Simin Vazirimehr, Abolghasem Davoodnia*, Mahboobeh Nakhaei-Moghaddam and Niloofar Tavakoli-Hoseini

Ultrasonic synthesis, characterization, and antibacterial evaluation of novel heterocycles containing hexahydroquinoline and pyrrole moieties

DOI 10.1515/hc-2016-0164
Received October 12, 2016; accepted December 28, 2016

Abstract: Condensation reaction of dimedone with 2-amino-1-methyl-4,5-diphenyl-1*H*-pyrrole-3-carbonitrile in ethanol containing a catalytic amount of *p*-toluenesulfonic acid (TsOH) afforded 2-(5,5-dimethyl-3-oxocyclohex-1-enylamino)-1-methyl-4,5-diphenyl-1*H*-pyrrole-3-carbonitrile. This compound was then treated with olefins, formed by Knoevenagel condensation of aryl aldehydes and malononitrile, in ethanol in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as catalyst to give novel cyclic compounds in high yields. A new hexacyclic heterocyclic compound was formed when 2-hydroxybenzaldehyde was used as the aldehyde. The reactions were done using ultrasonic irradiation. The synthesized compounds were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectra, elemental analysis and evaluated for their antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus* and *Micrococcus luteus*) and Gram-negative bacterium (*Escherichia coli*).

Keywords: antibacterial; hexahydroquinoline; pyrrole; ultrasonic irradiation.

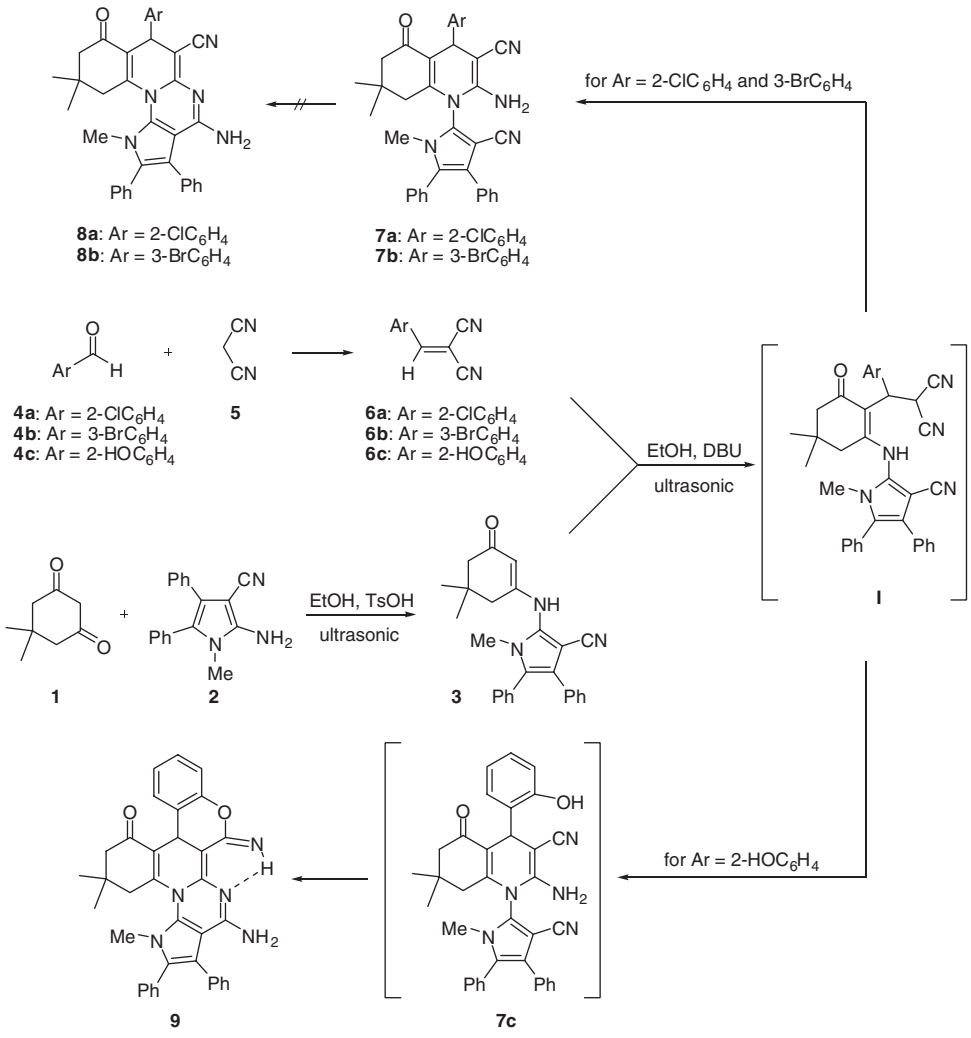
***Corresponding author: Abolghasem Davoodnia,** Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran, e-mail: adavoodnia@mshdiau.ac.ir; adavoodnia@yahoo.com
Simin Vazirimehr: Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran
Mahboobeh Nakhaei-Moghaddam: Department of Biology, Mashhad Branch, Islamic Azad University, Mashhad, Iran
Niloofar Tavakoli-Hoseini: Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran; and Department of Biochemistry and Clinical Laboratories, Tabriz University of Medical Sciences, Tabriz, Iran

Introduction

The 1,4-dihydropyridine (1,4-DHP) core is present in a range of compounds exhibiting a broad spectrum of biological activities [1, 2] including antimicrobial [3], antitubercular [4], insecticidal [5], and neuroprotectant [6] properties. In particular, 4-aryl-1,4-DHPs are well known as calcium channel blockers and have emerged as one of the most important class of drugs for the treatment of cardiovascular diseases [7, 8]. On the other hand, the pyrrole moiety has emerged as a privileged scaffold in drug design and discovery [9] and generated great attention because of various important biological properties such as anticancer [10–12], antiviral [12], antitubercular [13], antibacterial [14], analgesic [15], anti-inflammatory [15, 16], and antifungal [17] activities. They have also been widely employed as selective aldose reductase [18], CHK1 [19], JAK2 [20], and COX-2 [21] inhibitors. Because of the importance of these heterocycles we became interested in the synthesis of some novel heterocyclic compounds containing both hexahydroquinoline and pyrrole scaffolds.

Ultrasonic irradiation has increasingly been used as a very significant nontraditional technique for accelerating organic reactions [22, 23]. Compared with traditional methods, the salient features and benefits of ultrasonic irradiation technique includes reduced reaction times, reduced energy consumption, enhanced selectivity, and improved yields [24, 25]. Often, the reactions under ultrasound irradiation are commonly easier to work up than those in conventional methods [26–28].

Inspired by these facts and due to our interest in the synthesis of heterocyclic compounds with potential biological activities [29–38], we report here a convenient ultrasonic assisted synthesis of new compounds containing hexahydroquinoline and pyrrole moieties (Scheme 1). Antibacterial assay of the synthesized compounds was also conducted against two strains of Gram positive bacteria, *Staphylococcus aureus* (*S. aureus*, PTCC 1112) and *Micrococcus luteus* (*M. luteus*, PTCC 1110), and one strain



Scheme 1

of Gram negative bacterium, *Escherichia coli* (*E. coli*, PTCC 1330) by agar dilution method using 24-well microtiter plates. Gentamicin and chloramphenicol (100 μg/mL) were used as positive controls.

Results and discussion

Condensation of dimedone (**1**) with 2-amino-1-methyl-4,5-diphenyl-1*H*-pyrrole-3-carbonitrile (**2**) [39] in ethanol in the presence of *p*-toluenesulfonic acid (TsOH) as catalyst under ultrasonic irradiation at 60°C afforded 2-(5,5-dimethyl-3-oxocyclohex-1-enylamino)-1-methyl-4,5-diphenyl-1*H*-pyrrole-3-carbonitrile (**3**) in high yield (92%) after short reaction time (20 min) as the sole product. Only a trace amount of compound **3** was formed in the absence of TsOH. For comparison, a traditional method for the preparation of this compound was also investigated by refluxing **1** with **2** in the presence of TsOH in ethanol. The results showed that the classical approach for the synthesis of compound **3** is a tedious method affording a relatively lower yield (78%) of **3** after a much longer reaction time (120 min).

Compound **3** was allowed to react with olefins **6a** and **6b**, that had been obtained by Knoevenagel condensation of aromatic aldehydes **4a** and **4b** with malononitrile **5** [40, 41], in the presence of a basic catalyst under ultrasonic irradiation at 60°C. Under these conditions, nucleophilic conjugate addition followed by cyclization reaction occurred with the involvement of the presumed intermediate product **I**, giving the final new 1,4,5,6,7,8-hexahydroquinolines **7a** and **7b** in high yields and short reaction times. Without a catalyst, the yields were low even after a long time. Several bases including DBU, DMAP, morpholine, piperidine and Et_3N were tested as catalysts. The

reaction was also conducted in various solvents including EtOH, MeOH, H_2O, CH_3CN and $CHCl_3$. It was found that the reaction was more facile and proceeded with the highest yields with DBU in EtOH. Furthermore, to draw a comparison between ultrasonic irradiation and conventional heating for the preparation of the products **7a** and **7b**, a mixture of **3** and **6a** or **6b** in ethanol was heated under reflux. It was shown that the ultrasonic irradiation approach for the synthesis of compounds **7a** and **7b** is faster and the yields are higher than those using the conventional heating method. It should be mentioned that two cyano absorption bands in the IR spectra of the products are seen, which rules out the formation of the alternative cyclized isomers **8a** and **8b**.

Surprisingly, the reaction of compound **3** with the olefin **6c**, conducted under similar conditions, using DBU in EtOH under ultrasonic irradiation, gave the new hexacyclic heterocyclic compound **9**. This result can be explained in terms of nucleophilic attacks of the hydroxy and amino groups at the cyano moieties in the presumed intermediate product **7c**. As expected, the IR spectrum of **9** is devoid of the CN absorption bands. Structures of products **3**, **7a**, **7b** and **9** were established from their spectral and microanalytical data. For example, the ^{1}H NMR spectrum of **7a** in DMSO-d_6 shows two singlets at δ 0.95 and 1.02 for methyl groups, two doublets at δ 1.94 and 2.09 and two overlapping doublets at δ 2.27 for diastereotopic protons in two methylene groups. The IR spectrum of **7a** shows NH_2 absorption bands at 3456 and 3317 cm^{-1} and a strong band at 1662 cm^{-1} for C=O, in addition to two sharp bands at 2223 and 2188 cm^{-1} for two CN groups. The ^{13}C NMR spectrum of **7a** is also fully consistent with the assigned structure. Finally, this compound gave satisfactory results of elemental analysis corresponding to the molecular formula $C_{36}H_{30}ClN_5O$.

As shown in the expanded views of ^{1}H NMR spectra of compounds **7a, 7b** and **9** (Figure 1), the methine group in compounds **7a** and **7b** appears as singlet, as expected. By contrast, the signals for the methine and NH groups in the ^{1}H NMR spectrum of compound **9** are two doublets at δ 4.67 and 5.06 with the coupling constant $J = 3.6$ Hz. Long-range couplings across five bonds are rare, but can be observed under favorable circumstances in rigid conformations.

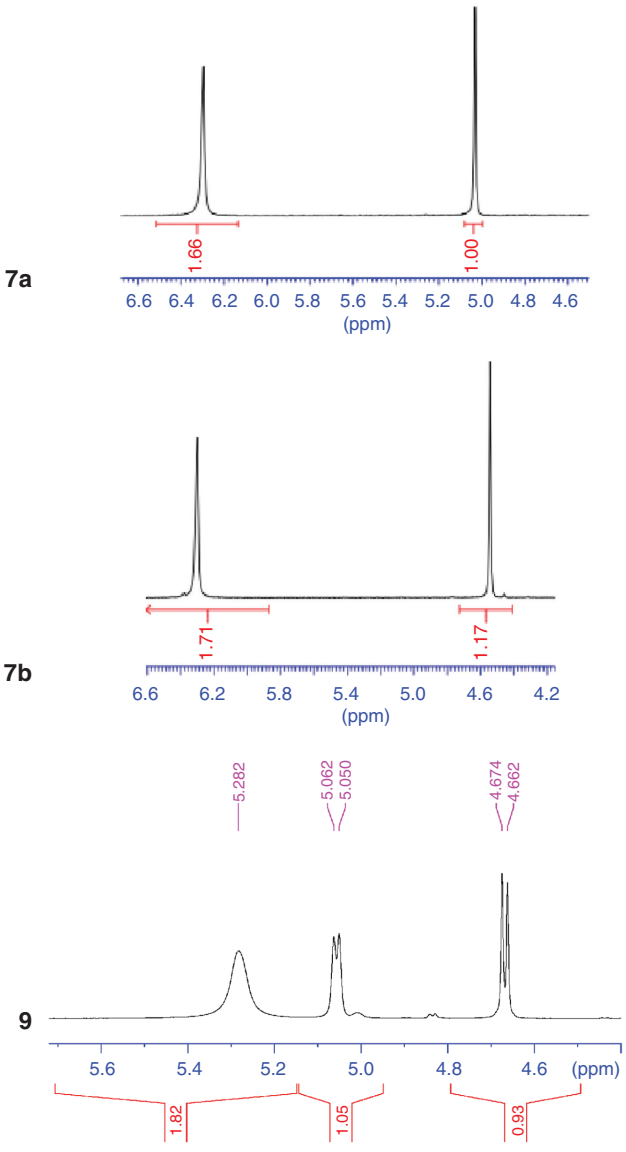


Figure 1 Expanded views of ^{1}H NMR spectra of compounds **7a**, **7b** and **9** in the methine group region.

Antibacterial activity

The synthesized compounds **3**, **7a**, **7b** and **9** were screened for the antibacterial activity against reference strains of *S. aureus*, *M. luteus* and *E. coli* bacteria. All compounds inhibit the growth of tested bacteria at the concentration of 6 mg/mL. The growth of *S. aureus* and *E. coli* is observed at the concentrations of 4 mg/mL and 5 mg/mL, respectively, for all compounds. Growth inhibition of bacteria is observed in the presence of the antibiotics gentamicin and chloramphenicol at a concentration of 100 μg/mL. Thus, the antibacterial activity of these compounds against tested bacteria is less than those of gentamicin and chloramphenicol.

Conclusion

Synthesis of new heterocyclic compounds **3**, **7a**, **7b** and **9** under ultrasonic irradiation and using a conventional

heating method was reported. Their growth-inhibiting effects on *S. aureus*, *M. luteus* and *E. coli* bacteria were assayed.

Experimental

Ultrasonication was performed using a Soltec sonicator at a frequency of 40 kHz and a nominal power of 260 W. IR spectra were obtained in KBr pellets using a Tensor 27 Bruker spectrophotometer. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker 300 FT spectrometer, using TMS as internal standard. Elemental analyses were performed on a Thermo Finnigan Flash EA microanalyzer. Melting points were recorded on a Stuart SMP3 melting point apparatus and are not corrected.

Synthesis of 2-(5,5-dimethyl-3-oxocyclohex-1-enylamino)-1-methyl-4,5-diphenyl-1*H*-pyrrole-3-carbonitrile (3)

Method A (ultrasonic irradiation) A mixture of dimedone **1** (0.140 g, 1 mmol), 2-amino-1-methyl-4,5-diphenyl-1*H*-pyrrole-3-carbonitrile **2** (0.273 g, 1 mmol), and TsOH (0.034 g, 0.2 mmol, 20 mol% based on dimedone) in ethanol (5 mL) was sonicated at 60°C for 20 min. The reaction was monitored using TLC plates eluting with *n*-hexane/ethyl acetate (volume ratio, 3:1). After completion of the reaction, the solvent was removed under reduced pressure. The residue was washed with cold water (2×5 mL), cold 96% ethanol (5 mL) and crystallized from ethanol/water to give the pure product **3** in 92% yield.

Method B (conventional heating) A mixture prepared as described above was heated under reflux for 120 min. Workup and purification conducted as described above gave product **3** in 78% yield.

General procedure for the synthesis of compounds 7a, 7b and 9

Method A (ultrasonic irradiation) A mixture of the olefin **6a–c** (1 mmol), 2-(5,5-dimethyl-3-oxocyclohex-1-enylamino)-1-methyl-4,5-diphenyl-1*H*-pyrrole-3-carbonitrile **3** (0.395 g, 1 mmol), and DBU (0.015 g, 0.1 mmol, 10 mol% based on dimedone) in ethanol (5 mL) was sonicated at 60°C for 10–15 min. The reaction was monitored and the product was isolated as described above: **7a**, yield 91%; **7b**, yield 92%; **9**, yield 90%.

Method B (conventional heating) The mixture prepared as described above was heated under reflux for 100–120 min. Workup and isolation of the product was conducted as described above: **7a**, yield 79%; **7b**, yield 77%; **9**, yield 76%.

2-(5,5-Dimethyl-3-oxocyclohex-1-enylamino)-1-methyl-4,5-diphenyl-1*H*-pyrrole-3-carbonitrile (3) Creamy crystals; mp 222–224°C; IR: ν 3196 (NH), 2221 (C≡N), 1635 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 6H, $2CH_3$), 2.18 (s, 2H, CH_2), 2.38 (s, 2H, CH_2), 3.24 (s, 3H, NCH_3), 5.06 (s, 1H, =CH), 6.93 (s br., 1H, NH), 7.08–7.32 (m, 10H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ 28.2, 31.6, 33.2, 41.8, 50.4, 89.2, 100.6, 115.8, 123.3, 126.9, 128.4, 128.7, 128.8, 128.9, 130.1, 130.2, 130.9, 132.4, 134.1, 163.4, 198.5. Anal. Calcd for $C_{26}H_{25}N_3O$: C, 78.96; H, 6.37; N, 10.62. Found: C, 78.81; H, 6.24; N, 10.81.

2-Amino-4-(2-chlorophenyl)-1-(3-cyano-1-methyl-4,5-diphenyl-1H-pyrrol-2-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (7a) White powder; mp 291–293°C; IR: ν = 3456 and 3317 (NH_2), 2223 and 2188 (two C≡N), 1662 cm^{-1} (C=O); ^{1}H NMR DMSO-d_6): δ 0.95 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.94 (d, 1H, J = 18.0 Hz, one proton of diastereotopic protons in CH_2), 2.09 (d, 1H, J = 15.0 Hz, one proton of diastereotopic protons in CH_2), 2.27 (d, two overlapping doublets, 2H, J = 15.0 Hz, two protons of diastereotopic protons in $2CH_2$), 3.33 (s, 3H, NCH_3), 5.03 (s, 1H, CH), 6.29 (s br., 2H, NH_2), 7.18–7.57 (m, 14H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ 27.4, 29.5, 32.4, 35.3, 40.3, 49.8, 66.3, 94.2, 113.5, 113.7, 119.1, 124.2, 126.9, 127.8, 128.3, 128.7, 128.8, 129.1, 129.2, 129.3, 129.6, 130.0, 130.5, 130.9, 131.1, 132.1, 133.2, 141.4, 149.0, 149.1, 195.1. Anal. Calcd for $C_{36}H_{30}ClN_5O$: C, 74.02; H, 5.18; N, 11.99. Found: C, 73.87; H, 5.35; N, 12.16.

2-Amino-4-(3-bromophenyl)-1-(3-cyano-1-methyl-4,5-diphenyl-1H-pyrrol-2-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (7b) White powder; mp 283–285°C; IR: ν 3446 and 3314 (NH_2), 2224 and 2189 (two C≡N), 1655 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6): δ 0.94 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.05 (d, 1H, J = 18.0 Hz, one proton of diastereotopic protons in CH_2), 2.15 (d, 1H, J = 15.0 Hz, one proton of diastereotopic protons in CH_2), 2.32 (t, two overlapping doublets, 2H, J = 15.0 Hz, two protons of diastereotopic protons in $2CH_2$), 3.33 (s, 3H, NCH_3), 4.54 (s, 1H, CH), 6.30 (s br., 2H, NH_2), 7.24–7.51 (m, 14H, H_{Ar}); ^{13}C NMR (DMSO-d_6): δ 27.1, 28.9, 31.9, 32.7, 36.9, 49.8, 60.8, 94.1, 113.0, 115.0, 121.0, 122.2, 123.4, 126.5, 127.7, 128.9, 129.2, 129.3, 129.5, 129.8, 130.0, 130.3, 131.3, 131.5, 131.8, 132.6, 148.9, 150.5, 150.9, 195.5. Anal. Calcd for $C_{36}H_{30}BrN_5O$: C, 68.79; H, 4.81; N, 11.14. Found: C, 68.96; H, 4.93; N, 11.01.

4-Amino-6-imino-1,14,14-trimethyl-2,3-diphenyl-1,6,11b,13,14,15-hexahydro-12H-chromeno[3,4-*c*]pyrrolo[3′,2′:5,6]pyrimido[1,2-*a*]quinolin-12-one (9) White powder; mp 270–272°C; IR: ν = 3429, 3309 and 3158 (NH_2 and NH), 1636 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 0.94 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.43 (s, 2H, CH_2), 2.65 (AB_q, 2H, $\Delta\nu$ = 39.9 Hz, J_{AB} = 17.4 Hz, CH_2), 3.70 (s, 3H, NCH_3), 4.67 (d, 1H, J = 3.6 Hz, CH), 5.06 (d, 1H, J = 3.6 Hz, =NH), 5.28 (s br., 2H, NH_2), 6.51 (d, 1H, J = 7.2 Hz, H_{Ar}), 6.88 (t, 1H, J = 7.2 Hz, H_{Ar}), 7.11 (d, 1H, J = 7.8 Hz, H_{Ar}), 7.22 (t, 1H, J = 8.4 Hz, H_{Ar}), 7.27–7.40 (m, 10H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ 27.3, 30.0, 32.2, 35.5, 41.7, 48.1, 50.9, 100.2, 109.9, 113.5, 116.3, 116.7, 118.5, 119.9, 124.3, 126.9, 128.2, 128.4, 128.5, 128.6, 128.7, 129.7, 130.5, 130.8, 134.5, 135.4, 151.0, 151.3, 155.2, 156.8, 168.6, 197.3. Anal. Calcd for $C_{36}H_{31}N_5O_2$: C, 76.44; H, 5.52; N, 12.38. Found: C, 76.71; H, 5.30; N, 12.64.

Biological assays

Bacterial strains *S. aureus* (PTCC 1112) and *M. luteus* (PTCC 1110) as Gram-positive bacteria and *E. coli* (PTCC 1330) as Gram negative bacterium were obtained from the Iranian Research Organization for Science and Technology (IROST) in Iran. Antimicrobial assay was conducted by an agar dilution method in 24-well microtiter plates by

using a standard procedure. All tests were repeated three times with controls.

Acknowledgements: The authors express their gratitude to the Islamic Azad University, Mashhad Branch for its financial support.

References

[1] Carosati, E.; Ioan, P.; Micucci, M.; Broccatelli, F.; Cruciani, G.; Zhorov, B. S.; Chiarini, A.; Budriesi, R. 1,4-Dihydropyridine scaffold in medicinal chemistry, the story so far and perspectives (part 2): action in other targets and antitargets. *Curr. Med. Chem.* **2012**, *19*, 4306–4323.

[2] Vo, D.; Matowe, W. C.; Ramesh, M.; Iqbal, N.; Wolowyk, M. W.; Howlett, S. E.; Knaus, E. E. Syntheses, calcium channel agonist-antagonist modulation activities, and voltage-clamp studies of isopropyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-pyridinylpyridine-5-carboxylate racemates and enantiomers. *J. Med. Chem.* **1995**, *38*, 2851–2859.

[3] Murthy, Y. L. N.; Rajack, A.; Taraka Ramji, M.; Jeson Babu, J.; Praveen, C.; Aruna Lakshmi, K. Design, solvent free synthesis, and antimicrobial evaluation of 1,4 dihydropyridines. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6016–6023.

[4] Trivedi, A.; Dodiya, D.; Dholariya, B.; Kataria, V.; Bhuva, V.; Shah, V. Synthesis and biological evaluation of some novel 1,4-dihydropyridines as potential antitubercular agents. *Chem. Biol. Drug Des.* **2011**, *78*, 881–886.

[5] Sun, C.; Chen, Y.; Liu, T.; Wu, Y.; Fang, T.; Wang, J.; Xing, J. *cis*-Nitenpyram analogues containing 1,4-dihydropyridine: synthesis, insecticidal activities, and molecular docking studies. *Chin. J. Chem.* **2012**, *30*, 1415–1422.

[6] Klusa, V. Cerebrocrast. Neuroprotectant, cognition enhancer. *Drugs Fut.* **1995**, *20*, 135–138.

[7] Miyashita, K.; Nishimoto, M.; Ishino, T.; Obika, S.; Imanishi, T. Novel and chiral Hantzsch-type 1,4-dihydropyridines having a *p*-tolylsulfinyl group. Synthesis and biological activities as calcium channel antagonists. *Chem. Pharm. Bull.* **1995**, *43*, 711–713.

[8] Bossert, F.; Meyer, H.; Wehinger, E. 4-Aryldihydropyridines, a new class of highly active calcium antagonists. *Angew. Chem. Int. Ed.* **1981**, *20*, 762–769.

[9] Biava, M.; Porretta, G. C.; Poce, G.; Battilocchio, C.; Alfonso, S.; De Logu, A.; Serra, N.; Manetti, F.; Botta, M. Identification of a novel pyrrole derivative endowed with antimycobacterial activity and protection index comparable to that of the current antitubercular drugs streptomycin and rifampin. *Bioorg. Med. Chem.* **2010**, *18*, 8076–8084.

[10] Boichuk, S.; Galembikova, A.; Zykova, S.; Ramazanov, B.; Khusnutdinov, R.; Dunaev, P.; Khaibullina, S.; Lombardi, V. Ethyl-2-amino-pyrrole-3-carboxylates are novel potent anti-cancer agents that affect tubulin polymerization, induce G2/M cell-cycle arrest, and effectively inhibit soft tissue cancer cell growth in vitro. *Anti-Cancer Drugs* **2016**, *27*, 620–634.

[11] Chen, J.; Zhang, Y.; Zhan, X.; Liu, Z.; Mao, Z. Synthesis and anti-tumor activity of novel 3-substitutedbenzoyl-4-substituted-thienyl-pyrroles. *Chin. J. Org. Chem.* **2016**, *36*, 572–579.

[12] Pegklidou, K.; Papastavrou, N.; Gkizis, P.; Komiotis, D.; Balzarini, J.; Nicolaou, I. N-substituted pyrrole-based scaffolds as potential anticancer and antiviral lead structures. *Med. Chem.* **2015**, *11*, 602–608.

[13] Saha, R.; Alam, Md. M.; Akhter, M. Novel hybrid-pyrrole derivatives: their synthesis, antitubercular evaluation and docking studies. *RSC Adv.* **2015**, *5*, 12807–12820.

[14] Lattmann, E.; Dunn, S.; Niamsanit, S.; Sattayasai, J.; Sattayasai, N. Antibacterial activity of 3-substituted pyrrole-2,5-diones against *Pseudomonas aeruginosa*. *Lett. Drug Des. Discovery* **2007**, *4*, 513–519.

[15] Battilocchio, C.; Poce, G.; Alfonso, S.; Porretta, G. C.; Consalvi, S.; Sautebin, L.; Pace, S.; Rossi, A.; Ghelardini, C.; Di Cesare Mannelli, L.; et al. A class of pyrrole derivatives endowed with analgesic/anti-inflammatory activity. *Bioorg. Med. Chem.* **2013**, *21*, 3695–3701.

[16] Mohamed, M. S.; Kamel, R.; Fathallah, S. S. Synthesis of new pyrroles of potential anti-inflammatory activity. *Arch. Pharm.* **2011**, *344*, 830–839.

[17] Jana, G. H.; Jain, S.; Arora, S. K.; Sinha, N. Synthesis of some diguanidino 1-methyl-2,5-diaryl-1H-pyrroles as antifungal agents. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3592–3595.

[18] Pegklidou, K.; Koukoulitsa, C.; Nicolaou, I.; Demopoulos, V. J. Design and synthesis of novel series of pyrrole based chemotypes and their evaluation as selective aldose reductase inhibitors. A case of bioisosterism between a carboxylic acid moiety and that of a tetrazole. *Bioorg. Med. Chem.* **2010**, *18*, 2107–2114.

[19] Eldebss, T. M. A.; Gomha, S. M.; Abdulla, M. M.; Arafa, R. K. Novel pyrrole derivatives as selective CHK1 inhibitors: design, regioselective synthesis and molecular modeling. *Med. Chem. Comm.* **2015**, *6*, 852–859.

[20] Brasca, M. G.; Nesi, M.; Avanzi, N.; Ballinari, D.; Bandiera, T.; Bertrand, J.; Bindi, S.; Canevari, G.; Carenzi, D.; Casero, D.; et al. Pyrrole-3-carboxamides as potent and selective JAK2 inhibitors. *Bioorg. Med. Chem.* **2014**, *22*, 4998–5012.

[21] Pham, V. C.; Shin, J. -S.;Choi, M. J.; Kim, T. W.; Lee, K.; Kim, K. J.; Huh, G.; Kim, J.; Choo, D. J.; Lee, K. -T.; et al. Biological evaluation and molecular docking study of 3-(4-sulfamoylphenyl)-4-phenyl-1H-pyrrole-2,5-dione as COX-2 inhibitor. *Bull. Korean Chem. Soc.* **2012**, *33*, 721–724.

[22] Ruiz, E.; Rodríguez, H.; Coro, J.; Salfrán, E.; Suárez, M.; Martínez-Alvarez, R.; Martín, N. Ultrasound-assisted one-pot, four component synthesis of 4-aryl 3,4-dihydropyridone derivatives. *Ultrason. Sonochem.* **2011**, *18*, 32–36.

[23] Zhang, S. M.; Li, H.; Zheng, X. C.; Li, B. Q.; Wu, S. H.; Huang, W. P.; Liu, Z. G.; Feng, Y. Application of ultrasound in organic reaction. *Chin. J. Org. Chem.* **2002**, *22*, 603–609.

[24] Cella, R.; Stefani, H. A. Ultrasound in heterocycles chemistry. *Tetrahedron* **2009**, *65*, 2619–2641.

[25] Cravotto, G.; Cintas, P. Power ultrasound in organic synthesis: moving cavitational chemistry from academia to innovative and large-scale applications. *Chem. Soc. Rev.* **2006**, *35*, 180–196.

[26] Mason, T. J.; Peters, D. Practical sonochemistry: power ultrasound uses and applications, 2nd ed.; Ellis Horwood: London, **2002**.

[27] Li, J. -T.; Bian, Y. -J.; Zang, H. -J.; Li, T. -S. Pinacol coupling of aromatic aldehydes and ketones using magnesium in aqueous ammonium chloride under ultrasound. *Synth. Commun.* **2002**, *32*, 547–551.

[28] Zang, H.; Wang, M.; Cheng, B. -W.; Song, J. Ultrasound-promoted synthesis of oximes catalyzed by a basic ionic liquid [bmim]OH. *Ultrason. Sonochem.* **2009**, *16*, 301–303.
[29] Davoodnia, A.; Bakavoli, M.; Pooryaghoobi, N.; Roshani, M. A convenient approach for the synthesis of new substituted isoxazolo[5,4-d] pyrimidin-4(5H)-ones. *Heterocycl. Commun.* **2007**, *13*, 323–325.
[30] Davoodnia, A.; Bakavoli, M.; Mohseni, S.; Tavakoli-Hoseini, N. Synthesis of pyrido[3′,2′:4,5]thieno[2,3-e][1,2,4]triazolo[4,3-a] pyrimidin-5(4H)-one derivatives. *Monatsh. Chem.* **2008**, *139*, 963–965.
[31] Davoodnia, A.; Rahimizadeh, M.; Atapour-Mashhad, H.; Tavakoli-Hoseini, N. Investigation into the Reaction of 2-Amino-4,5-dimethylthiophene-3-carboxamide with Iso(and Isothio) cyanates under Microwave Irradiation. *Heteroat. Chem.* **2009**, *20*, 346–349.
[32] Davoodnia, A.; Bakavoli, M.; Soleimany, M.; Tavakoli-Hoseini, N. New route to 2-arylthieno[2,3-d]pyrimidin-4(3H)-ones and isolation of the unoxidized intermediates. *Monatsh. Chem.* **2009**, *140*, 355–358.
[33] Davoodnia, A.; Bakavoli, M.; Moloudi, R.; Khashi, M.; Tavakoli-Hoseini, N. 7-Deazapurines: synthesis of new pyrrolo[2,3-d]pyrimidin-4-ones catalyzed by a Brønsted-acidic ionic liquid as a green and reusable catalyst. *Chin. Chem. Lett.* **2010**, *21*, 1–4.
[34] Davoodnia, A.; Khashi, M.; Tavakoli-Hoseini, N.; Moloudi, R.; Zamani, H. A. 7-Deazaadenines: synthesis of some new pyrrolo[2,3-d]pyrimidin-4-amines. *Monatsh. Chem.* **2013**, *144*, 677–680.
[35] Davoodnia, A.; Bakavoli, M.; Moloudi, R.; Tavakoli-Hoseini, N.; Khashi, M. Highly efficient, one-pot, solvent-free synthesis of 2,4,6-triarylpyridines using a Brønsted-acidic ionic liquid as reusable catalyst. *Monatsh. Chem.* **2010**, *141*, 867–870.
[36] Khashi, M.; Davoodnia, A.; Chamani, J. DMAP-catalyzed synthesis of novel pyrrolo[2,3-d]pyrimidine derivatives bearing an aromatic sulfonamide moiety. *Phosphorus Sulfur Silicon Relat. Elem.* **2014**, *189*, 839–848.
[37] Gholipour, S.; Davoodnia, A.; Nakhaei-Moghaddam, M. Synthesis, characterization, and antibacterial evaluation of new alkyl 2-amino-4-aryl-4*H*-chromene-3-carboxylates. *Chem. Heterocycl. Compd.* **2015**, *51*, 808–813.
[38] Khashi, M.; Davoodnia, A.; Prasada Rao Lingam, V. S. DMAP catalyzed synthesis of some new pyrrolo[3,2-e][1,2,4]triazolo[1,5-c] pyrimidines. *Res. Chem. Intermed.* **2015**, *41*, 5731–5742.
[39] Roth, H. J.; Eger, K. Synthese von 2-amino-3-cyano-pyrrolen. *Arch. Pharm.* **1975**, *308*, 179–185.
[40] Khan, F. A.; Dash, J.; Satapathy, R.; Upadhyay, S. K. Hydrotalcite catalysis in ionic liquid medium: a recyclable reaction system for heterogeneous Knoevenagel and nitroaldol condensation. *Tetrahedron Lett.* **2004**, *45*, 3055–3058.
[41] Tavakoli-Hoseini, N.; Heravi, M. M.; Bamoharram, F. F. Knoevenagel Condensation Reaction Using Brønsted Acidic Ionic Liquids as Green and Reusable Catalysts. *Asian J. Chem.* **2010**, *22*, 7208–7212.