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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Further derivatives of 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid and their antibacterial activities

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Abstract Compound **4**, **5**, **6**, **7,** and **8** were synthesized from 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid **1** as a starting material. The pyrazolo[4,3-*d*]oxazinone **4** was obtained from direct reaction of the acid **1** with hydroxylamine hydrochloride. Acid chloride **2** was converted easily into the new derivatives consisting of 1-(4-benzoyl-1,5-diphenyl-1*H*-pyrazol-3-oyl)-sulfamide **5** and 3,4-dibenzoyl-1,5-diphenyl-1*H*-pyrazole **6**. The nitrile derivative 7 was obtained by dehydration of the amide **3** in a mixture of $SOCl_2$ and Dimethylformamide (DMF). Cyclocondensation reaction of 7 with anhydrous hydrazine led to the formation of 7-aminopyrazolo[3,4-*d*]pyridazine **8** derivative. These new synthesized compounds evaluated for their antibacterial activities against Gram-positive and Gram-negative bacteria using the tube dilution method. The finding of antibacterial activity study showed that the sulfamide derivative **5** was the best compound of the series, exhibiting antibacterial activity against both Gram-positive and Gram-negative bacteria.

Introduction

Natural antibiotic compounds have become indispensable to the current health care system, assisting and complementing the natural immune system against microbial pathogens. However, because conventional antibiotics are often abused to treat microbial infections, some microorganisms have developed tolerance to these antibiotics. Because of the appearance of antibiotics-resistant strains, the continuous development of novel efficient antibiotic agents is more crucial than ever (Berber *et al*., 2003; Mitscher *et al*., 1999; Sung *et al*., 2007). So the medical community faces a serious problem against infections caused by pathogen bacteria and needs an

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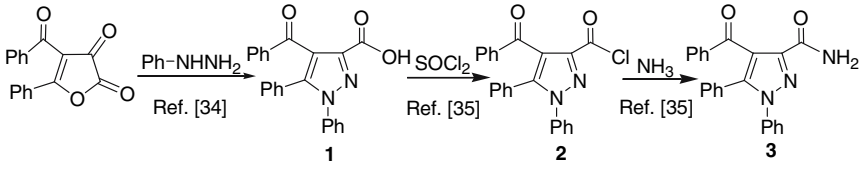
effective therapy and search for novel antibacterial agents (Lee and Hecker, 1999). It has been reported that some pathogen bacteria are susceptible to sulfamide or sulfonamide derivatives (Pellerin *et al*., 1998; Peraira *et al*., 2003).

\On the other hand, pyrazole and fused pyrazole compounds possess numerous chemical, biological, medicinal, and agricultural applications because of their versatile biological activities appearing as antimicrobial (Akbas and Berber, 2005; Mahajan *et al*., 1991; Sridhar *et al*., 2004; Sivaprasad *et al*., 2006), antiviral (Baraldi *et al*., 1998; Janus *et al*., 1999), antitumor (Suzuki and Inoue, 1990; Hatheway *et al*., 1978; Katayama and Oshiyama, 1997; Manfredini *et al*., 1992), anti-inflammatory (Badawey and El-Ashmawey, 1998; Bruno *et al*., 1992; Manfredini *et al*., 1996; Tewari and Mishra, 2001), antihistaminic (Mishra *et al*., 1998), pesticidal (Londershausen, 1996), antifungal (Badiger and Bennur, 1996; Graneto and Phillips, 1992), and antipyretic (Wiley and Wiley, 1964) agents. Concerning the attempt to synthesize novel pyrazole and fused pyrazole derivatives from 4-benzoyl-5-phenyl-2,3-furandione **1** and various hydrazines or hydrazones, the synthesis of 4-benzoyl-1,5-substituted-1*H*-pyrazole-3-carboxylic acids and some of their derivatives have recently been reported (Şener *et al*., 2002; Şener and Bildirici, 2004; Şener *et al*., 2004a-c; Şener *et al*., 2007). A literature survey revealed that, so far, the following reactions of some of these 1,4,5-trisubstitute-pyrazol-3-carboxylic acids, particularly 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid **1**, obtained 4-benzoyl-5-phenyl-2,3-furandione have been partly investigated. In an attempt to help remedy this situation we decided both to extend our previous studies (Akçamur *et al*., 1986; Akçamur *et al*., 1997) on the further reactions of 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid **1** and to evaluate the antibacterial activities of the resulting compounds.

Results and discussion

Chemistry

Compounds **4**, **5**, **6**, **7**, and **8,** which been studied for their antibacterial activities, were mainly synthesized from pyrazole-3-carboxylic acid **1** together with acid chloride **2** and its amide **3** derivatives. Both pyrazole-3-carboxylic acid **1** and its derivatives **2** and **3** were synthesized via published procedures (Akçamur *et al*., 1986; Akçamur *et al*., 1997) (Scheme 1).

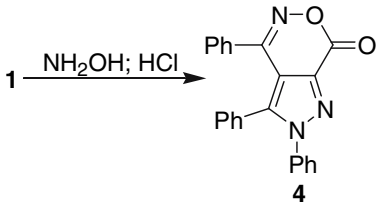


Scheme 1

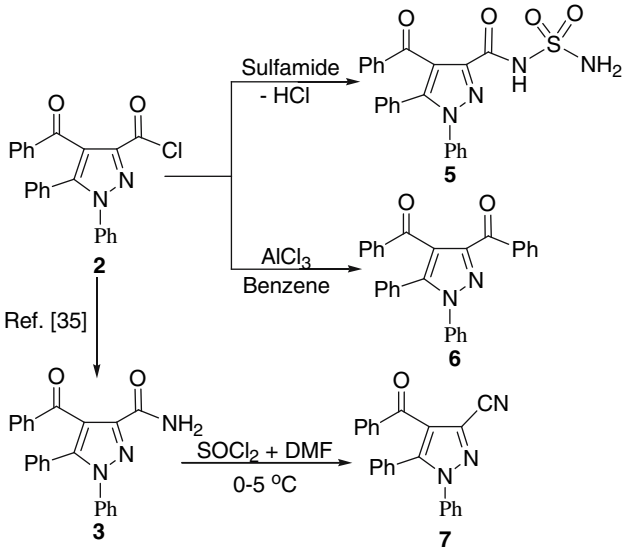
Direct reaction of the acid **1** with hydroxylamine hydrochloride, on an oil bath at approximately 150–155°C led to the formation of the pyrazolo[4,3-*d*]oxazinone **4** in about 55% yield (Scheme 2). The structure of **4** was proven based on elemental analysis and spectral data (see the Experimental section).

Acid chloride **2** was converted into new derivatives consisting of 1-(4-benzoyl-1,5-diphenyl-1*H*-pyrazol-3-oyl)-sulfamide **5** and 3,4-dibenzoyl-1,5-diphenyl-1*H*-pyrazole **6** via its reactions with sulfamide and benzene, containing a catalytic amount of $AlCl_3$, respectively. Furthermore, a cold solution of the acid amide **3** in a mixture of DMF and Thionylchloride ($SOCl_2$) was stirred at 0–5°C for 2 hours to give a nitrile **7** derivative (Scheme 3). The structures of the title compounds **5**, **6,** and **7** were confirmed by analytical, infrared (IR), ^{1}H nuclear magnetic resonance (NMR) and ^{13}C-NMR spectroscopic data. ^{13}C-NMR and IR absorptions of the nitrile group in **7** were found at 114.51 ppm and 2239 cm^{-1}, respectively (see the Experimental section).

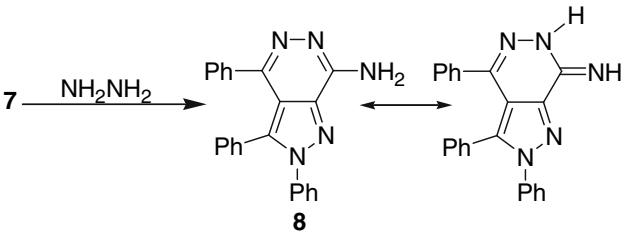
Pyrazole-3-carbonitrile **7** with anhydrous hydrazine in boiling *n*-butanol containing a catalytic amount metallic sodium was also cyclized to the 7-aminopyrazolo[3,4-*d*]pyridazine **8** derivative in approximately 40% yield



Scheme 2



Scheme 3



Scheme 4

(Scheme 4). Structure elucidation of **8** was mainly based on ^{13}C-NMR spectroscopy (see the Experimental section for details).

In vitro antibacterial activity

In the present study, the antibacterial activities of five different newly synthesized derivatives of 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid were evaluated against ten test microorganisms: the Gram-positive and Gram-negative bacteria shown in Table 1. The antimicrobial effects of new synthesized agents **4**, **5**, **6**, **7,** and **8** *(some part omitted)* were investigated by the microdilution method (Clause, 1989; Lee *et al*., 1999; Lee *et al*., 2003) and the minimum inhibitory concentration (MIC) was determined. In the current study, a bioassay with the commercial antibiotic chloroamphenicol as a standard was carried out for comparison. It is well known that chloroamphenicol is active against a wide range of Gram-positive and Gram-negative bacteria. Since chloroamphenicol is poorly soluble in water, esterifications of the primary alcohol at C-3 with palmitoyl chloride were carried out to produce the water-insoluble palmitate of chloroamphenicol (Mascaretti, 2003). The comparative activities of the new synthesized agents **4**, **5**, **6**, **7**, and **8** and the control antibiotic chloroamphenicol on the bacterial test strains are summarized in Table 1.

Compound **5** exhibited a strong inhibition effect against most of test bacteria except *Enterococcus facealis* and *Bacillus subtilus*, whereas compound **6** exhibited the weakest effect, showing an inhibition effect only against one of the test strains, namely, *Proteus vulgaris*. An important point is that most of compounds exerted inhibition effects at the 512 μg/mL concentration while the minimal inhibition concentration (MIC) of compound **5** was 32 μg/mL. Chloroamphenicol showed significant antibacterial activity against all the investigated bacteria strains with MIC values of 32–512 μg/mL. It may be suggested that compound **5** has a better inhibition effect than the other compounds. Interestingly, none of compounds showed inhibition effects against *Enterococcus facealis*. However, four out of the five compounds were active against *Escherichia coli*, while the growth of *Proteus vulgaris* was inhibited by all of compounds. Also, *Salmonella enteridis* was inhibited only by one compound, **5**. It may be concluded that compound **5** showed reasonably good inhibitory activity against the investigated bacterial strains. In

Table 1 The MICs of antibacterial activity of the newly synthesized pyrazole derivatives compounds

Bacterial strains	Newly synthesized compounds (μg/mL)*					
	4	5	6	7	8	Control**
Escherichia coli B3704	512	32	–	512	512	6
Pseudomonas aeruginosa ATCC 9027	–	32	–	–	32	24
Klebsiella pneumonia A137	–	32	–	–	–	12
Proteus vulgaris Kuk. 1329	512	32	512	512	512	24
Staphylococcus aureus ATCC 29213	–	32	–	–	–	6
Streptococcus pyogenes ATCC 176	512	32	–	–	–	12
Enterococcus facealis ATCC 29122	–	–	–	–	–	12
Bacillus subtilis ATCC 6633	–	–	–	–	–	24
Salmonella enteridis ATCC 1376	–	32	–	–	–	24
Xanthomonas compestris A235	256	32	512	512	512	12

–, No activity; *, minimal inhibitory concentrations (MICs) of compounds and antibiotics expressed as (μg/mL); **, Chloramphenicol

general, only one of the compounds exhibited excellent antibacterial activity against human pathogens. Therefore, it could be expected that compound **5** may have potential as an anti-infective agent in human microbial infections. The results obtained clearly indicate that some of the derivatives of 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid discussed here are active in terms of growth inhibition of selected human pathogens. However, further studies are required to determine their potential against a wide range of human pathogens, their MIC mode of actions, and to assess the usefulness of the synthesized compounds.

Experimental

All melting points were determined on an Electrothermal Gallenkamp apparatus and are uncorrected. The compounds were routinely checked for their homogeneity by thin-layer chromatography (TLC) using a DC Alufolien Kieselgel 60 F 254 Merck and Camag TLC lamp (254/366 nm). Microanalyses were performed on a Carlo Erba elemental analyzer model 1108. The IR spectra were obtained as potassium bromide pellets using a Mattson 1000 Fourier-transform infrared (FTIR) spectrometer. The ^{1}H- and ^{13}C-NMR spectra were recorded on Varian XL-200 (200 MHz) and (50 MHz) spectrometers, respectively, using Tetramethylsilane (TMS) as an internal standard. The title compounds **1**, **2,** and **3** were prepared according to the literature procedure (Akçamur *et al*., 1986; Akçamur *et al*., 1997).

2,3,4-Triphenyl-pyrazolo[4,3-*d*][1,2]oxazin-7(2*H*)-one (**4**)

Pyrazole acid **1** (0.37 g, 1 mmole) and a large excess of hydroxylamine hydrochloride were heated to about 150–155°C on an oil bath for approximately

30 min, until sublimation of excess hydroxylamine hydrochloride ceased, with stirring. After cooling to room temperature, the resulting mixture was first washed with water then treated with ether; the crude product formed in this way was recrystallized from isobutanol to give 0.20 g (55%) of pure **4**, m.p. 240°C. IR: 1685 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$-d_6): $\delta = 7.37–6.77$ ppm (Ar-H); ^{13}C-NMR ($CDCl_3$-d_6): $\delta = 156.36$ (C=O), 143.54 (C-7a), 140.57 (C-3), 139.65 (C-4), 132.24, 132.13, 131.71, 131.53, 131.46, 130.54, 130.31, 130.20, 130.12, 129.99, 129.89, 128.71, 127.76 ppm.

Anal. calcd. for $C_{23}H_{15}N_3O_2$: C, 75.60; H, 4.14; N, 11.50. Found: C, 75.70; H, 4.13; N, 11.49.

1-(4-benzoyl-1,5-diphenyl-1*H*-pyrazol-3-oyl)-sulfamide (5)

An equimolar mixture of acid chloride **2** (0.39 g, 1 mmole) and sulfamide (0.096 g, 1 mmole) was heated to 165–170°C for approximately 120 min without any solvent. After cooling to room temperature, the residue was treated with ether and the formed crude product was recrystallized from butyl alcohol to give 0.20 g (45%) of **5**, m.p. 259°C. IR: 3444, 3367 cm^{-1} (NH), 3062 cm^{-1} (Ar-H), 1749 cm^{-1} (C=O, CONH-), 1670 cm^{-1} (C=O, Benzoyl); ^{13}C-NMR ($CDCl_3$-d_6): $\delta = 192.94$ (C=O, benzoyl), 159.62 (C=O, CONH-), 146.28 (C-3), 146.37 (C-5), 140.83, 139.91, 135.17, 131.76, 131.40, 131.04, 130.60, 130.33, 129.75, 127.24, 125.20 ppm.

Anal. calcd. for $C_{23}H_{18}N_4O_4S$: C, 61.87; H, 4.06; N, 12.55; S, 7.18. Found: C, 62.00; H, 4.06; N, 12.53; S, 7.17.

3,4-Dibenzoyl-1,5-diphenyl-1*H*-pyrazole (**6**)

Compound **2** (0.412 g, 1 mmole) and anhydrous $AlCl_3$ (0.133 g, 1 mmole) were refluxed for 2 h in benzene (20 mL). Then, reaction mixture was made alkaline by adding solution of NaOH within ethyl alcohol (96%). Later, the formed precipitate was removed by filtration and the filtrate was evaporated under vacuum. Resulting crude product was crystallized from ethanol, to give yield 0.180 g (42%), m.p. 175°C. IR: 3080 cm^{-1} (Ar-H), 1676 and 1651 cm^{-1} (C=O, benzoyl); ^{13}C-NMR ($CDCl_3$-d_6): $\delta = 193.41$ and 188.78 (C=O, benzoyl), 152.02 (C–3), 145.44 (C–5), 141.08, 140.10, 138.61, 135.03, 134.93, 132.60, 131.94, 131.27, 131.21, 131.05, 130.52, 130.44, 130.33, 130.21, 130.00, 127.44, 126.29 ppm.

Anal. calcd. for $C_{29}H_{20}N_2O_2$: C, 81.29; H, 4.70; N, 6.54. Found: C, 82.03; H, 4.69; N, 6.53.

4-Benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carbonitrile (7)

A cold solution of the acid amide **6a** (0.37 g, 1 mmol) in a mixture of DMF (0.7 mL) and $SOCl_2$ (0.15 mL) was stirred at 0–5°C for 2 h and the solution was left stirring overnight. Then the reaction mixture was poured over crushed ice and

the solid formed was isolated by filtration, washed with water and recrystallized from methyl alcohol to give 0.245 g (70%) of **7**, m.p. 167°C. IR: 3081 cm^{-1} (Ar-H), 2239 cm^{-1} (-C≡N), 1649 cm^{-1} (C=O, benzoyl); ^{13}C-NMR ($CDCl_3$-d_6): δ = 190.32 (C=O, benzoyl), 147.26 (C-3), 140.21 (C-5), 138.68, 135.39, 132.21, 131.82, 131.62, 131.24, 130.57, 130.29, 128.96, 128.79, 127.47, 126.77, 114.51 ppm (-C≡N).

Anal. calcd. for $C_{23}H_{15}N_3O$: C, 79.07; H, 4.33; N, 12.03. Found: C, 78.98; H, 4.34; N, 12.05.

2,3,4-Triphenyl-2*H*-pyrazolo[3,4-d]pyridazin-7-yl-amine (**8**)

Compound **6** (0.35 g, 1 mmole) and anhydrous hydrazine (0.032 g, 1 mmole) were refluxed in 1-butanol containing a catalytic amount of metallic sodium on an oil bath for 7 h. The precipitate formed in boiling 1-butanol was isolated by filtration and recrystallized from methyl alcohol to give 0.145 g (40%) of **8**, m.p. 307°C. IR: 3490–3180 cm^{-1} (NH), 3055 cm^{-1} (Ar-H), 1680 cm^{-1} (C=NH); ^{13}C-NMR ($CDCl_3$-d_6): δ = 158.83 (C=NH), 147.09 (C-3), 144.59 (C-4), 142.22 (C-7a), 140.92, 136.06, 132.47, 131.08, 130.89, 130.75, 130.56, 130.45, 129.93, 129.67, 127.98, 119.07 ppm (C-3a).

Anal. calcd. for $C_{23}H_{17}N_5$: C, 76.01; H, 4.71; N, 19.27. Found: C, 75.93; H, 4.72; N, 19.30.

Antimicrobial assay

Bacterial strains used in the present study were taken from Biology Department of Science and Art Faculty of Yüzüncü Yil University, Van, Turkey. The bacterial strains were *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, *Enterobacter facealis* ATCC 29212, *Klebsiella pneumonia* A137, *Proteus vulgaris* Kukem 1329, *Streptococcus pyogenes* ATCC 176, *Bacillus subtilis* ATCC 6633, *Salmonella enteridis* ATCC 1376, and *Xanthomonas compestris* A235 (Table 1). Bacterial test organisms were maintained a nutrient agar (Merck) slants at 4°C and subcultured in Petri plates prior to use. Each combination of test microorganism and newly synthesized compounds were repeated three times. The microdilution broth susceptibility assay (Clause, 1989; Lee *et al*., 1999; Lee *et al*., 2003) was used for the antimicrobial evaluation of compounds. Stock solutions of the samples were prepared in distilled water and serial dilutions were ranged from 2 to 512 μg/mL in micro test tubes and than transferred into 10 mL test tubes containing 5 mL nutrient broth. Test microorganisms were inoculated and incubated overnight. Also, one tube without inoculation was used as a negative control while one that contained chloramphenicol antibiotic was used as a positive control. After incubation overnight, the first tube with clear appearance determined the minimal inhibitory concentration (MIC). The biological screening results of the five newly synthesized compounds and the control antibiotic chloroamphenicol are detailed in Table 1.

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