Synthesis and Characterization of New 5-Aryl-2-[*para*-(4-chlorophenylsulfonyl)phenyl]-4-methyloxazoles

THEODORA-VENERA APOSTOL[1*], IOANA SARAMET[1], CONSTANTIN DRAGHICI[2], STEFANIA-FELICIA BARBUCEANU[1], LAURA ILEANA SOCEA[1], GABRIELA LAURA ALMAJAN[1]

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

[2] Romanian Academy, Organic Chemistry Center "C.D. Nenitzescu, 202B Splaiul Independentei, 060023, Bucharest, Romania

Acylaminoacylation of aromatic hydrocarbons (benzene, toluene, m-xylene) with 2-[4-(4-chlorophenylsulfonyl)phenyl]-4-methyloxazol-5(4H)-one or 2-[4-(4-chlorophenylsulfonyl)-benzamido]propanoyl chloride in the presence of anhydrous aluminum chloride led to N-(1-aryl-1-oxopropan-2-yl)-4-(4-chlorophenylsulfonyl)benzamides. These new intermediates were cyclized under the action of phosphorus oxychloride to the corresponding 5-aryl-2-[4-(4-chlorophenylsulfonyl)phenyl]-4-methyloxazoles. The newly synthesized compounds were characterized by elemental analysis and spectral studies (FT-IR, UV, ^{1}H- and ^{13}C-NMR).

Keywords: N-acyl-α-amino acid, α-acylaminoketone, 1,3-oxazole, 1,3-oxazol-5(4H)-one, acylaminoacylation

Oxazoles and 5(4*H*)-oxazolones are five-membered heterocyclic compounds that have a large number of applications in medicinal, agrochemical products, optical materials, etc. and have been used as highly versatile intermediates in the synthesis of a variety of organic molecules. The wide range of biological activities of oxazoles includes pharmaceutical properties such as anti-inflammatory [1], analgesic [2], antibacterial, antifungal [3], hypoglycemic [4], antiproliferative [5], anti-tuberculosis [6], muscle relaxant [7], antipsychotic [8] and HIV-inhibitory activity [9]. A broad spectrum of natural products of peptide origin containing oxazoles was usually identified as secondary metabolites of algae, fungi and primitive marine organisms [10]. These compounds exhibit several biological properties, including cytotoxicity [11], immunosuppressive [12], antibacterial [13], antiviral [14], antimycobacterial [15] and anti-tumoral activities [16]. In addition, oxazoles derivatives are useful synthetic intermediates and can be used as diversity scaffolds in combinatorial chemistry [17] and also as peptidomimetics [18]. Arylated oxazoles are of interest not only due to their biological properties, but also due to their importance as organic materials. They have various applications due to their strong fluorescence, namely as pigments, lubricants, fluorescent whitening agents, fluorescent probes and labels in biology and medicine and also as dye-based lasers and efficient luminophores for liquid and plastic scintillators for detecting nuclear radiations and in high throughput screening of chemicals obtained by combinatorial chemistry [19]. It is known that many compounds from 1,3-oxazol-5(4*H*)-ones class present antimicrobial [20], anticancer [21], anti-inflammatory activities [22]. Further, many literature reports have indicated that diphenylsulfone derivatives were also found to possess antimicrobial and antioxidant activities. The incorporation of diphenylsulfone moiety into various heterocyclic systems was found to increase their pharmacological properties [23]. Therefore, there is considerable interest of having available efficient routes to these heterocycles, which contain a diphenylsulfone moiety, with potential biological action.

In continuation of the previous part in this series [24], we now report the preparation of new 2,5-diaryl-4-methyloxazoles wherein the 2-aryl group is *para*-(4-chlorophenylsulfonyl)phenyl. The synthetic method used in this approach consisted in the *N*-acylation of α-alanine by the Steiger procedure [25-27], followed by cyclization of *N*-acyl-α-alanine **3** to the corresponding azlactone **4** [26-31]. Friedel-Crafts acylaminoacylation of aromatic hydrocarbons (benzene, toluene, *m*-xylene) with saturated 1,3-oxazol-5(4*H*)-one (2-oxazolin-5-one) **4** [26-28,31-34] or *N*-acyl-α-alanyl chloride **5** [35] in the presence of anhydrous aluminum chloride afforded the corresponding α-acylaminoketones **6a-c**. These intermediates were converted into 1,3-oxazoles **7a-c** by Robinson-Gabriel cyclodehydration with phosphorus oxychloride [26-28,31-34] or concentrated sulfuric acid in the presence of acetic anhydride in ethyl acetate [36] (scheme 1).

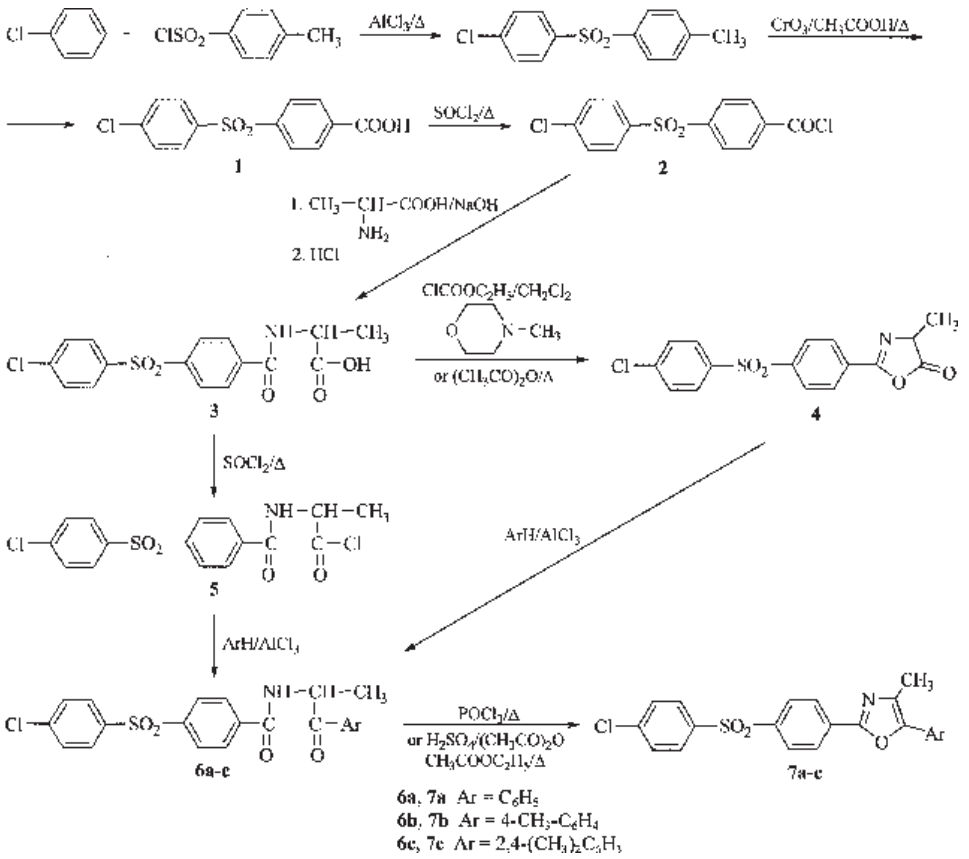
Experimental part

Melting points were measured on a Böetius apparatus and are uncorrected. FT-IR spectra were registered on a Bio-Rad FTS-135 IR spectrophotometer using the standard KBr pellet disc technique, in the 4000-400 cm^{-1} region. UV spectra were recorded in methanolic solution (2.5×10^{-5} M) on an Analytik Jena SPECORD 40 spectrophotometer, within the range 200-600 nm. NMR spectra were recorded on a Varian Gemini 300BB apparatus, operating at 300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR, using DMSO-d_6 and $CDCl_3$ as solvents. Chemical shifts are expressed in parts per million downfield from tetramethylsilane (TMS) as an internal standard and coupling constants are given in hertz (where, s = singlet, d = doublet, dd = double doublet, t = triplet, tt = triple triplet, q = quartet, cv = quintet, m = multiplet). Elemental analyses for C, H, N and S was obtained using a Carlo-Erba Analyser Series L-1108 apparatus.

*Preparation of 4-(4-chlorophenylsulfonyl)benzoyl chloride (**2**)*

4-(4-Chlorophenylsulfonyl)benzoic acid **1** (5.93 g, 20 mmol) was converted into the corresponding acid chloride

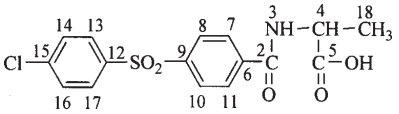
* *email: theodoraapostol@yahoo.com*



Scheme 1. Synthesis of the title compounds

2 by refluxing with excess of thionyl chloride (35 mL) [37]. Excess of $SOCl_2$ was removed *in vacuo* and the product was used in the next reaction without further purification. Colorless crystals, yield 99%, 6.24 g, m.p. 138-139°C (lit. [27] 138°C). IR (KBr, cm^{-1}): 3097s, 3038m (νCH_{aryl}); 1781s, 1740vs ($\nu C=O$); 1580m, 1475m ($\nu C=C_{aryl}$); 1332vs, 1302s, 1284m ($\nu_{as}SO_2$); 1162vs ($\nu_{sim}SO_2$); 851m (γCH_{aryl}); 762vs (νC-Cl).

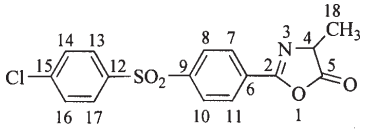
*Acylation of α-alanine to afford 2-[4-(4-chlorophenylsulfonyl)benzamido]propanoic acid (**3**)*



3

α-Alanine (1.78 g, 20 mmol) was treated with 20 mL of 1 N sodium hydroxide solution. Into this solution cooled to 0-5 °C, two solutions were added dropwise simultaneously under stirring during 30 min, the crude acid chloride **2** (6.30 g, 20 mmol) in 45 mL anhydrous methylene chloride and 10 mL of 2 N sodium hydroxide solution [25-27]. After one hour stirring at room temperature, the lower layer was separated and the aqueous layer was acidified with 2 N hydrochloric acid. The product **3** was filtered off and recrystallized from water as white needles, yield 94%, 6.91 g, m.p. 193-195°C. UV (methanol, λ_{max}, nm, logε): 202.6 (4.48), 223.8 (4.15), 250.2 (4.36). IR (KBr, cm^{-1}): 3372s (νNH); 3091m, 3066m (νCH_{aryl}); 2996m ($\nu_{as}CH_3$); 2944m (νCH); 2872w ($\nu_{sim}CH_3$); 1709vs ($\nu O=C$-O); 1644vs ($\nu O=C$-N); 1577s, 1523vs, 1488m, 1478s ($\nu C=C_{aryl}$); 1324vs, 1296vs ($\nu_{as}SO_2$); 1158vs ($\nu_{sim}SO_2$); 853s (γCH_{aryl}); 758vs (νC-Cl). ^{1}H-NMR (300 MHz, DMSO-d_6, δ_H, ppm): 1.38 (3H, d, $^3J_{HH}$ = 7.3 Hz, H-18), 4.42 (1H, cv, $^3J_{HH}$ = 7.3 Hz, H-4), 7.71 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-14, H-16), 8.00 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-13, H-17), 8.02 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-7, H-11), 8.09 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-8, H-10), 8.95 (1H, d, $^3J_{HH}$ = 7.3 Hz, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, δ_C, ppm): 16.79 (C-18), 48.36 (C-4), 127.66 (C-8, C-10), 128.89 (C-7, C-11), 129.50 (C-13, C-17), 130.05 (C-14, C-16), 138.73 (C-6), 139.16 (C-15), 139.51 (C-12), 142.82 (C-9), 164.88 (C-2), 173.91 (C-5). Anal. Calcd. for $C_{16}H_{14}ClNO_5S$ (367.80 g/mol): C, 52.25; H, 3.84; N, 3.81; S, 8.72%, Found: C, 52.41; H, 3.82; N, 3.78; S, 8.72%.

*Cyclization of **3** to 2-[4-(4-chlorophenylsulfonyl)phenyl]-4-methyloxazol-5(4H)-one (**4**)*



4

Method 1. At room temperature into 50 mL methylene chloride, 3.86 g (10.5 mmol) of 2-[4-(4-chlorophenylsulfonyl)benzamido]propanoic acid **3** and 1.15 mL (10.5 mmol) of *N*-methylmorpholine were added under stirring. Then an equimolar quantity of ethyl chloroformate (1 mL) was poured dropwise over the reaction mass [26-29]. The mixture was magnetically stirred for 30 min at ambient temperature and then it was poured over 100 mL cold water. The organic layer was separated and washed with 5% sodium hydrogen carbonate solution and then with water. After drying over $MgSO_4$, the solvent was removed under reduced pressure. Cyclodehydration afforded **5** as white crystals, 97% yield, 3.56 g, m.p. 169-171°C (from cyclohexane).

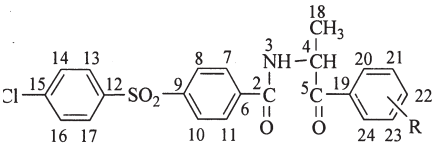
*Method 2.*2-[4-(4-Chlorophenylsulfonyl) benzamido]-propanoic acid **3** (1.84 g, 5 mmol) in a eightfold amount of acetic anhydride (3.77 mL), is heated with stirring on a hot plate at 140°C for about 1 h until all acid had gone into solution [30,31]. Then reaction mixture is heated for another 30 min with constant stirring. The acetic anhydride-acetic acid mixture was completely evaporated under reduced pressure on a water bath. The distillation residue was collected with a small amount of cool absolute ethanol

and filtered off. The azlactone thus obtained is nearly pure, white crystals, 98% yield, 1.71 g, m.p. (crude) 170-171°C. UV (methanol, λ_{max}, nm, logε): 202.6 (4.45), 223.8 (4.11), 250.2 (4.32). IR (KBr, cm^{-1}): 3092m, 3071m (νCH_{aryl}); 2992m ($\nu_{as} CH_3$); 2944m (νCH); 2875w ($\nu_{sim} CH_3$); 1822vs (νC=O); 1650vs (νC=N); 1581s, 1478s ($\nu C=C_{aryl}$); 1332vs, 1303vs, 1295vs ($\nu_{as} SO_2$); 1255s (ν_{as} C-O-C); 1165vs ($\nu_{sim} SO_2$); 1047s (ν_{sim} C-O-C); 847s (γCH_{aryl}^{as}); 765vs (νC-Cl). ^{1}H-NMR (300 MHz, $CDCl_3$, δ_H, ppm): 1.59 (3H, d, $^3J_{HH}$ = 7.7 Hz, H-18), 4.49 (1H, q, $^3J_{HH}$ = 7.7 Hz, H-4), 7.51 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-14, H-16), 7.90 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-13, H-17), 8.04 (2H, d, $^3J_{HH}$ = 8.5 Hz, H-7, H-11), 8.13 (2H, d, $^3J_{HH}$ = 8.5 Hz, H-8, H-10). ^{13}C-NMR (75 MHz, $CDCl_3$, δ_C, ppm): 16.86 (C-18), 61.41 (C-4), 128.20 (C-7, C-11), 128.98 (C-8, C-10), 129.46 (C-13, C-17), 129.99 (C-14, C-16), 130.60 (C-6), 139.40 (C-15), 140.66 (C-12), 145.09 (C-9), 160.28 (C-2), 178.13 (C-5). Anal. Calcd. for $C_{16}H_{12}ClNO_4S$ (349.79 g/mol): C, 54.94; H, 3.46; N, 4.00; S, 9.17%, Found: C, 54.97; H, 3.51; N, 3.95; S, 9.13%.

*Preparation of 2-[4-(4-chlorophenylsulfonyl) benzamido] propanoyl chloride (**5**)*

2-[4-(4-Chlorophenylsulfonyl)benzamido]propanoic acid **3** (2.02 g, 5.5 mmol) was reacted with excess of thionyl chloride (10 mL) and heated on a water-bath until evolution of sulfur dioxide and hydrogen chloride gas ceased [37]. Excess of thionyl chloride was removed under reduced pressure on a water-bath and the crude acid chloride obtained as yellow crystals was used without further purification, 98% yield, 2.08 g, m.p. 110-112°C. IR (KBr, cm^{-1}): 3315m (νNH); 3092m, 3071m (νCH_{aryl}); 2986m ($\nu_{as} CH_3$); 2922m (νCH); 2851m ($\nu_{sim} CH_3$); 1827s, 1787s (νO=C-Cl); 1652s (νO=C-N); 1577s, 1525s, 1477s ($\nu C=C_{aryl}$); 1327vs, 1292vs ($\nu_{as} SO_2$); 1160vs ($\nu_{sim} SO_2$); 850m (γCH_{aryl}); 762vs (νC-Cl).

*General synthetic procedures for the preparation of N-(1-aryl-1-oxopropan-2-yl)-4-(4-chlorophenylsulfonyl) benzamides (**6a-c**)*



6a R = H
6b R = 4-CH_3
6c R = 2,4-$(CH_3)_2$

Method 1. The crude azlactone **4** (1.75 g, 5 mmol) in 25 mL of aromatic hydrocarbon (solvent and reactant) was treated portionwise under stirring with 2.0 g (15 mmol) anhydrous aluminum chloride at room temperature [26-28,31-34]. The reaction mixture was stirred for 20 h and then it was poured over 100 mL ice-water with 5 mL concentrated HCl. The crude product was filtered off and washed with cold water and a cool mixture of water : ethanol (1:1, v/v). The layers of the filtrate were separated and the aqueous layer was extracted twice with 15 mL methylene chloride. The combined organic layers were washed with water, dried over sodium sulfate and evaporated under reduced pressure, leaving a second crop of crude product. Recrystallization from ethanol or cyclohexane affords the products as colorless crystals in 94-98% yields.

Method 2. To the crude 2-[4-(4-chlorophenylsulfonyl) benzamido]propanoyl chloride **5** (1.93 g, 5 mmol) in 25 mL of aromatic hydrocarbon (solvent and reactant), 2.0 g (15 mmol) anhydrous $AlCl_3$ were added portionwise at ambient temperature [35]. Stirring was continued until the HCl was not longer released (~ 20 h) and then the reaction mixture was poured over 100 mL ice-hydrochloric acid. The organic component was extracted with methylene chloride and the organic layer was washed with water, then with 5% $NaHCO_3$ solution and dried (Na_2SO_4). Evaporation of the solvent mixture under reduced pressure and recrystallization from ethanol or cyclohexane affords colorless solids in 80-85 % yields.

*4-(4-Chlorophenylsulfonyl)-N-(1-oxo-1-phenylpropan-2-yl)benzamide (**6a**)*, by reaction with benzene: Colorless crystals, 94% yield, 2.01 g (Method 1), 80% yield, 1.71 g (Method 2), m.p. 118-120°C (from cyclohexane). UV (methanol, λ_{max}, nm, logε): 203.5 (4.46), 249.3 (4.33). IR (KBr, cm^{-1}): 3349s (νNH); 3091m, 3063m (νCH_{aryl}); 2984m ($\nu_{as} CH_3$); 2935m (νCH); 2876w ($\nu_{sim} CH_3$); 1692s (νO=C-C); 1650vs (νO=C-N); 1597m, 1577s, 1537vs, 1521vs, 1478s, 1450s ($\nu C=C_{aryl}$); 1324vs, 1293vs ($\nu_{as} SO_2$); 1159vs ($\nu_{sim} SO_2$); 854m (γCH_{aryl}); 755vs (νC-Cl). ^{1}H-NMR (300 MHz, DMSO-d_6, δ_H, ppm): 1.40 (3H, d, $^3J_{HH}$ = 6.9 Hz, H-18), 5.52 (1H, cv, $^3J_{HH}$ = 6.9 Hz, H-4), 7.53 (2H, t, $^3J_{HH}$ = 7.7 Hz, H-21, H-23), 7.64 (1H, tt, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.4 Hz, H-22), 7.71 (2H, d, $^3J_{HH}$ = 8.2 Hz, H-14, H-16), 8.00 (2H, dd, $^4J_{HH}$ =1.4 Hz, $^3J_{HH}$ = 7.7 Hz, H-20, H-24), 8.01 (2H, d, $^3J_{HH}$ = 8.2 Hz, H-13, H-17), 8.03 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-7, H-11), 8.09 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-8, H-10), 9.15 (1H, d, $^3J_{HH}$ = 6.9 Hz, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, δ_C, ppm): 16.59 (C-18), 50.50 (C-4), 127.59 (C-8, C-10), 128.18 (C-13, C-17), 128.74 (C-7, C-11), 128.81 (C-21, C-23), 129.43 (C-20, C-24), 129.97 (C-14, C-16), 133.32 (C-22), 134.79 (C-19), 138.13 (C-6), 139.08 (C-15), 139.43 (C-12), 142.83 (C-9), 164.63 (C-2), 198.80 (C-5). Anal. Calcd. for $C_{22}H_{18}ClNO_4S$ (427.90 g/mol): C, 61.75; H, 4.24; N, 3.27; S, 7.49%, Found: C, 61.71; H, 4.19; N, 3.32; S, 7.52%.

*4-(4-Chlorophenylsulfonyl)-N-(1-oxo-1-p-tolylpropan-2-yl)benzamide (**6b**)*, by reaction with toluene: Colorless cystals, 96% yield, 2.12 g (Method 1), 82% yield, 1.81 g (Method 2), m.p. 143-145°C (from absolute ethanol). UV (methanol, λ_{max}, nm, logε): 203.5 (4.47), 254.6 (4.37). IR (KBr, cm^{-1}): 3381s (νNH); 3090m, 3067m (νCH_{aryl}); 2979m ($\nu_{as} CH_3$); 2937m (νCH); 2877w ($\nu_{sim} CH_3$); 1685vs (νO=C-C); 1651vs (νO=C-N); 1605s, 1572s, 1525vs, 1482s, 1451m ($\nu C=C_{aryl}$); 1320vs, 1285vs ($\nu_{as} SO_2$); 1156vs ($\nu_{sim} SO_2$); 852s (γCH_{aryl}); 767vs (νC-Cl). ^{1}H-NMR (300 MHz, DMSO-d_6, δ_H, ppm): 1.39 (3H, d, $^3J_{HH}$ = 7.0 Hz, H-18), 2.36 (3H, s, *para*-CH_3), 5.50 (1H, cv, $^3J_{HH}$ = 7.0 Hz, H-4), 7.33 (2H, d, $^3J_{HH}$ = 7.9 Hz, H-21, H-23), 7.71 (2H, d, $^3J_{HH}$ = 8.8, H-14, H-16), 7.91 (2H, d, $^3J_{HH}$ = 7.9 Hz, H-20, H-24), 8.00 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-13, H-17), 8.03 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-7, H-11), 8.09 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-8, H-10), 9.11 (1H, d, $^3J_{HH}$ = 7.0 Hz, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, δ_C, ppm): 16.72 (C-18), 21.09 (*para*-CH_3), 50.34 (C-4), 127.56 (C-8, C-10), 128.30 (C-20, C-24), 128.80 (C-7, C-11), 129.28 (C-21, C-23), 129.41 (C-13, C-17), 129.95 (C-14, C-16), 132.21 (C-19), 138.58 (C-6), 139.06 (C-15), 139.44 (C-12), 142.89 (C-22), 143.73 (C-9), 164.57 (C-2), 198.22 (C-5). Anal. Calcd. for $C_{23}H_{20}ClNO_4S$ (441.93 g/mol): C, 62.51; H, 4.56; N, 3.17; S, 7.26%, Found: C, 62.57; H, 4.52; N, 3.11; S, 7.23%.

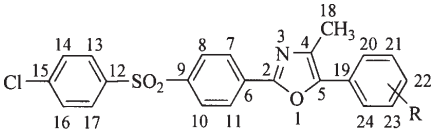
*4-(4-Chlorophenylsulfonyl)-N-(1-oxo-1-m-xylylpropan-2-yl)benzamide (**6c**)*, by reaction with *m*-xylene: Colorless crystals, 98% yield, 2.23 g (Method 1), 85% yield, 1.93 g (Method 2), m.p. 96-98°C (from ethanol : wather). UV (methanol, λ_{max}, nm, logε): 203.5 (4.47), 252.9 (4.31). IR (KBr, cm^{-1}): 3362m (νNH); 3089m, 3066w (νCH_{aryl}); 2981m ($\nu_{as} CH_3$); 2928m (νCH); 2874w ($\nu_{sim} CH_3$); 1686s (νO=C-C); 1653vs (νO=C-N); 1612m, 1572m, 1537s, 1478m, 1452m ($\nu C=C_{aryl}$); 1325vs, 1296s ($\nu_{as} SO_2$); 1160vs

($\nu_{sim}SO_2$); 856m (γCH_{aryl}); 757vs (νC-Cl). ^{1}H-NMR (300 MHz, DMSO-d_6, δ_H, ppm): 1.33 (3H, d, $^3J_{HH}$ = 7.0 Hz, H-18), 2.28 (3H, s, *para*-CH_3), 2.35 (3H, s, *ortho*-CH_3), 5.26 (1H, cv, $^3J_{HH}$ = 7.0 Hz, H-4), 7.10 (2H, m, H-21, H-23), 7.70 (2H, d, $^3J_{HH}$ = 8.8, H-14, H-16), 7.72 (1H, d, $^3J_{HH}$ = 8.8 Hz, H-24), 8.00 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-13, H-17), 8.03 (2H, d, $^3J_{HH}$ = 8.5 Hz, H-7, H-11), 8.08 (2H, d, $^3J_{HH}$ = 8.5 Hz, H-8, H-10), 9.10 (1H, d, $^3J_{HH}$ = 7.0 Hz, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, δ_C, ppm): 15.99 (C-18), 20.24 (*ortho*-CH_3), 20.82 (*para*-CH_3), 52.60 (C-4), 126.09 (C-21), 127.57 (C-8, C-10), 128.35 (C-24), 128.74 (C-7, C-11), 129.41 (C-13, C-17), 129.95 (C-14, C-16), 132.18 (C-23), 133.39 (C-19), 137.65 (C-22), 138.57 (C-6), 139.06 (C-15), 139.41 (C-20), 141.18 (C-12), 142.78 (C-9), 164.68 (C-2), 202.26 (C-5). Anal. Calcd. for $C_{24}H_{22}ClNO_4S$ (455.95 g/mol): C, 63.22; H, 4.86; N, 3.07; S, 7.03%, Found: C, 63.25; H, 4.91; N, 3.03; S, 7.03%.

*General synthetic procedures for the preparation of 5-aryl-2-[4-(4-chlorophenylsulfonyl)phenyl]-4-methyloxazoles (**7a-c**)*

Method 1. The *N*-(1-aryl-1-oxopropan-2-yl)-4-(4-chlorophenylsulfonyl)benzamides **6a-c** (10 mmol) were refluxed in 20 mL phosphorus oxychloride for 4 h [26-28,31-34]. The excess of $POCl_3$ was removed under reduced pressure. After cooling, the oily residue was treated with ice-water, extracted twice with 20 mL methylene chloride, the organic layers were combined and washed with water, then with 5% $NaHCO_3$ solution and dried over sodium sulfate. After removing the solvent, the crude oxazoles **7a-c** were recrystallized from absolute ethanol as colorless crystals in 90-94% yields.

Method 2. The 2-aza-1,4-diaryl-3-methyl-1,4-butanediones **6a-c** (10.51 mmol) were dissolved in 40 mL ethyl acetate. Acetic anhydride (3 mL) and 95-98% sulfuric acid (0.17 mL) in 2.5 mL ethyl acetate were added [36]. The reaction mass was heated at reflux for 3 h. After cooling to room temperature, a 2.52 N sodium hydroxide solution (25 mL) was added. The reaction mixture was heated at reflux for 30 min and then cooled to room temperature. The precipitate obtained was filtered off and washed with 1 N hydrochloric acid, then with 10% brine and finally, with cool water. The layers of the filtrate were separated and the organic layer was washed with 1 N HCl, then with 10% brine, dried (Na_2SO_4) and concentrated *in vacuo*. The resulted slurry was stirred overnight at room temperature, diluted with hexane, cooled at 0°C for 1 h and filtered off, leaving a second crop of crude product. The 1,3-oxazoles **7a-c** with high purity as colorless crystals were obtained in above 95% yields.



7a R = H
7b R = 4-CH_3
7c R = 2,4-$(CH_3)_2$

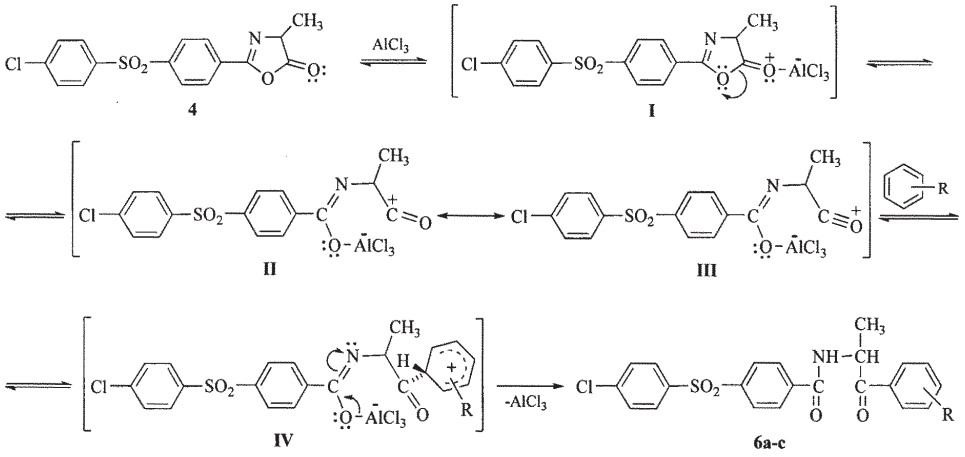
*2-[4-(4-Chlorophenylsulfonyl)phenyl]-4-methyl-5-phenyloxazole (**7a**).* Colorless needles, 90% yield, 3.69 g (Method 1), 94% yield, 4.05 g (Method 2), m.p. 184-186°C (from absolute ethanol). UV (methanol, λ_{max}, nm, logε): 203.5 (4.47), 247.6 (4.26), 337.4 (4.39). IR (KBr, cm^{-1}): 3090m, 3064w (νCH_{aryl}); 2932w ($\nu_{as}CH_3$); 2863w ($\nu_{sim}CH_3$); 1593s (νC=N); 1582m, 1545m, 1496m, 1474m, 1444m ($\nu C{=}C_{aryl}$); 1324vs, 1280s ($\nu_{as}SO_2$); 1154vs ($\nu_{sim}SO_2$); 1090vs (ν_{sim}C-O-C); 840m (γCH_{aryl}); 769vs (νC-Cl). ^{1}H-NMR (300 MHz, $CDCl_3$, δ_H, ppm): 2.50 (3H, s, H-18), 7.37 (1H, tt, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.4 Hz, H-22), 7.49 (2H, t, $^3J_{HH}$ = 7.4, H-21, H-23), 7.49 (2H, d, $^3J_{HH}$ = 8.5 Hz, H-14, H-16), 7.68 (2H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.4 Hz, H-20, H-24), 7.92 (2H, d, $^3J_{HH}$ = 8.5 Hz, H-13, H-17), 8.01 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-7, H-11), 8.19 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-8, H-10). ^{13}C-NMR (75 MHz, $CDCl_3$, δ_C, ppm): 13.59 (C-18), 125.69 (C-20, C-24), 126.98 (C-8, C-10), 128.36 (C-7, C-11, C-22), 129.05 (C-21, C-23), 129.32 (C-13, C-17), 129.88 (C-14, C-16), 131.93 (C-6), 134.30 (C-19), 138.88 (C-15), 139.99 (C-12), 142.17 (C-9), 147.04 (C-4), 157.46 (C-5), 175.70 (C-2). Anal. Calcd. for $C_{22}H_{16}ClNO_3S$ (409.89 g/mol): C, 64.47; H, 3.93; N, 3.42; S, 7.82%, Found: C, 64.53; H, 3.90; N, 3.38; S, 7.86%.

*2-[4-(4-Chlorophenylsulfonyl)phenyl]-4-methyl-5-p-tolyloxazole (**7b**).* Colorless needles, 93% yield, 3.94 g (Method 1), 95% yield, 4.23 g (Method 2), m.p. 214-216°C (from absolute ethanol). UV (methanol, λ_{max}, nm, logε): 203.5 (4.46), 248.5 (4.29), 342.7 (4.36). IR (KBr, cm^{-1}): 3089m, 3068m (νCH_{aryl}); 2917m ($\nu_{as}CH_3$); 2862w ($\nu_{sim}CH_3$); 1595s (νC=N); 1509s, 1478s, 1447m ($\nu C{=}C_{aryl}$); 1326vs, 1293s ($\nu_{as}SO_2$); 1156vs ($\nu_{sim}SO_2$); 1089vs (ν_{sim}C-O-C); 847s (γCH_{aryl}); 770vs (νC-Cl). ^{1}H-NMR (300 MHz, $CDCl_3$, δ_H, ppm): 2.41 (3H, s, *para*-CH_3), 2.48 (3H, s, H-18), 7.28 (2H, d, $^3J_{HH}$ = 8.2 Hz, H-21, H-23), 7.50 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-14, H-16), 7.56 (2H, d, $^3J_{HH}$ = 8.2 Hz, H-20, H-24), 7.91 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-13, H-17), 8.01 (2H, d, $^3J_{HH}$ = 8.5 Hz, H-7, H-11), 8.19 (2H, d, $^3J_{HH}$ = 8.5 Hz, H-8, H-10). ^{13}C-NMR (75 MHz, $CDCl_3$, δ_C, ppm): 13.55 (C-18), 21.47 (*para*-CH_3), 125.66 (C-20, C-24), 126.91 (C-8, C-10), 128.35 (C-7, C-11), 129.31 (C-13, C-17), 129.74 (C-21, C-23), 129.87 (C-14, C-16), 132.09 (C-6), 133.65 (C-19), 138.45 (C-15), 140.00 (C-12), 140.28 (C-22), 141.96 (C-9), 147.22 (C-4), 157.15 (C-5), 175.70 (C-2). Anal. Calcd. for $C_{23}H_{18}ClNO_3S$ (423.91 g/mol): C, 65.17; H, 4.28; N, 3.30; S, 7.56%, Found: C, 65.14; H, 4.28; N, 3,34; S, 7.50%.

*2-[4-(4-Chlorophenylsulfonyl)phenyl]-4-methyl-5-m-xylyloxazole (**7c**).* Colorless needles, 94% yield, 4.11 g (Method 1), 95% yield, 4.37 g (Method 2), m.p. 164-166°C (from absolute ethanol). UV (methanol, λ_{max}, nm, logε): 203.5 (4.47), 246.7 (4.10), 326.0 (4.08). IR (KBr, cm^{-1}): 3094m, 3068w (νCH_{aryl}); 2923m ($\nu_{as}CH_3$); 2862w ($\nu_{sim}CH_3$); 1602m (νC=N); 1582s, 1494m, 1473s, 1448m, ($\nu C{=}C_{aryl}$); 1328vs, 1291s ($\nu_{as}SO_2$); 1158vs ($\nu_{sim}SO_2$); 1094s (ν_{sim}C-O-C); 843s (γCH_{aryl}); 771vs (νC-Cl). ^{1}H-NMR (300 MHz, $CDCl_3$, δ_H, ppm): 2.28 (3H, s, *para*-CH_3), 2.34 (3H, s, *ortho*-CH_3), 2.38 (3H, s, H-18), 7.11 (1H, d, $^3J_{HH}$ = 8.2 Hz, H-23), 7.15 (1H, s, H-21), 7.25 (1H, d, $^3J_{HH}$ = 8.2 Hz, H-24), 7.50 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-14, H-16), 7.91 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-13, H-17), 8.00 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-7, H-11), 8.17 (2H, d, $^3J_{HH}$ = 8.8 Hz, H-8, H-10). ^{13}C-NMR (75 MHz, $CDCl_3$, δ_C, ppm): 12.53 (C-18), 20.44 (*ortho*-CH_3), 21.39 (*para*-CH_3), 126.74 (C-23), 126.84 (C-8, C-10), 128.37 (C-7, C-11), 129.31 (C-13, C-17), 129.86 (C-14, C-16), 129.89 (C-24), 131.84 (C-21), 132.22 (C-6), 134.97 (C-19), 137.43 (C-20), 138.33 (C-15), 139.65 (C-22), 140.03 (C-12), 142.02 (C-9), 147.81 (C-4), 158.00 (C-5), 175.70 (C-2). Anal. Calcd. for $C_{24}H_{20}ClNO_3S$ (437.94 g/mol): C, 65.82; H, 4.60; N, 3.20; S, 7.32%, Found: C, 65.86; H, 4.58; N, 3.24; S, 7.37%.

Results and discussions

The reaction sequences employed for synthesis of the title compounds are presented in scheme 1. Firstly, we focused our attention on the synthesis of the key intermediate **1** and corresponding acid chloride **2**, which were already described in literature [27]. The 4-(4-chlorophenylsulfonyl)benzoic acid **1** was prepared by a Friedel-Crafts reaction between chlorobenzene and *p*-toluenesulfochloride (4-methylbenzene-1-sulfonyl



Scheme 2. Proposed mechanism for obtaining 2-aza-1,4-diaryl-3-methyl-1,4-butanediones **6a-c** from 2-aryl-4-methyloxazol-5(4*H*)-one **4**

chloride) in the presence of anhydrous aluminum chloride at reflux, followed by oxidation of 4-(4-chlorophenylsulfonyl)-1-methylbenzene with chromic acid in glacial acetic acid at reflux [38]. The 4-(4-chlorophenylsulfonyl)benzoic acid **1** was then converted into the corresponding acid chloride **2** [37], which was employed without further purification for *N*-acylating α-alanine according to Steiger's procedure in order to obtain 2-[4-(4-chlorophenylsulfonyl)benzamido]propanoic acid **3** [25-27]. This compound was then cyclodehydrated to the corresponding 2-aryl-4-methyloxazol-5(4*H*)-one **4** by two methods using either ethyl chloroformate in the presence of *N*-methylmorpholine in methylene chloride at room temperature [26-29] or acetic anhydride at reflux [30,31]. The ring closure reaction in basic medium may be considered to take place according to the mechanism similar to that described in literature for other 2,4-disubstituted-5(4*H*)-oxazolone [24,39].

Subsequently, the $AlCl_3$-catalyzed acylaminoacylation was accomplished at ambient temperature by using excess of the aromatic hydrocarbons both as reactant and as solvent [26-28,31-34]. The saturated 5(4*H*)-oxazolone **4** was reacted with aromatic hydrocarbons affording the 2-aza-1,4-diaryl-3-methyl-1,4-butanediones **6a-c** in excellent yields, which increase in the order benzene < toluene < *m*-xylene in agreement with the increasing nucleophilicity of these hydrocarbons and stability of the corresponding σ-complexes **IV** in electrophilic aromatic substitution (scheme 2). This ring-opening reaction is possible because azlactones have a structure which bears similarities with carboxylic acid anhydrides. In the first step of the reaction mechanism for this reaction, the aromatic ring, which is benzene, toluene and *m*-xylene, respectively, undergoes nucleophilic attack at the acylium cation **II**, which is an electrophile stabilized by an oxonium type resonance structure **III** and is formed through a donor-acceptor complex **I**. This leads to the formation of an arenium cation (Wheland intermediate) **IV**, stabilized by resonance, which allows the positive charge to be distributed over three carbon atoms. In the second stage of the reaction, N-2 atom which functions as a Lewis base donates electrons to the hydrogen atom at the point of electrophilic attack and the electrons shared by the hydrogen return to the π system, restoring aromaticity of aromatic ring. Thus, the *N*-acyl-2-aminoketones **6a-c** are formed and the $AlCl_3$ catalyst is regenerated. Due to the electron-withdrawing effect of the carbonyl group, the *N*-acylaminoacylation product is always less reactive than the original molecule, so multiple acylations do not occur.

For the confirmation of **6a-c** structure, we have also attempted the synthesis of these compounds through the Friedel-Crafts acylation of aromatic hydrocarbons with 2-[4-(4-chlorophenylsulfonyl)benzamido]propanoyl chloride **5** according to the literature data [35], but in lower yields. This results proof that the use of 5(4*H*)-oxazolones as *N*-acylating reagent instead of *N*-acyl-α-amino acid chlorides is a substantial simplification.

In the Robinson-Gabriel synthesis conditions, using phosphorus oxychloride [26-28,31-34] or concentrated sulfuric acid in the presence of acetic anhydride in ethyl acetate [36], the above *N*-(1-aryl-1-oxopropan-2-yl)-4-(4-chlorophenylsulfonyl)benzamides **6a-c** were dehydrated and cyclized affording 2,5-diaryl-4-methyloxazoles **7a-c** in good yields.

The formation of the mentioned compounds was confirmed on the basis of their elemental analysis and spectroscopy (UV, IR, ^{1}H-NMR, ^{13}C-NMR). The values for the longest-wavelength absorption band of the three oxazoles are comparable with those reported for 2,5-diaryloxazoles [26-28,31-34].

IR Spectral Data

Presence of the characteristic absorption bands in IR spectra of the synthesized products provides useful information for determining the structure of new compounds **3-7**. Thus, 2-[4-(4-chlorophenylsulfonyl) benzamido]propanoic acid **3** and *N*-(1-aryl-1-oxopropan-2-yl)-4-(4-chlorophenylsulfonyl)benzamides **6a-c** exhibited the following characteristic absorption bands at 3349-3381 cm^{-1} due to the ν(N-H) stretching, at 1685-1709 cm^{-1} due to carbonyl group, ν(O=C-C) and at 1644-1653 cm^{-1} due to amidic carbonyl group, ν(O=C-N). In addition, the O-H stretching absorption for hydrogen-bonded dimer of compound **3** is strong and very broad, extending from 2500 to 3300 cm^{-1}. This absorption band is superimposed on the medium sharper C-H stretching peaks, which may be seen extending beyond the O-H envelope. The smaller peaks protruding at 2649 and 2573 cm^{-1} were characteristic of the dimer.

The IR spectra of heterocyclic compounds **4** and **7a-c** were clearly distinguished from those of corresponding acyclic intermediates **3** and **6a-c**, respectively by having different characteristic wavenumbers [27,40]. In IR spectra of compound **4** the absorption band due to the valence vibration of carbonyl group was found at 1822 cm^{-1}, while the ν(N-H),ν(O-H) and ν(O=C-N) from **3** were not observed. The IR spectra of **7a-c** revealed the absence of signals in the NH and C=O regions. The peaks at 1650 cm^{-1} (from **4**) and in the range 1582-1602 cm^{-1} (from **7a-c**), respectively were assigned to the C=N stretching vibration of these new heterocycles. The compounds **4**

and **7a-c** showed additional sharp bands at 1047 - 1094 cm^{-1} due to ν_{sim}(C-O-C), which also confirmed the formation of the 5(4*H*)-oxazolone and oxazole ring, respectively. The C-O-C asymmetric absorption band appears in azlactone **4** at 1255 cm^{-1}, but in oxazoles **7a-c** it is overlapped with the sulfonyl asymmetric stretch, which shows up at 1280-1293 cm^{-1}.

NMR Spectra

The formation of compounds **3**, **4**, **6**, **7** was further confirmed by the ^{1}H-NMR spectra. Assignments of the signals are based on the chemical shift and intensity pattern. The ^{1}H-NMR spectra of the compounds **3** and **6a-c** exhibited a doublet (with J = 6.9-7.3 Hz) attributed to secondary amide proton at a chemical shift comprised between 8.95-9.16 ppm.

The ^{1}H-NMR spectra of compounds **4** and **7a-c** contain two sub-spectra characteristic of the diphenylsulfone moiety and of the 5(4*H*)-oxazolone and oxazole ring, respectively. In the ^{1}H-NMR spectra of these compounds the signal attributed to the one proton from NH group of **3** and **6a-c** is absent and this proves that these heterocycles have been obtained.

In the ^{1}H-NMR spectra of the compounds **3** and **6a-c**, the methine proton from C-4 appears as a quintet at 4.42-5.52 ppm, while the same signal of the azlactone **4** was observed at 4.49 ppm as a quartet and in oxazoles **7a-c** it is absent.

Evidence for the formation of the oxazoles **7a-c** was provided by their ^{1}H-NMR spectra, which revealed a downfield shift in the signal attributed to the three protons of the methyl group in 4-position from δ_H 1.33-1.40 ppm as a doublet in α-acylaminoketones **6a-c** to 2.38-2.50 ppm as a singlet in **7a-c**. Also, the C-4 methyl doublet of the azlactone **4** showed a discernible downfield shift of 0.21 ppm relative to the same signal of the starting material **3**.

From the chemical shifts, one can observe that there is a slight deshielding of the protons in the chloro-substituted ring due to the electronegativity of the chloro substituent.

The signals in ^{13}C-NMR spectra are also in good agreement with the proposed structures for the newly synthesized compounds. The assignment of the signals in ^{13}C-NMR spectra of **3**, **4**, **6**, **7** resulted from the 2D-HETCOR spectra. The ^{13}C-NMR spectra of the heterocyclic compounds **4** and **7a-c** are not presenting any remaining characteristic signal of the carbon atoms from intermediates **3** and **6a-c**. The chemical shift of the C-4 atom from *N*-acyl-α-amino acid **3** at 48.36 ppm is moved to downfield after intramolecular cyclodehydration to 5(4*H*)-oxazolone **4** with 13.05 ppm. Also, in the oxazoles **7a-c** the C-4 signal was more deshielded (with ~ 96 ppm) by comparasion of the signal of the same atom from **6a-c** and this confirmed that cyclization of the α-acylaminoketones took place. It can be noticed the apparition of the downfield signal attributed to the C-2 atom of the oxazole nucleus at 175.70 ppm, while the amidic carbon signal of the intermediates **6a-c** (in the range 164.57-164.68 ppm) is absent. In the ^{13}C-NMR spectra of **7a-c**, the tertiary C-5 atom resonated at δ_C 157.15-158.00 ppm, whereas the secondary carbonyl carbon of the compounds **6a-c** resonated at 198.22-202.26 ppm revealing an upfield shift for this carbon in the oxazole structure, a further indication that the ring closure had taken place [27,41].

Other characteristic spectral data of new compounds **3-7** are given in the Experimental Part.

Conclusions

Nine new heterocyclic compounds from *N*-acyl-α-amino acid, 1,3-oxazol-5(4*H*)-one, α-acylaminoketone and 1,3-oxazole class were synthesized and characterized. The new azlactone **4** has been resulted by the reaction of acyl chloride **2** with α-alanine, followed by cyclodehydration of the new *N*-acyl-α-alanine **3**. The α-acylaminoketones **6a-c** have been obtained by treatment of 5(4*H*)-oxazolone **4** or *N*-acyl-α-alanyl chloride **5** with aromatic hydrocarbons under Friedel-Crafts reaction conditions. Finally, these new intermediates **6a-c**, heating with phosphorus oxychloride or sulfuric acid in the presence of acetic anhydride, underwent intramolecular ring closure with formation of the new 1,3-oxazoles **7a-c**. The structure of new obtained compounds was confirmed by elemental analysis and spectral methods.

References

1. (a) KARA, I.M., POLAT, S., INCE, F., GÜMÜŞ, C., J. Oral Maxillofac. Surg., **68**, no. 5, 2010, p. 1018. (b) SINGH, N., BHATI, K., KUMAR, A., Eur. J. Med. Chem., **43**, no. 11, 2008, p. 2597
2. (a) PERNER, R.J., KOENIG, J.R., DIDOMENICO, S., GOMTSYAN, A., SCHMIDT, R.G., LEE, C.-H., HSU, M.C., MCDONALD, H.A., GAUVIN, D.M., JOSHI, S., TURNER, T.M., REILLY, R.M., KYM, P.R., KORT, M.E., Biorg. Med. Chem., **18**, no. 13, 2010, p. 4821. (b) KIMBALL, F.S., ROMERO, F.A., EZZILI, C., GARFUNKLE, J., RAYL, T.J., HOCHSTATTER, D.G., HWANG, I., BOGER, D.L., J. Med. Chem., **51**, no. 4, 2008, p. 937. (c) DEMARTINO, J.K., GARFUNKLE, J., HOCHSTATTER, D.G., CRAVATT, B.F., BOGER, D.L., Biorg. Med. Chem. Lett., **18**, no. 22, 2008, p. 5842.
3. (a) KASPADY, M., NARAYANASWAMY, V.K., RAJU, M., RAO, G.K., Lett. Drug Des. Disc., **6**, no. 1, 2009, p. 21. (b) BROWN, P., DAVIES, D.T., O'HANLON, P.J., WILSON, J.M., J. Med. Chem., **39**, no. 2, 1996, p. 446.
4. CONTI, P., DALLANOCE, C., AMICI, M.D., MICHELI, C.D., KLOTZ, K.N., Bioorg. Med. Chem., **6**, no. 4, 1998, p. 401
5. (a) KUMAR, D., KUMAR, N.M., SUNDAREE, S., JOHNSON, E.O., SHAH, K., Eur. J. Med. Chem., **45**, no. 3, 2010, p. 1244. (b) LIU, X.-H., LV, P.-P., XUE, J.-Y., SONG, B.-A., ZHU, H.-L., Eur. J. Med. Chem., **44**, no. 10, 2009, p. 3930. (c) DELBECQ, F., CORDONNIER, G., POMMERY, N., BARBRY, D., HÉNICHART, J.-P., Bioorg. Med. Chem. Lett., **14**, no. 5, 2004, p. 1119
6. MORASKI, G.C., CHANG, M., VILLEGAS-ESTRADA, A., FRANZBLAU, S.G., MÖLLMANN, U., MILLER, M.J., Eur. J. Med. Chem., **45**, no. 5, 2010, p. 1703
7. WHITE, R.L., WESSELS, F.L., SCHWAN, T.J., ELLIS, K.O., J. Med. Chem., **30**, no. 2, 1987, p. 263
8. GRADILLAS, A., LÓPEZ, B., BRA A, SANCHO, I., PÉREZ-GARCÍA, C., ALGUACIL, L.F., Arzneim.-Forsch./Drug Res., 55, no. 12, 2005, p. 725
9. ZHANG, F., CHAPMAN, K.T., SCHLEIF, W.A., OLSEN, D.B., STAHLHUT, M., RUTKOWSKI, C.A., KUO, L.C., JIN, L., LIN, J.H., EMINI, E.A., TATA, J.R., Bioorg. Med. Chem. Lett., **13**, no. 15, 2003, p. 2573
10. PALMER, D.C., VENKATRAMAN, S., "The Chemistry of Heterocyclic Compounds, Oxazoles: Synthesis, Reactions, and Spectroscopy", Vol. **60**, Part A, Palmer, D. C. Eds., Wiley, New York, 2004, p. 255
11. D'AMBROSIO, M., GUERRIERO, A., DEBITUS, C., PIETRA, F., Helv. Chim. Acta, **79**, no. 1, 1996, p. 51
12. SASSE, F., STEINMETZ, H., SCHUPP, T., PETERSEN, F., MEMMERT, K., HOFMANN, H., HEUSSER, C., BRINKMANN, V., VON MATT, P., HÖFLE, G., REICHENBACH, H., J. Antibiot. (Tokyo), **55**, no. 6, 2002, p. 543
13. (a) NAKAMURA, Y., OKUMURA, K., KOJIMA, M., TAKEUCHI, S., Tetrahedron Lett., **47**, no. 2, 2006, p. 239. (b) SCHLESSINGER, R.H., LI, Y.J., J. Am. Chem. Soc., **118**, no. 13, 1996, p. 3301
14. ICHIBA, T., YOSHIDA, W.Y., SCHEUER, P.J., HIGA, T., GRAVALOS, D.G., J. Am. Chem. Soc., **113**, no. 8, 1991, p. 3173
15. GIDDENS, A.G., BOSHOFF, I.M., FRANZBLAU, S.G., BARRY, III, C.E., COPP, B.R., Tetrahedron Lett., **46**, no. 43, 2005, p. 7355

16. MINHAS, G.S., PILCH, D.S., KERRIGAN, J.E., LA VOIE, E.J., RICE, J.E., Bioorg. Med. Chem. Lett., **16**, no. 15, 2006, p. 3891
17. SMITH, R.A., BARBOSA, J., BLUM, C.L., BOBKO, M.A., CARINGAL, Y.V., DALLY, R., JOHNSON, J.S., KATZ, M.E., KENNURE, N., KINGERY-WOOD, J., LEE, W., LOWINGER, T.B., LYONS, J., MARSH, V., ROGERS, D.H., SWARTZ, S., WALLING, T., WILD, H., Bioorg. Med. Chem. Lett., **11**, no. 20, 2001, p. 2775
18. (a) BIRON, E., CHATTERJEE, J., KESSLER, H., Org. Lett., **8**, no. 11, 2006, p. 2417. (b) FALORNI, M., GIACOMELLI, G., PORCHEDDU, A., DETTORI, G., Eur. J. Org. Chem., **2000**, no. 18, 2000, p. 3217
19. (a) ESEOLA, A.O., LI, W., SUN, W.-H., ZHANG, M., XIAO, L., WOODS, J.A.O., Dyes and Pigments, **88**, no. 3, 2011, p. 262. (b) LUKAVENKO, O.N., ELTSOV, S.V., GRIGOROVICH, A.V., MCHEDLOV-PETROSSYAN, N.O., J. Mol. Liq., **145**, no. 3, 2009, p. 167. (c) IONESCU, S., POPOVICI, D., BALABAN, A.T., HILLEBRAND, M., Spectrochim. Acta A, **66**, no. 4-5, 2007, p. 1165
20. SANDHAR, R.K., SHARMA, J.R., MANRAO, M.R., Indian J. Heterocycl. Chem., **13**, 2003, p. 119
21. (a) SUNEL, V., BASU, C., An. St. Univ. "Al. I. Cuza" Iasi, Chimie, **7**, 1999, p. 111. (b) SUNEL, V., CIOVICA, S., ASANDEI, N., SOLDEA, C., Cellulose Chem. Tech., **29**, 1995, p. 11. (c) BUDEANU, C., IVAS, E., SUNEL, V., Rev. Chim.(Bucharest), **32**, no. 5, 1981, p. 454
22. DÜNDAR, Y., ÜNLÜ, S., BANO LU, E., ENTRENA, A., COSTANTINO, G., NUNEZ, M.-T., LEDO, F., ŢAHIN, M.F., NOYANALPAN, N., Eur. J. Med. Chem., **44**, no. 5, 2009, p. 1830
23. (a) ALMAJAN, G.L., BARBUCEANU, S.-F., SARAMET, I., DRAGHICI, C., Eur. J. Med. Chem., **45**, no. 7, 2010, p. 3191. (b) BARBUCEANU, S.-F., BANCESCU, G., CRETU, O.D., DRAGHICI, C., BANCESCU, A., NEAGU, A., RADU-POPESCU, M., ALMAJAN, G.L., Rev. Chim. (Bucharest), **61**, no. 11, 2010, p. 1017. (c) CHO, S.C., RHIM, J.H., SON, Y.H., LEE, S.J., PARK, S.C., Exp. Mol. Med., **42**, 2010, p. 223. (d) BARBUCEANU, S.-F., ALMAJAN, G.L., SARAMET, I., DRAGHICI, C., TARCOMNICU, A.I., BANCESCU, G., Eur. J. Med. Chem., **44**, nr. 11, 2009, p. 4752. (e) ALMAJAN, G.L., SARAMET, I., BARBUCEANU, S.-F., DRAGHICI, C., BANCESCU, G., Rev. Chim. (Bucharest), **60**, no. 9, 2009, p. 896. (f) WOLF, R., MATZ, H., ORION, E., TUZUN, Y., Dermatol. Online J., **8**, 2002, p. 2
24. APOSTOL, T.-V., DRAGHICI, C., DINU, M., BARBUCEANU, S.-F., SOCEA, L.I., SARAMET, I., Rev. Chim. (Bucharest), **62**, no. 2, 2011, p. 142
25. STEIGER, R.E., J. Org. Chem., **9**, no. 5, 1944, p. 396
26. SCHIKETANZ, I., DRAGHICI, C., SARAMET, I., BALABAN, A.T., Rev. Roum. Chim., **47**, no. 3-4, 2002, p. 235
27. SCHIKETANZ, I., DRAGHICI, C., SARAMET, I., BALABAN, A.T., Arkivoc, **ii**, 2002, p. 64
28. SCHIKETANZ, I., ISTRATI, D., DRAGHICI, C., BALABAN, A.T., Rev. Roum. Chim., **44**, no. 2, 1999, p. 137
29. CHEN, F.M.F., SLEBIODA, M., BENITOIN, N.L., Int. J. Pept. Protein Res., **31**, 1988, p. 339
30. (a) CONWAY, P.A., DEVINE, K., PARADISI, F., Tetrahedron, **65**, no. 15, 2009, p. 2935. (b) SUNEL, V., POPA, M., DESBRIČRES, J., PROFIRE, L., PINTILIE, O., LIONTE, C., Molecules, **13**, no. 1, 2008, p. 177. (c) PINTILIE, O., MOISE, M., PROFIRE, L., SUNEL, V., Farmacia, **54**, no. 5, 2006, p. 61
31. BALABAN, A.T., BALLY, I., FRANGOPOL, P.T., BACESCU, M., CIORANESCU, E., BIRLADEANU, L., Tetrahedron, **19**, no. 1, 1963, p. 169
32. POPOVICI, D., MAIOR, O., SCHIKETANZ, A., ANDREI, M., BALABAN A.T., An. Univ. Bucuresti Chim., **2**, 1993, p. 91
33. BALABAN, M.-C., SCHIKETANZ, I., BALABAN, A.T., SCHIKETANZ, A., GHEORGHIU, M.D., Rev. Roum. Chim., **32**, no. 9-10, 1987, p. 975
34. FRANGOPOL, P.T., BALABAN, A.T., BIRLADEANU, L., CIORANESCU, E., Tetrahedron, **16**, no. 1-4, 1961, p. 59
35. (a) OSORIO-OLIVARES, M., REZENDE, M.C., SEPÚLVEDA-BOZA, S., CASSELS, B.K., BAGGIO, R.F., MU OZ-ACEVEDO, J.C., Tetrahedron: Asym., **14**, no. 11, 2003, p. 1473. (b) DI GIOIA, M.L., LEGGIO, A., LIGUORI, A., NAPOLI, A., SICILIANO, C., SINDONA, G., J. Org. Chem., **66**, no. 21, 2001, p. 7002. (c) NORDLANDER, J.E., NJOROGE, F.G., PAYNE, M.J., WARMAN, D., J. Org. Chem., **50**, no. 23, 1985, p. 3481. (d) ZINNER, H., BROSSMANN, G., J. Prakt. Chem. [4], **5**, 1957, p. 91
36. GODFREY, A.G., BROOKS, D.A., HAY, L.A., PETERS, M., MCCARTHY, J.R., MITCHELL, S., J. Org. Chem., **68**, no. 7, 2003, p. 2623
37. (a) TANDEL, R.C., MAMMEN, D., Indian J. Chem., **47B**, no. 6, 2008, p. 932. (b) FIESER, F., FIESER, M., "Reagents for Organic Synthesis", Vol. **1**, Wiley, New York, 1967, p. 286
38. MAVRODIN, A., ZOTTA, V., STROENESCU, V.M., OTELEANU, D., Pharm. Zentr. Dtschl., **95**, no. 9, 1956, p. 353
39. SUNEL, V., DOROHOI, D.-O., MOISE, M., STROIA, L., J. Mol. Liquids, **154,** no. 1, 2010, p. 58
40. HEGELUND, F., LARSEN, R.W., PALMER, M.H., J. Mol. Spectrosc., **241**, no. 1, 2007, p. 26
41. WEITMAN, M., LERMAN, L., COHEN, S., NUDELMAN, A., MAJOR, D.T., GOTTLIEB, H.E., Tetrahedron, **66**, no. 7, 2010, p. 1465

Manuscript received: 27.01.2011