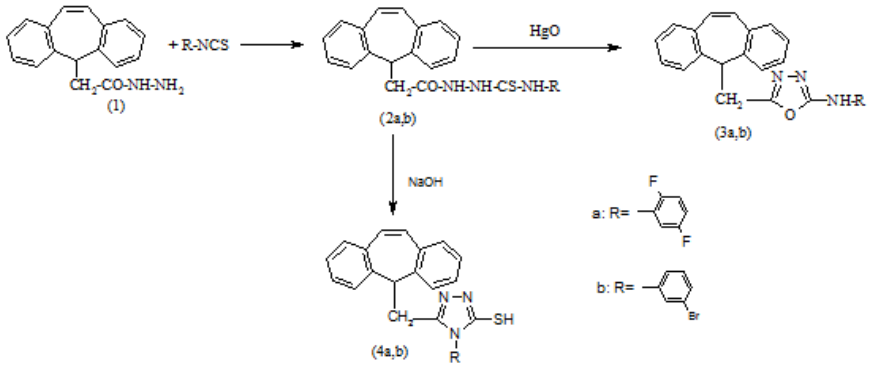


Scheme 1. Synthesis of the new compounds

Synthesis and characterization of compounds

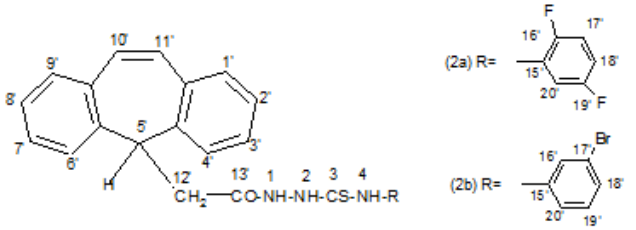
The first step was the preparation of 2-(5H-dibenzo[a,d][7]annulen-5-ylacetyl)-N-arylhydrazinecarbothioamides (2a,b) from 2,5-difluorophenyl or 3-bromophenyl isothiocyanate and 2-(5*H*-dibenzo[a,d][7]annulen-5-yl)acetohydrazide (1), in ethanol at room temperature, by the methods described in the our previously papers [31-33]. On treatment with HgO, acylhydrazinecarbothioamides (2a,b) yielded 2-amino-1,3,4-ozadiazoles (3a,b). The cyclization of acyl-hydrazinecarbothioamides (2a,b) with 2N sodium hydroxide give the corresponding 1,2,4-triazol-3-thioles (4a,b).

Synthesis of 2-(5H-dibenzo[a,d][7]annulen-5-ylacetyl)-N-arylhydrazinecarbothioamides (2a,b)

An equimolar mixture of hydrazide 1 (2 mmol) and 2,5-difluorophenyl or 3-bromophenyl isothiocyanate in ethanol (20 mL) was heated to reflux for 8 h. The reaction mixture was cooled and the separated product was filtered off, dried and recrystallized from ethanol.

2-(5H-dibenzo[a,d][7]annulen-5-ylacetyl)-N-(2,5-difluorphenyl)hydrazinecarbothioamide (2a): Yield: 89%; m.p.: 194-196°C; elemental analysis: anal. calcd. for $C_{24}H_{19}F_2N_3OS$ (435.50 g/mol): C, 66.19 %; H, 4.40%; N, 9.65%; found: C, 66.16 %; H, 4.41%; N, 9.67%; IR (KBr, cm^{-1}): 3345, 3198, 3059, 3023, 2974, 2868, 1696, 1528, 1494, 1479, 1237; 1222; ^{1}H-NMR (DMSO-d_6, δ, ppm, *J*, Hz): 9.83 (1H, s, NH), 9.77 (H, *s*, NH), 8.79 (H, *s*, NH), 7.45-7.20 (12H, *m*, aromatic), 7.03 (2H, *s*, $H^{10'}$, $H^{11'}$), 4.65 (1H, *t*, 6.9, $H^{5'}$) - axial isomer, 3.86 (1H, *t*, 6.9, $H^{5'}$)- equatorial isomer 2.60 (2H, *d*, 7.1, $H^{12'}$); ^{13}C-RMN (DMSO-d_6, δ, ppm): 181.59 (C^3), 170.26 ($C^{13'}$), 157.13 (d, 239.6, $C^{19'}$), 153.72 (d, 243.8, $C^{16'}$), 140.05 (C_q), 139.52 (C_q), 137.99 (C_q), 138.86 (2C_q), 133.75 (C_q), 131.28 (CH); 130.80 (2CH), 129.63 (2CH), 129.52 (2CH), 128.75 (2CH), 128.71 (CH), 128.07 (C_q), 127.528 (CH), 126.49 (2CH), 125.50 (CH), 122.91 (CH), 116.66 (CH), 114.27 (CH), 48.49 ($C^{5'}$), 34.49 ($C^{12'}$) - axial isomer, 33.15 ($C^{12'}$) - equatorial isomer;

2-(5H-dibenzo[a,d][7]annulen-5-ylacetyl)-N-(3-bromophenyl)hydrazinecarbothioamide (2b): Yield: 87%; m.p.: 193-195°C; elemental analysis: anal. calcd. for $C_{24}H_{20}BrN_3OS$ (478.41 g/mol): C, 60.25%; H, 4.21%; N, 8.78%; found C, 60.26%; H, 4.22%; N, 8.79%; IR (KBr, cm^{-1}): 3353, 3283, 3153, 3062, 3020, 2959, 2862, 1669, 1593, 1576, 1487, 1476, 1258; 622; ^{1}H-NMR (DMSO-d_6, δ, ppm, *J*, Hz): 9.86 (1H, s, NH), 9.76 (H, *s*, NH), 9.62 (H, *s*, NH), 9.10 (H, *s*, NH), 7.65 (H, *s*, NH), 7.40-7.20 (12H, *m*, aromatic), (2H, *s*, $H^{10'}$, $H^{11'}$), 4.66 (1H, *t*, 6.8, $H^{5'}$)- axial isomer, 3.75 (1H, *t*, 7.4 Hz, $H^{5'}$)- equatorial isomer, 3.41 (d, 7.4, 2H, $H^{12'}$) - equatorial isomer, 2.61 (2H, *d*, 6.8, $H^{12'}$); ^{13}C-NMR (DMSO-d_6, δ, ppm): 180.65 (C^3), 170.32 ($C^{13'}$), 140.67 (C_q), 140.08 (C_q), 139.55 (C_q), 134.87 (C_q), 133.76 (C_q), 131.29 (CH), 130.82 (2CH)- axial isomer, 129.95 (CH), 129.65 (CH), 129.53 (2CH), 128.77 (2CH) axial isomer, 127.60 (CH) axial isomer, 126.51 (2CH) axial isomer, 128.53 (CH)- equatorial isomers, 126.51 (CH), 125.53 (CH) equatorial isomer, 129.97 (CH) equatorial isomer, 120.47($C^{17'}$), 48.47 ($C^{5'}$), 34.61 ($C^{12'}$) axial isomers, 34.56 ($C^{12'}$) axial isomers, 33.20 ($C^{12'}$) - equatorial isomer;



Scheme 2. Atom numbering of general structures (2a,b)

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

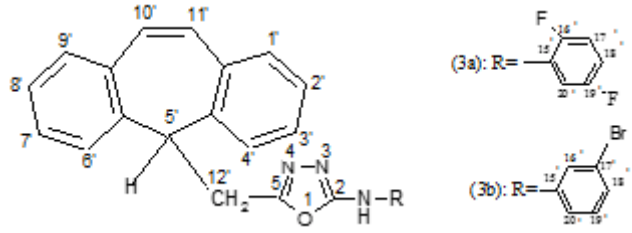
To a solution of 2-acylhydrazinecarbothioamide (2a,b) (1 mmol) in ethanol yellow mercuric oxide (2 mmol) was added. The mixture was refluxed for 9 h. The resulted product was filtered of in order to remove the HgS, and after cooling, the corresponding 2-arylamino-1,3,4-oxadiazole precipitate was obtained.

5-(5H-dibenzo[a,d][7]annulen-5-ylmethyl)-N-(2,5-difluorophenyl)-1,3,4-oxadiazol-2-amines (3a)

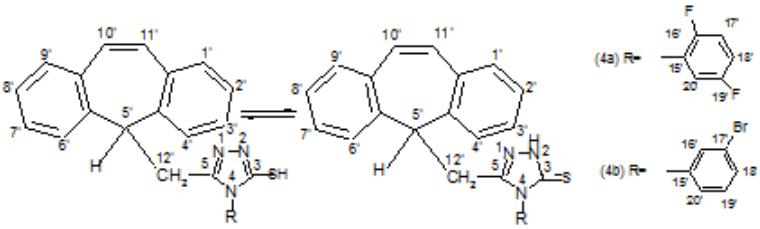
Yield: 49.4%; m.p.: 168-170°C; elemental analysis: anal. calcd. for $C_{24}H_{17}F_2N_3O$ (401.42 g/mol): C, 71.81%; H, 4.27%; N, 10.47%; found C, 71.80%; H, 4.27%; N, 10.49% IR (KBr, cm^{-1}): 3415, 3067, 3022, 2915, 2868, 1656, 1585, 1510, 1494, 1196; ^{1}H-NMR ($CDCl_3$, δ, ppm, *J*, Hz): 8.90 (s, NH); 7.58 (m,1H, Harom); 7.05-7.38 (m, Harom); 7.02 (s, 2H, $H^{10'}$, $H^{11'}$); 6.65 (m,1H, Harom); 3.23 (d, 8.0, $H^{12'}$); 6.91 (d, 8.5, $H^{16'}$, $H^{20'}$); 4.54 (t, 8.1, $H^{5'}$); 3.24 (2H, *d*, 8.1, $H^{12'}$); ^{13}C-NMR ($CDCl_3$, δ, ppm): 160.25 (C^2), 158.90 (C^5), 158.99 (d, 241.6, $C^{19'}$-F), 147.86 (d, 239.8, $C^{16'}$-F), 138.68 (2Cq), 134.10 (2Cq), 131.13 (CH), 130.21 (CH), 129.58 (CH), 129.23 (CH), 127.29 (CH), 115.48 (dd, 21.2; 9.7) ,108.74 (dd, 24.3; 7.3), 106.27 (d, 31.3), 52.80 ($C^{5'}$), 26.32 ($C^{12'}$).

5-(5H-dibenzo[a,d][7]annulen-5-ylmethyl)-N-(3-bromophenyl)-1,3,4-oxadiazol-2-amines (3b)

Yield: 44.2 %; m.p.: 148-150°C; elemental analysis: anal. calcd. for $C_{24}H_{18}BrN_3O$ (444.33 g/mol): C, 64.88%; H, 4.08; N, 9.46%; found: C, 64.86%; H, 4.09; N, 9.46%; IR (KBr, cm^{-1}): 3411, 3063, 3021, 2961, 2866, 1673, 1595, 1569, 611;^{1}H-NMR ($CDCl_3$, δ, ppm, *J*, Hz): 9.45 (s, NH); 6.95-7.40 (12H, m, Haromatic); 7.02 (s, $H^{10'}$, $H^{11'}$); 4.51 (t, 8.0, $H^{5'}$); 3.24 (d, 8.0, $H^{12'}$); ^{13}C-NMR ($CDCl_3$, ä/ ppm): 160.77 (C^2), 159.75 (C^5), 139.36 (2Cq), 138.63 (2Cq), 131.09 ($C^{10'}$, $C^{11'}$), 130.59 (CH), 130.17 (2CH), 129.79 (2CH), 129.51(2CH), 129.19 (2CH), 127.21 (2CH), 122.98 ($C^{17'}$), 120.07 (CH), 116.21 (CH), 53.02 ($C^{5'}$), 26.40 ($C^{12'}$).



Scheme 3. Atom numbering of general structures (3a,b)



Scheme 4. Atom numbering of general structures (4a,b)

Synthesis of 5-(5H-dibenzo[a,d][7]annulen-5-ylmethyl)-4-aryl)-4H-1,2,4-triazole-3-thioles (4a,b)

Acylhydrazinecarbothioamide (2a,b) (1 mmole) was added to 10 mL of NaOH 8% solution and the reaction mixture was heated under reflux for 9 h . After cooling, the solution was acidified with acetic acid. The obtained white precipitate was filtered off recrystallized from $CHCl_3$: petroleum ether (1:2/v:v).

5-(5H-dibenzo[a,d][7]annulen-5-ylmethyl)-4-(2,5-difluorophenyl)-4H-1,2,4-triazole-3-thiol (4a): Yield: %; m.p.: °C; Anal. calcd. for $C_{24}H_{17}F_2N_3S$ (417.48 g/mol): C, 69.05%; H, 4.10; N, 10.07%; found: C, 69.06%; H, 4.09; N, 10.06%; IR (KBr, cm^{-1}): 3413, 3136, 3070, 3022, 2927, 2830, 1571, 1512, 1493, 1436, 1183; ^{1}H-NMR ($CDCl_3$, δ, ppm, *J*, Hz): 11.99 (1H, *s*, SH), 7.45-7.05 (10H, *m*, aromatic), 6.73 (1H, *d*, 11.9, $H^{10'}$), 6.64 (1H, *d*, 11.9, $H^{11'}$), 6.38 (m,1H, $H^{20'}$), 4.40 (dd, 5.5, 10.3, 1H, $H^{5'}$), 3.12 (dd, 10.3, 15.0, 1H, $H^{12'}$), 3.12 (dd, 15.0, 5.5, 1H, $H^{12'}$); ^{13}C-NMR ($CDCl_3$, δ, ppm): 167.87 (C^3), 158.07 (d, 245.3, $C^{19'}$), 153.46 (d, 247.9, $C^{16'}$), 151.84 (C^5), 138.65 (Cq), 137.95 (Cq), 133.92 (Cq), 133.77 (Cq), 131.10 (CH), 130.29 (CH), 130.03 (CH), 129.91 (CH), 129.46 (CH), 129.34 (CH), 129.29 (CH), 127.37 (CH), 127.30 (CH), 59.48 ($C^{5'}$), 25.93 ($C^{12'}$).

5-(5H-dibenzo[a,d][7]annulen-5-ylmethyl)-4-(3-bromophenyl)-4H-1,2,4-triazole-3-thiol (4b):

Yield: %; m.p.: °C; Anal. calcd. for $C_{24}H_{18}BrN_3S$ (460.40 g/mol): C, 62.61%; H, 3.94; N, 9.13%; found: C, 62.61%; H, 3.92; N, 9.14%; IR (KBr, cm^{-1}): 3415, 3133, 3066, 3021, 2928, 2830, 1580, 1567, 1481, 1432, 685; ^{1}H-NMR ($CDCl_3$, δ, ppm, *J*, Hz):10.76 (1H, *s*, SH), 7.66 (1H, *dl*, 7.7, 1H, $H^{18'}$), 7.35 (tl, 7.7, 1H, $H^{19'}$), 7.28-7.18 (8H, *m*, aromatic), 6.86 (sl, 1H, $H^{16'}$), 6.85 (dl, 7.7, 1H, $H^{20'}$), 6.62 (2H, s, $H^{10'}$, $H^{11'}$), 4.44 (1H, *t*, 7.7, $H^{5'}$), 2.98 (2H, *d*, 7.7, $H^{12'}$); ^{13}C-NMR ($CDCl_3$, δ, ppm):167.83 (triazole-C^3), 151.57 (triazole-C^5), 138.27 (2Cq), 134.08 (C_q), 133.91 (2Cq), 133.85 ($2C_q$), 133.15 (CH), 131.46 (CH), 130.84 (CH), 130.70 ($C^{10'}$, $C^{11'}$), 130.14 (2CH), 129.64 (2CH), 129.32 (2CH), 127.33 (2CH), 126.95 (CH), 122.96 ($C^{17'}$), 53.46 ($C^{5'}$), 25.89 ($C^{12'}$).

Results and discussions

The structures of the new compounds synthesized were confirmed by their spectral data,^{1}H-NMR, ^{13}C-NMR, IR and elemental analysis.

The IR spectrum of the newly acylhydrazinecarbothioamides included a characteristic band at 1237-1258 cm^{-1} which was due to vibration of C=S group. Also, in the IR spectrum of this compounds a band appears at 1666-1696 cm^{-1} attributed to the vibration of C=O group. The stretching bands corresponding to NH groups were observed in range 3153–3345 cm^{-1}. The band at 1666-1696 cm^{-1} and 1237-1258 cm^{-1} assigned to the stretching frequency of C=O and C=S bond observed in the spectrum of the acylhydrazinecarbothioamides disappeared from the spectrum of the new 1,3,4-oxadiazoles (3a,b). In IR spectra of this compounds appear a new band generated by the stretching vibration of a C=N group (1656-1673 cm^{-1}), and this confirm that cyclization reaction had occurred.

Acylhydrazinecarbothioamides (2a,b) were present as two conformational isomers, 5'-axial and 5'-equatorial in about 3:1 ratio, confirmed by ^{1}H-NMR spectra. The ^{1}H-NMR spectra of these compounds showed three NH proton singlet signals in region 8.79-9.86 ppm and the ^{13}C-NMR spectra present two characteristic signals of carbon atoms from C=O and C=S groups at ~ 170 ppm and ~ 181 ppm respectively. In the ^{13}C-NMR spectra of compounds (2a), the carbon atoms signals of $C^{16'}$ and $C^{19'}$ appear as a doublet because of the strong germinal coupling (J^1 = 239 Hz and 241 Hz respectively) of the fluorine atoms with the carbon atoms.

IR spectra of compounds (3a,b) and (4a,b) obtained from acylhydrazinecarbothioamides (2a,b) do not show the absorption band characteristic of C=O group, confirming that the cyclization reaction of these new intermediates (2a,b) took place. The ^{1}H-NMR spectra of 1,3,4-oxadiazoles (3a,b) and 1,2,4-triazoles (4a,b) indicated the presence of a single conformational isomer, namely the axial one.

The ^{1}H-NMR spectra of 2-amino-1,3,4-oxadiazoles (3a,b) show the N-H signal as singlet at 8.90-9.45 ppm and IR spectra of same compounds present characteristic absorption band of stretching vibrations of NH group at 3411-3415 cm^{-1}.

In the ^{13}C-NMR spectra of compounds (3a,b), the carbon atoms signals of carbonyl and thiocarbonyl from acylhydrazinecarbothioamides are not found, but there are two new signals characteristic of the quaternary atoms from the 1,3,4-oxadiazole nucleus : C^2 carbon at ~160 ppm and C^5 at ~159 ppm.

2-Amino-1,3,4-oxadiazole (3a), which contains an aromatic ring substituted with two fluorine atoms, the carbon atom signals in the aromatic ring appear as a doublet (J^1 = 239 Hz and 241 Hz).

The 1,2,4-triazole derivatives (4a,b) show IR spectrum (in KBr) only two bands at 3133-3136 and 3413-3415 cm^{-1} characteristic for –NH-CS because in solid state (KBr) this compounds exists in the form of their thionic tautomers.

In the ^{1}H-NMR spectra of 1,2,4-triazoles (4a,b) the NH signals totally disappeared being replaced by a singlet at δ=10.76-11.99 ppm attributable to SH proton. Thus, in solution the above tautomeric equilibrium is shifted towards the thiolic form. In ^{13}C-NMR spectra for 1,2,4-triazol-

3-thioles appears a new quaternary carbon signal (for C^3) at δ=167.87-167.83 ppm (scheme 3) and a signal for C^5 at = 151.57-151.84 ppm.

In 1,2,4-triazole (4a) substituted with the 2,5-difluorophenyl substituent, the double bond protons $H^{10'}$ and $H^{11'}$ appears as an AB system with a vicinal coupling constant J^3 = 11 Hz, because of to the axial configuration. The double bond protons $H^{10'}$ and $H^{11'}$ are shielded with ≈ 0.4 ppm comparative with the hydrazinecarbothioamide (2a). Moreover the $H^{11'}$ protons are *nonequivalent and* appears as a doublet of doublets at 3.12 and 2.82 ppm, with a geminal coupling constant J^2 = 15 Hz and a vicinal coupling constants with $H^{5'}$, J^3= 10.3 Hz and 5.4 Hz respectively.

In the ^{13}C-NMR spectra of compounds (4a), the carbon atoms signals of $C^{16'}$ and $C^{19'}$ appear as a doublet (J^1 = 247.9 Hz and 245.3 Hz respectively).

The synthesis of the newly 1,2,4-triazoles or 1,3,4-oxadiazole compounds was realized aiming to discover some new potent SrtA inhibitors.

Conclusions

In this work we described the synthesis and characterization of six new compounds, respectively two acylhydrazinecarbothioamides, two 1,3,4-oxadiazoles and two 1,2,4-triazoles with 5H-dibenzo[a,d][7]annulene moiety. The chemical structure was determined by spectral analysis. The inhibitory activities of the newly compounds against SrtA will be evaluated.

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