TÜBİTAK

Turkish Journal of Chemistry

http://journals.tubitak.gov.tr/chem/

Research Article

Turk J Chem
(2017) 41: 502 – 513

doi:10.3906/kim-1612-45

Diastereoselective synthesis of novel 2,5-dioxopyrrolidine derivatives via biocatalytic domino reactions

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Received: 16.12.2016 • **Accepted/Published Online:** 06.03.2017 • **Final Version:** 05.09.2017

Abstract: A series of novel 2,5-dioxopyrrolidines were synthesized by the one-pot reaction of coumarin-3-carboxylic acids **1** with thiourea derivatives and alkyl isocyanides in the presence of Fe_3O_4 NPs @ lipase as heterogeneous reusable nanobiocatalysts with high yields.

Key words: Diastereoselective synthesis, 2,5-dioxopyrrolidine derivatives, biocatalytic reactions

1. Introduction

The pyrrolidine ring is found in large compounds demonstrating a significant range of biological activities. Review of the literature has shown that pyrrolidines are well known for their remarkable biological properties, such as anticonvulsant,[1,2] anti-HIV-1,[3] antitumor,[4] ketoamide-based cathepsin K inhibitor,[5,6] antimicrobial,[7–9] and sphingosine-1-phosphate (S1P) receptor agonist[10,11] activities.

Multicomponent reactions (MCRs) are useful tools for the efficient synthesis of heterocyclic compounds due to their environmental friendliness, atomic economy, and green specifications. These reactions proceed through one-pot reactions to form complex heterocyclic structures.[12–14] Therefore, MCRs can decrease the cost of starting materials and the formation of chemical waste, and they can give higher yields in shorter reaction times than multistep syntheses.[15–20] Moreover, MCRs that can form compounds that are bioactive molecules from simple starting materials have been considered in recent years.[21]

Biocatalysts are among the most powerful tools in both organic and bioorganic synthesis because of their good selectivity, high efficiency, and environmental tolerability.[22–24] It has been shown that several hydrolases like lipases are valuable and useful catalysts in organic reactions such as aldol reactions,[25–28] Mannich reactions,[29] Markovnikov reactions, Michael addition,[30] Diels–Alder reactions,[31] and some other domino reactions. Recently, Wang et al. reported a novel lipase-catalyzed direct three-component reaction.[29]

As a result of these observations and in continuation of our previous works on the synthesis of novel heterocyclic compounds,[32–35] we would like to report an efficient and straightforward protocol for the diastereoselective synthesis of new pharmaceutically relevant 2,5-dioxopyrrolidines using Fe_3O_4 NPs @ lipase as heterogeneous reusable nanobiocatalysts (NBCs) in a three-component fashion.

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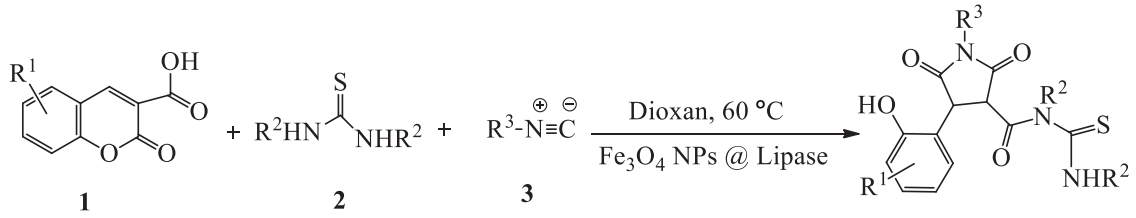
2. Results and discussion

Initially, a three-component reaction of coumarin-3-carboxylic acid **1a**, thiourea **2a**, and cyclohexyl isocyanide **3a** was performed in dioxane at room temperature and after 1 week the yield was measured. Thereafter, we examined the formation of 2,5-dioxopyrrolidine **7a** at 50, 60, and 70 °C such that **7a** was isolated in 30% yield after 72 h at 50 °C (Table 1, entry 2) and 60% yield after 48 h at 60 and 70 °C (Table 1, entries 3 and 4).

Table 1. Optimization of reaction conditions.

Entry	Solvent	T (°C)	Catalyst (mg)	Time	Yield (%)
1	Dioxane	25	-	1 week	Trace
2	Dioxane	50	-	72 h	30
3 4	Dioxane Dioxane	60 70	- -	48 h 48 h	60 60
5	Dioxane	25	Fe_3O_4 NPs @ANL (25)	1 week	Trace
6	Dioxane	25	Fe_3O_4 NPs@ANL (50)	72 h	35
7	Dioxane	50	Fe_3O_4 NPs@ANL (25)	24 h	50
8	Dioxane	60	Fe_3O_4 NPs@ANL (25)	4 h	85
9	Dioxane	70	Fe_3O_4 NPs@ANL (25)	4 h	85
10	Dioxane	60	Fe_3O_4 NPs@ANL (10)	4 h	40
11	Dioxane	60	Fe_3O_4 NPs (25)	4 h	Trace
12	Dioxane	60	ANL (25)	4 h	20
13	Dioxane	60	Baker's yeast (25)	4 h	Trace
14	Dioxane	60	Fe_3O_4 NPs@ANL (50)	4 h	85
15	DMSO	60	Fe_3O_4 NPs@ANL (25)	4 h	85
16	Ethanol	60	Fe_3O_4 NPs@ANL (25)	4 h	Trace
17	Acetonitrile	60	Fe_3O_4 NPs@ANL (25)	4 h	Trace
18	H_2O	60	Fe_3O_4 NPs@ANL (25)	4 h	0

The synthesis of 2,5-dioxopyrrolidines utilizing NBCs (Fe_3O_4 NPs @ lipase) as done in a previous work[36] was investigated in this reaction. The reaction rate was increased and **7a** was isolated in good yield in a short time (Figure 1).



R^1 = H, Br, Ph, OCH_3, NO_2

R^2 = H, Ph

R^3 = Cyclohexyl, t-Bu, 2,6-Dimethyl phenyl, (S)-(-)-a-Methylbenzyl

Figure 1. Synthesis of 2,5-dioxopyrrolidine derivatives in the presence of Fe_3O_4 NPs @ lipase at 60 °C in dioxane.

Thereafter, reaction conditions such as solvent, catalyst (Fe_3O_4 nanoparticles, baker's yeast, free lipase from *Aspergillus niger* (ANL), and catalyst amount), and temperature were further optimized (Table 1). In addition, the influence of enzyme concentration on the reaction was examined. As shown in Table 1, when 10 mg of NBC was used in the reaction, the yield was only 40% (Table 1, entry 10), and when the amount of

NBC was increased to 25 and 50 mg (Table 1, entries 8 and 14), the corresponding yields were increased. These results implied that 25 mg of NBC was enough to catalyze this reaction. Moreover, when 25 mg of Fe_3O_4 nanoparticles, baker's yeast, and free ANL were used in the reaction, the yield was calculated (Table 1, entries 11–13).

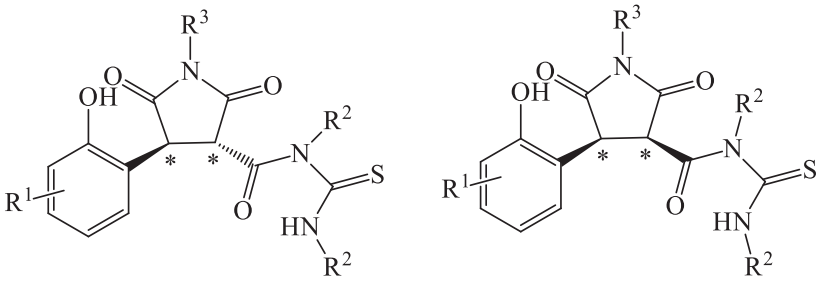
Subsequently, this three-component reaction was investigated in various solvents such as H_2O, ethanol, dioxane, and MeCN at 60 °C using 25 mg of NBC (Table 1, entries 12–15). As indicated in Table 1, dioxane was chosen as the most suitable solvent for this reaction at 60 °C in the presence of 25 mg of NBC.

To study the scope of the reaction, this methodology was examined employing different coumarin-3-carboxylic acids, alkyl isocyanides, and thiourea derivatives. The corresponding 2,5-dioxopyrrolidines **7a**–**7m** were diastereoselectively synthesized in good isolated yields in dioxane at 60 °C after 4 h in the presence of 25 mg of NBC (Table 2).

The structures of 2,5-dioxopyrrolidine derivatives were confirmed by FT-IR and ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.

The mass spectrum of **7a** showed the molecular ion ($M^{+\bullet}$) peak at m/z: 375.5, which was in line with that of the product's structure. The ^{1}H NMR spectrum of **7a** in DMSO demonstrated one broad singlet at 10.20 ppm, one singlet at 9.97 ppm, and another broad singlet at 8.11 ppm corresponding to OH, NH, and NH_2 groups, respectively. In addition, two doublets at 3.75 and 4.20 ppm ($^3J_{HH}$ = 5.2 Hz) for two methine groups of the pyrrolidine ring, two multiplets at 3.87–3.93 and 1.23–1.79 ppm corresponding to the cyclohexyl ring, and two multiplets at 6.75–6.80 and 7.13–7.21 ppm for four aromatic protons were observed. The ^{13}C NMR spectrum of **7a** showed one signal at 186.81 corresponding to the C=S group; three signals at 176.80, 172.08, and 168.97 ppm for three C=O groups; and 14 other signals that are consistent with the structure of **7a**. The ^{1}H and ^{13}C NMR spectra of **7b**–**7m** are similar to those of **7a** except for their substituents in dioxopyrrolidine and phenol moieties, which demonstrated characteristic resonances in the appropriate regions of the spectra (see Section 3).

As shown in Figure 2, compounds **7a**–**7l** possess two chirality centers and they can exist as two diastereoisomers, namely **7(a–l) I** (RR) or their enantiomer (SS) and **7(a–l) II** (RS) or their enantiomer (SR). The ^{1}H and ^{13}C NMR spectra of compounds **7a**–**7l** showed only one diastereoisomer. The vicinal coupling constant ($^3J_{HH}$ = 5.2 Hz) for two methine groups indicates that a thermodynamically stable trans isomer of 2,5-dioxopyrrolidine **7(a–l) I** was formed. In addition, compound **7m** possesses three chirality centers, and it can exist as four diastereoisomers, namely SRR, SSS, SRS, and SSR. The ^{1}H and ^{13}C NMR spectra of compound **7m** showed only one diastereoisomer. Thus, the reaction is diastereoselective.



7(a-l) I **7(a-l) II**

Figure 2. Two diastereoisomers of **7a**–**7l**.

Table 2. The synthesis of 2,5-dioxopyrrolidine derivatives catalyzed by Fe_3O_4 NPs @ lipase at 60 °C.

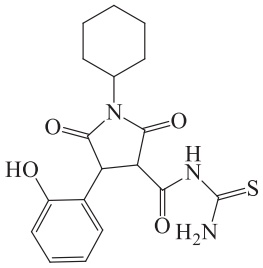
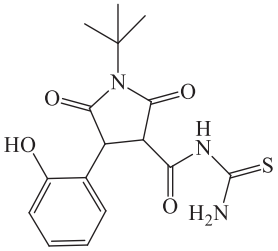
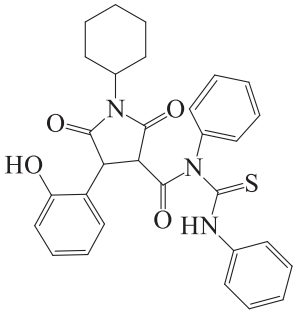
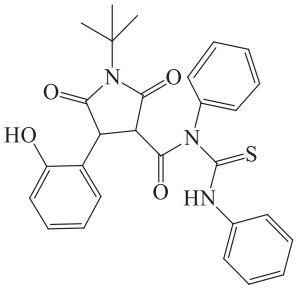
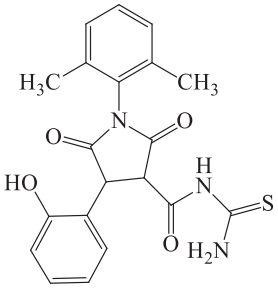
Entry	Product	Yield (%)	M.P. °C	
1	 **7a**	85	103-105	
2	 **7b**	75	110-113	
3	 **7c**	85	242-245	
4	 **7d**	75	251-253	
5	 **7e**	85	210-212	

Table 2. Continued.

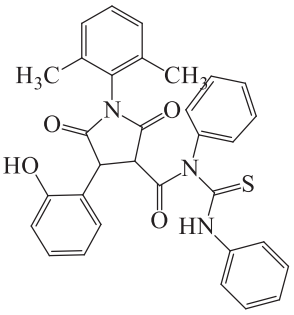
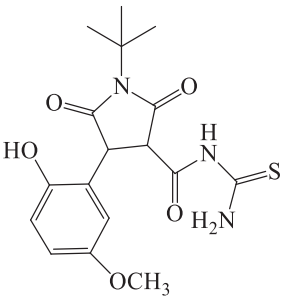
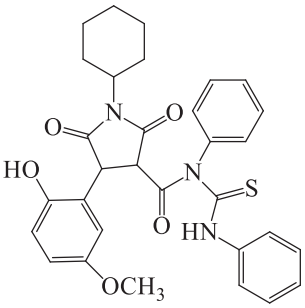
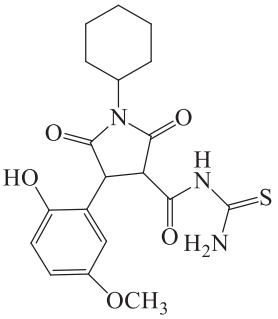
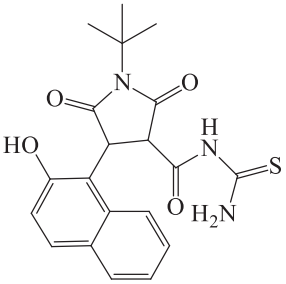
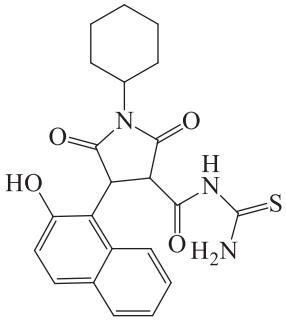
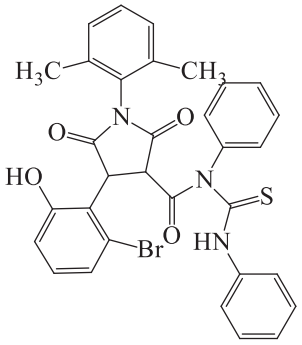
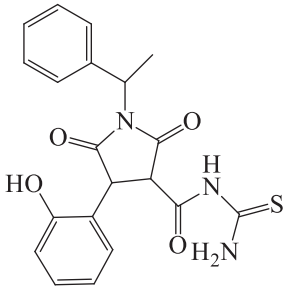
6	 **7f**	80	232-234
7	 **7g**	85	100-103
8	 **7h**	85	252-254
9	 **7i**	85	98-100
10	 **7j**	70	148-150

Table 2. Continued.

11	 **7k**	75	160-162
12	 **7l**	55	270-272
13	 **7m**	80	120-122

In the proposed mechanism, in the first step the chiral amino acid residue of histidine activates the carbonyl of the carboxylic acid group by hydrogen bonding and therefore differentiates between the two sides of the double bond in compound **1** for Michael addition of isocyanide **3**. Trans iminolactone **4** is then formed diastereoselectively through preferential Michael addition reaction of **3** to one side of the α,β-double bond of **1**. The nucleophilic attack of the NH group of thiourea **2**, followed by an intramolecular nucleophilic reaction, yields intermediate **6**. Intermediate **6** contains an electrophilic thioimide moiety, and it is well known that imides have strong acylating properties.[37,38] Therefore, intramolecular nucleophilic reaction of the thioimide moiety of **6** with the amide NH group produces trans 2,5-dioxopyrrolidines **7** diastereoselectively. Meanwhile, the NBCs (Fe_3O_4 NPs @ lipase) with the amino acid residue of histidine and aspartic anion result in the activation of carbonyl and NH groups via hydrogen bonding in different steps [39–44] (Figure 3).

The reusability of the NBC was also investigated in the synthesis of **7a** as a model reaction. The recovered catalyst was washed five times with ethanol, dried for 24 h at 25 °C, and reused for the next run of the reaction. The results showed that the catalyst could be reused for six cycles without significant loss in the product yield (Figure 4).

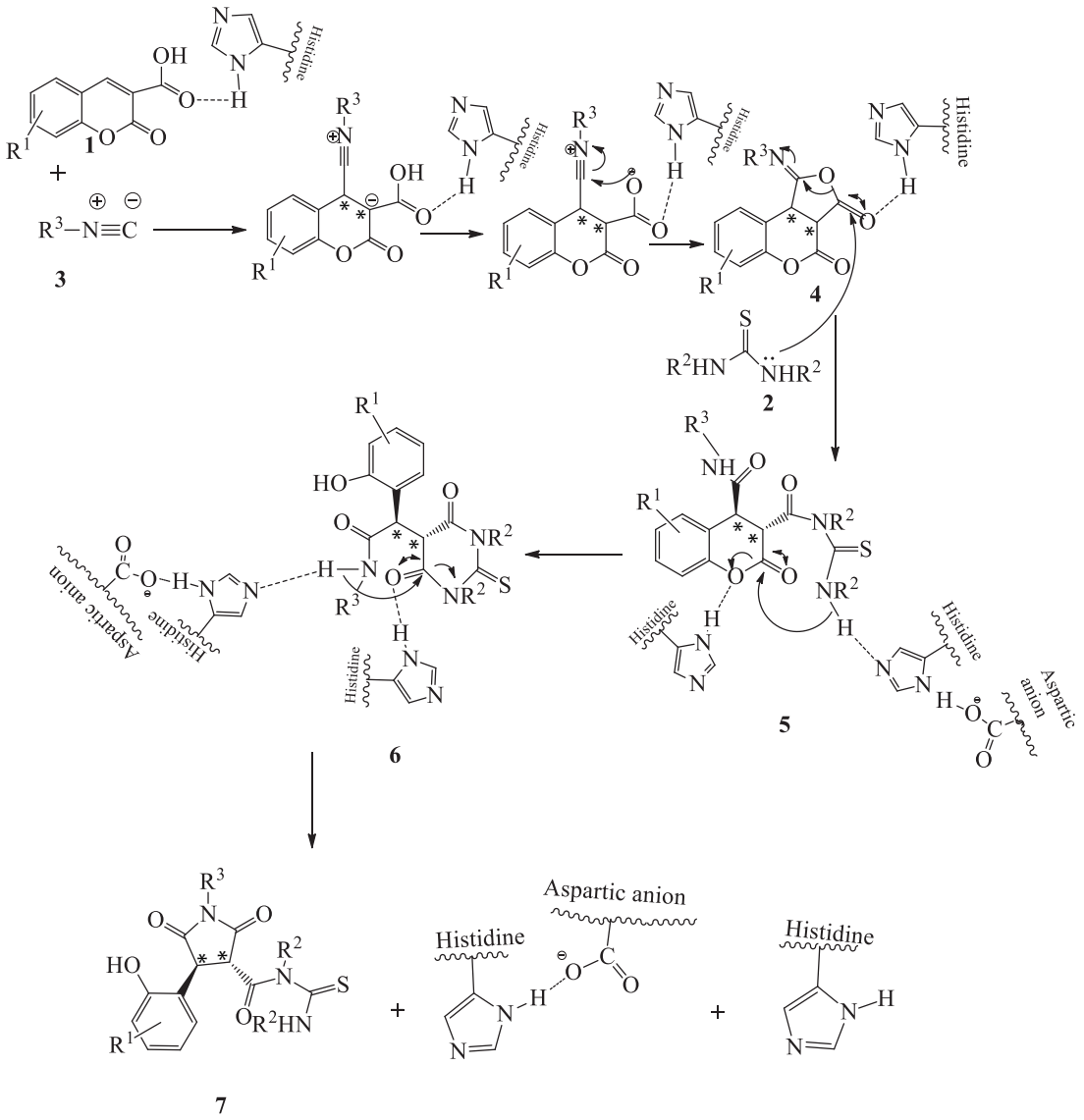


Figure 3. Proposed biocatalytic mechanism for the synthesis of 2,5-dioxopyrrolidine derivatives.

In summary, we have developed an efficient and straightforward protocol for the synthesis of novel 2,5-dioxopyrrolidines using Fe_3O_4 NPs @ lipase as heterogeneous reusable NBCs. This protocol has several advantages, including excellent yield, environmental friendliness, and short reaction time. An important aspect in this work is that we used a heterogeneous catalyst, which can be easily separated from the reaction mixture using a magnet. The produced 2,5-dioxopyrrolidines can be examined for their biological and medicinal activities.

3. Experimental

All chemicals and solvents were purchased from Merck and Sigma-Aldrich and were used without further purification. The progress of the reactions was monitored via TLC using silica gel SIL G/UV 254 plates. Melting points were measured with an Electrothermal 9100 apparatus and were uncorrected. ^{1}H and ^{13}C

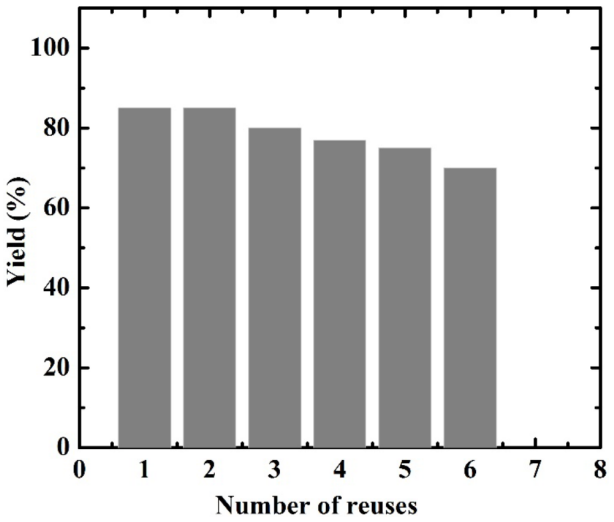


Figure 4. Recycling studies of NBC in the synthesis of **7a.**

NMR spectra were recorded with a Bruker DRX-400 Advance instrument (400 and 100 MHz, respectively) in $CDCl_3$ and DMSO. Mass spectra was recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV (ESI). IR spectra (KBr) were recorded on a FT-IR Bruker Vector 22 spectrometer.

3.1. General procedure for the preparation of 2,5-dioxopyrrolidines

A mixture of coumarin-3-carboxylic acid derivative (1 mmol), alkyl isocyanide (1 mmol), thiourea derivative (1 mmol), and NBC (25 mg) in 10 mL of dioxane was stirred at 60 °C for 4 h. When the reaction (TLC, eluent: AcOEt/n-hexane 2/3) was completed, the NBC was separated using a magnet. The solvent was removed under reduced pressure and the residue was separated by chromatography plates using n-hexane/AcOEt as an eluent.

3.2. Physical and spectral data for the synthesized new compounds 7a–7m

3.2.1. N-Carbamothioyl-1-cyclohexyl-4-(2-hydroxyphenyl)-2,5-dioxopyrrolidine-3-carboxamide (7a)

White powder, mp: 103–105 °C; yield (85%); IR (KBr) ν_{max}: 3749, 3460, 1872, 1748, 1699, 1613 cm^{-1}; MS (ESI) m/z: 375 (M^+); Calcd for $C_{18}H_{21}N_3O_4S$ (375.4); ^1H NMR (400 MHz, DMSO-d_6) δ: 1.23–1.87 (10H, m, $5CH_2$ of cyclohexyl), 3.76 (1H, d, $^3J_{HH}$ = 5.2 Hz, CH), 3.87–3.93 (1H, m, CH-N), 4.21 (1H, d, $^3J_{HH}$ = 5.2 Hz, CH), 6.75–6.80 and 7.13–7.21 (4H, 2m, Ar-H), 8.11 (2H, bs, NH_2), 9.97 (H, s, NH), 10.20 (1H, bs, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.6, 25.3, 25.7, 28.6, 30.9, 47.6, 51.9, 53.3, 115.7, 119.5, 123.6, 129.7, 131.9, 155.4, 168.9, 172.1, 176.8, 186.8.

3.2.2. 1-(Tert-butyl)-N-carbamothioyl-4-(2-hydroxyphenyl)-2,5-dioxopyrrolidine-3-carboxamide (7b)

White powder, mp: 110–112 °C; yield (75%); IR (KBr) ν_{max}: 3849, 3340, 1945, 1740, 1687, 1601 cm^{-1}; MS (ESI) m/z: 349 (M^+); Calcd for $C_{16}H_{19}N_3O_4S$ (349.4); ^1H NMR (400 MHz, DMSO-d_6) δ: 1.54 (9H, s, $C(CH_3)_3$), 3.67 (1H, d, $^3J_{HH}$ = 6.0 Hz, CH), 4.11 (1H, d, $^3J_{HH}$ = 6.0 Hz, CH), 6.75–6.81 and 7.12–7.17 (4H,

2m, Ar-H), 8.21 (2H, d, NH_2), 9.95 (H, s, NH), 10.30 (1H, bs, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 28.2, 47.8, 53.8, 58.4, 115.8, 119.5, 123.9, 129.6, 131.8, 155.4, 168.7, 173.1, 177.6, 186.8.

3.2.3. 1-Cyclohexyl-4-(2-hydroxyphenyl)-2,5-dioxo-N-phenyl-N-(phenylcarbamothioyl)pyrrolidine-3-carboxamide (7c)

Pink powder, mp: 242–244 °C; yield (85%); IR (KBr) ν_{max}: 3749, 3409, 1924, 1698, 1607 cm^{-1}; MS (ESI) m/z: 528 (M^+ + 1); Calcd for $C_{30}H_{29}N_3O_4S$ (527.6); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.14–1.81 (10H, m, 5CH_2 of cyclohexyl), 3.97 (1H, d, $^3J_{HH}$ = 4.8 Hz, CH), 4.17 (1H, d, $^3J_{HH}$ = 4.8 Hz, CH), 4.55 (1H, bs, CH-N), 6.73–7.59 (14H, m, Ar-H), 9.97 (H, s, NH), 10.43 (1H, s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.6, 25.3, 25.5, 28.6, 30.9, 42.5, 48.4, 51.9, 118.6, 122.2, 124.1, 124.5, 128.9, 129.2, 129.3, 130.4, 130.8, 138.9, 139.9, 140.1, 155.4, 168.9, 172.08, 176.8, 186.8.

3.2.4. 1-(Tert-butyl)-4-(2-hydroxyphenyl)-2,5-dioxo-N-phenyl-N-(phenylcarbamothioyl)pyrrolidine-3-carboxamide (7d)

Pink powder, mp: 251–253 °C; yield (75%); IR (KBr) ν_{max}: 3749, 3409, 1924, 1698, 1607 cm^{-1}; MS (ESI) m/z: 500 (M^+ – 1); Calcd for $C_{28}H_{27}N_3O_4S$ (501.6); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.14 (9H, s, $C(CH_3)_3$), 4.36 (1H, d, $^3J_{HH}$ = 9.2 Hz, CH), 4.53 (1H, d, $^3J_{HH}$ = 9.2 Hz, CH), 6.75–7.77 (14H, m, Ar-H), 10.10 (H, s, NH), 10.43 (1H, s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 28.6, 43.1, 56.0, 58.5, 117.8, 122.9, 123.1, 124.2, 128.6, 128.7, 128.9, 129.3, 129.4, 129.5, 140.0, 142.4, 146.6, 155.4, 166.3, 157.2, 179.6, 187.5.

3.2.5. N-Carbamothioyl-1-(2,6-dimethylphenyl)-4-(2-hydroxyphenyl)-2,5-dioxopyrrolidine-3-carboxamide (7e)

Beige powder, mp: 210–212 °C; yield (85%); IR (KBr) ν_{max}: 3749, 3446, 1924, 1784, 1744, 1625 cm^{-1}; MS (ESI) m/z: 397 (M^+); Calcd for $C_{20}H_{19}N_3O_4S$ (397.4); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.10, 2.18 (6H, s, 2CH_3), 4.20 (1H, d, $^3J_{HH}$ = 6.0 Hz, CH), 4.61 (1H, d, $^3J_{HH}$ = 6.0 Hz, CH), 6.80–6.90 and 7.19–7.31 (7H, 2m, Ar-H), 7.73–7.93 (2H, s, NH_2), 10.02 (H, s, NH), 10.29 (1H, s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 17.6, 17.8, 48.6, 53.5, 115.8, 119.7, 122.5, 128.7, 128.9, 129.8, 130.1, 130.9, 132.3, 136.1, 136.9, 155.4, 169.0, 171.1, 175.6, 177.9.

3.2.6. 1-(2,6-Dimethylphenyl)-4-(2-hydroxyphenyl)-2,5-dioxo-N-phenyl-N-(phenylcarbamothioyl) pyrrolidine-3-carboxamide (7f)

Pink powder, mp: 232–234 °C; yield (80%); IR (KBr) ν_{max}: 3748, 3325, 1943, 1870, 1797, 1648 cm^{-1}; MS (ESI) m/z: 549 (M^+); Calcd for $C_{32}H_{27}N_3O_4S$ (549.6); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.08, 2.09 (6H, s, 2CH_3), 4.19 (1H, d, $^3J_{HH}$ = 6.0 Hz, CH), 4.61 (1H, d, $^3J_{HH}$ = 6.0 Hz, CH), 6.80–7.84 (17H, m, Ar-H), 10.04 (H, s, NH), 10.28 (1H, s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 17.6, 17.8, 48.6, 53.5, 115.8, 116.7, 118.3, 119.7, 120.8, 122.6, 124.6, 125.1, 125.6, 128.7, 128.8, 129.0, 129.8, 130.9, 132.3, 133.9, 136.9, 138.1, 138.3, 144.1, 152.8, 153.8, 155.4, 157.5, 166.6, 168.9, 171.1, 175.6.

3.3. 1-(Tert-butyl)-N-carbamothioyl-4-(2-hydroxy-5-methoxyphenyl)-2,5-dioxopyrrolidine-3-carboxamide (7g)

Beige powder, mp: 100–103 °C; yield (85%); IR (KBr) ν_{max}: 3386, 3168, 1876, 1765, 1678, 1607 cm^{-1}; MS (ESI) m/z: 379 (M^+); Calcd for $C_{17}H_{21}N_3O_5S$ (379.4); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.63 (9H, s, $C(CH_3)_3$), 3.75 (1H, d, $^3J_{HH}$ = 6.0 Hz, CH), 3.88 (3H, s, OCH_3), 4.42 (1H, d, $^3J_{HH}$ = 6.0 Hz, CH), 6.74–6.76 and 6.82–6.84 (3H, 2m, Ar-H), 8.80 (2H, s, NH_2), 9.97 (H, s, NH), 10.29 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.3, 36.3, 43.1, 56.5, 58.5, 110.3, 119.9, 122.4, 124.1, 143.3, 146.7, 168.7, 177.9, 179.4, 186.8.

3.3.1. 1-Cyclohexyl-4-(2-hydroxy-5-methoxyphenyl)-2,5-dioxo-N-phenyl-N-(phenylcarbamothioyl) pyrrolidine-3-carboxamide (7h)

Pink powder, mp: 252–254 °C; yield (85%); IR (KBr) ν_{max}: 3706, 3342, 1885, 1774, 1697, 1592 cm^{-1}; MS (ESI) m/z: 557 (M^+); Calcd for $C_{31}H_{31}N_3O_5S$ (557.6); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.27–1.84 (10H, m, $5CH_2$ of cyclohexyl), 3.88 (3H, s, OCH_3), 3.95 (1H, d, $^3J_{HH}$ = 5.6 Hz, CH), 4.06–4.09 (1H, m, CH-N), 4.54 (1H, d, $^3J_{HH}$ = 5.6 Hz, CH), 6.84–7.38 (13H, m, Ar-H), 8.91 (H, s, NH), 8.39 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1, 25.5, 25.8, 28.6, 28.8, 35.9, 45.3, 52.6, 52.9, 110.8, 113.0, 113.6, 117.7, 118.2, 119.0, 119.9, 120.4, 121.1, 121.9, 123.9, 124.1, 124.7, 129.0, 129.1, 129.4, 143.1, 143.5, 157.8, 168.9, 170.9, 175.1, 195.8.

3.3.2. N-Carbamothioyl-1-cyclohexyl-4-(2-hydroxy-5-methoxyphenyl)-2,5-dioxopyrrolidine-3-carboxamide (7i)

Beige powder, mp: 98–100 °C; yield (85%); IR (KBr) ν_{max}: 3850, 3432, 1885, 1751, 1683, 1603 cm^{-1}; MS (ESI) m/z: 405 (M^+); Calcd for $C_{19}H_{23}N_3O_5S$ (405.4); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.97–2.26 (10H, m, $5CH_2$ of cyclohexyl), 3.75 (3H, s, OCH_3), 3.80 (1H, d, $^3J_{HH}$ = 5.2 Hz, CH), 3.87–3.93 (1H, m, CH-N), 4.20 (1H, d, $^3J_{HH}$ = 5.2 Hz, CH), 6.75–6.71 and 6.84–6.85 (3H, 2m, Ar-H), 8.25–8.75 (2H, s, NH_2), 9.97 (H, bs, NH), 10.20 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1, 25.9, 28.6, 28.6, 35.9, 42.8, 51.9, 56.0, 110.4, 120.0, 122.4, 123.8, 143.3, 146.7, 168.9, 176.9, 178.4, 186.8.

3.3.3. 1-(Tert-butyl)-N-carbamothioyl-4-(2-hydroxynaphthalen-1-yl)-2,5-dioxopyrrolidine-3-carboxamide (7j)

Beige powder, mp: 148–150 °C; yield (70%); IR (KBr) ν_{max}: 3706, 3376, 1886, 1768, 1690, 1630 cm^{-1}; MS (ESI) m/z: 399 (M^+); Calcd for $C_{20}H_{21}N_3O_4S$ (399.4); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.68 (9H, s, $C(CH_3)_3$), 3.67 (1H, d, $^3J_{HH}$ = 6.0 Hz, CH), 4.10 (1H, d, $^3J_{HH}$ = 6.0 Hz, CH), 6.83–7.81 (6H, m, Ar-H), 8.69 (2H, s, NH_2), 9.95 (H, s, NH), 10.28 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.4, 47.8, 53.8, 58.6, 116.6, 117.7, 121.5, 123.2, 127.0, 128.9, 129.1, 129.5, 133.1, 151.5, 168.7, 173.1, 178.5, 180.9.

3.3.4. N-Carbamothioyl-1-cyclohexyl-4-(2-hydroxynaphthalen-1-yl)-2,5-dioxopyrrolidine-3-carboxamide (7k)

Beige powder, mp: 160–162 °C; yield (75%); IR (KBr) ν_{max}: 3780, 3426, 1924, 1792, 1723, 1627 cm^{-1}; MS (ESI) m/z: 424 ($M^+ - 1$); Calcd for $C_{22}H_{23}N_3O_4S$ (425.5); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.23-1.2.30 (10H, m, $5CH_2$ of cyclohexyl), 3.15 (1H, d, $^3J_{HH}$ = 8.8 Hz, CH), 4.08–4.16 (1H, m, CH-N), 4.68 (1H, d, $^3J_{HH}$ =

8.8 Hz, CH), 6.93–7.76 (6H, m, Ar-H), 8.25 (2H, s, NH_2) 10.06 (H, s, NH), 10.13 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1, 25.9, 28.6, 28.6, 35.9, 37.8, 52.0, 53.8, 116.1, 117.8, 121.4, 123.1, 127.0, 128.9, 129.1, 129.5, 133.1, 151.9, 163.7, 174.2, 177.5, 180.1.

3.3.5. 4-(5-Bromo-2-hydroxyphenyl)-1-(2,6-dimethylphenyl)-2,5-dioxo-N-phenyl-N-(phenylcarbamothioyl)pyrrolidine-3-carboxamide (7l)

Beige powder, mp: 270–272 °C; yield (55%); IR (KBr) ν_{max}: 3780, 3297, 1887, 1725, 1699, 1594 cm^{-1}; MS (ESI) m/z: 629 ($M^+ + 1$); Calcd for $C_{32}H_{26}BrN_3O_4S$ (628.5); ^1H NMR (400 MHz, $CDCl_3$) δ: 2.07, 2.17 (6H, s, $2CH_3$), 4.01 (1H, bs, CH), 4.48 (1H, bs, CH), 6.72–7.29 (16H, m, Ar-H), 9.98 (H, s, NH), 10.21 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.5, 49.0, 51.6, 112.1, 113.4, 118.3, 119.6, 122.3, 123.2, 123.4, 124.0, 124.9, 127.5, 128.3, 128.6, 129.0, 129.2, 129.3, 129.4, 129.4, 129.5, 131.3, 133.4, 134.2, 135.6, 138.7, 159.8, 168.8, 171.9, 175.0, 187.3.

3.3.6. N-Carbamothioyl-4-(2-hydroxyphenyl)-2,5-dioxo-1-(1-phenylethyl)pyrrolidine-3-carboxamide (7m)

White powder, mp: 120–122 °C; yield (80%); IR (KBr) ν_{max}: 3831, 3747, 3237, 1956, 1882, 1708, 1608 cm^{-1}; MS (ESI) m/z: 397 (M^+); Calcd for $C_{20}H_{19}N_3O_4S$ (397.4); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.63 (3H, d, $^3J_{HH}$ = 6.8 Hz, CH_3), 3.71 (1H, d, $^3J_{HH}$ = 6.8 Hz, CH), 4.80 (1H, d, $^3J_{HH}$ = 8.0 Hz, CH), 5.75 (1H, q, $^3J_{HH}$ = 6.8 Hz, CH-N), 7.27–7.41 (9H, m, Ar-H), 7.85 and 8.85 (2H, bs, NH_2), 9.22 (H, s, NH), 9.40 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.9, 22.3, 49.6, 51.9, 125.3, 126.1, 126.2, 127.2, 127.6, 128.4, 128.8, 129.2, 129.8, 134.1, 140.0, 154.7, 166.8, 181.6, 187.7, 190.5.

Acknowledgment

This research was supported by the Research Council of the University of Mazandaran, Iran.

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