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Chinese Chemical Letters 22 (2011) 883–886
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Synthesis of 5-benzylidene-3-(3-fluoro-4-yl-morpholin-4-yl-phenylimino)-thiazolidin-4-one derivatives catalyzed by [BmIm]OH and their anti-microbial activity

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Received 8 October 2010
Available online 18 May 2011

Abstract

A series of novel 5-benzylidene-3-(3-fluoro-4-yl-morpholin-4-yl-phenylimino)thiazolidin-4-one derivatives were synthesized using [bmIm]OH as a catalyst and were tested for their antibacterial and antifungal activities. These compounds showed moderate *in vitro* activities against the microorganisms tested.

Keywords: Basic ionic liquid; [bmIm]OH; Antimicrobials; Anti-bacterial; Anti-fungal; Iminothizolidin-4-one

4-Phenyl-morpholine derivatives are reported to possess antimicrobial [1,2] and antiinflammatory [3–5] activities. 4-Thiazolidinone derivatives are also known to possess antibacterial [6–10], antifungal [11–13], antiviral [14] and antituberculosis [15–17] properties. Linezolide (PNU-10766, commercially available antimicrobial drug) possess 4-(2-flourophenyl) morpholine moiety, these observations led to the conception that 5-benzylidene derivatives of 3-ethyl-2-(3-fluoro-4-morpholin-4-yl-phenylimino)-thiazolidin-4-one would possess potential anti-microbial properties (Fig. 1). Several methods were reported in the literature for the preparation of thiazolidinone derivatives [18] and iminothiazolidin-4-one derivatives [19].

In the present study a novel series of 5-benzylidene-3-ethyl-2-(3-fluoro-4-morpholin-4-yl-phenylimino)-thiazolidin-4-ones were synthesized. The key steps of formation of iminothiazolidinone (**5**) and its Knovengel condensation with aryl aldehyde to 5-benzylidene-3-(3-fluoro-4-yl-morpholin-4-yl-phenylimino)-thiazolidin-4-one (**6**) were carried using basic ionic liquid [bmIm]OH [20] as a catalyst as well as solvent, with excellent yields.

Our synthetic strategy for thiazolidinone derivatives is illustrated in Scheme 1. The synthesis starts with reaction of 2,4-difluoro-1-nitrobenzene (**1**) with morpholine and potassium carbonate in dimethylformamide at 80 °C afforded 4-(3-fluoro-4-nitrophenyl)morpholine (**2**) which on catalytic reduction using H_2/Pd/C in methanol afforded 2-fluoro-4-morpholin-4-yl-phenylamine (**3**) [21]. The phenylamine (**3**) was futher treated with ethylisothiocynate in ethanol at

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1001-8417/$ – see front matter
doi:10.1016/j.cclet.2011.03.002

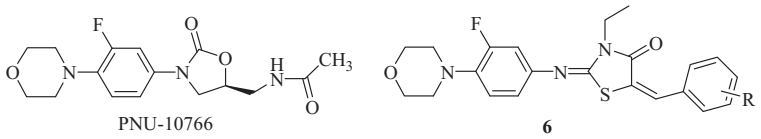


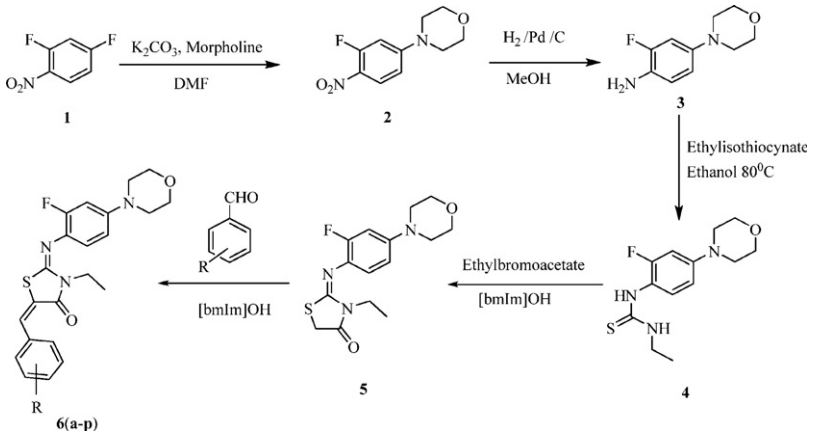
Fig. 1. Structure of PNU-10766 and 5-benzylidene-3-ethyl-2-(3-fluoro-4-morpholin-4-yl-phenylimino)-thiazolidin-4-one **6**.

80 °C afforded 1-ethyl-3-(2-fluoro-4-morpholin-4-yl-phenyl)-thiourea (**4**) [22]. 1-Ethyl-3-(2-fluoro-4-morpholin-4-yl-phenyl)thiourea (**4**) was treated with ethylbromoacetate in basic ionic liquid [bmIm]OH at room temperature, the key intermediate 3-ethyl-2-(2-fluoro-4-morpholin-4-yl-phenylimino)thiazolidin-4-one (**5**) was isolated with 95% yield [23]. ^{1}H NMR spectrum of compound **5** shows a singlet at 4.02 ppm for two protons is characteristic value of C-5 protons of the iminothiazolidinone nucleus. The strong absorption bands at 1708 cm^{-1} and at 1620 cm^{-1} confirms the presence of C=O and C=N functional groups respectively and hence confirms the formation of iminothiazolidinone compound **5**. This clearly indicates that basic ionic liquid [bmIm]OH catalyzes cyclization of thiourea with ethyl bromoacetate which is a key step in the current synthesis.

This key intermediate iminothiazolidin-4-one (**5**) on Knovengel condensation with different substituted aryl aldehydes in [bmIm]OH afforded the 5-benzylidene-3-(3-fluoro-4-yl-morpholin-4-yl-phenylimino)thiazolidin-4-one **6**(**a**–**p**) in excellent yields (Table 1) [24]. The ionic liquid used in the reaction was recovered from aqueous layer and washed with diethyl ether to remove any organic impurities and dried under vacuum to get the pure ionic liquid and was reused for the above reactions. We have tested reusability of ionic liquid for compound (**6j**), upon use of three times, showed no loss of its activity and does not vary yield of final product. All these compounds were characterized by IR, ^{1}H NMR and MS [26]. These compounds were furter used for the biological studies.

The antimicrobial activity of the compuond was assayed by antimicrobial susceptibilty test [25]. 100 μL of 24 h growth of each microorganism was spread on the surface of nutrient agar for bacteria (Mac Conkey's agar for *Escherichia coli*) and potato dextrose agar for fungi, in Petri plates. 50 μL compound at the concentration of 100 μg/mL in DMSO saturated on discs of 6 mm diameter were kept on agar surface. The plates refrigerated for two hours to allow prediffusion of the compound from the discs in to the seeded agar layer and then incubated at 37 °C for 24 h for bacteria and 28 °C for 48 h for fungi. Zones of inhibition were measured in mm and size of the disc was subtracted from the zone size to measured final activity. DMSO saturated discs served as solvent control or negative control and Streptomycin saturated discs (30 μg) for bacteria and Nystatin (30 μg) for fungi as a reference or positive control.

The newly synthesized compounds were tested to evaluate their antibacterial and antifungal activity. All these compounds were found to exhibit moderate antibacterial and antifungal activity against different species of bacteria and fungi. From the activity data (Table 1) it was observed that among all the compounds tested, compound **6o** shows good activity against all the tested bacteria and fungi. Among all tested bacteria and fungi compound **6o** showed good



Scheme 1. Synthetic scheme for compound **6**(**a**–**p**).

Table 1
Yield and antimicrobial activity[a] of benzilidene derivatives (**6a**–**6p**).

Aldehyde	Yield (%)[b]	Zone of inhibition (mm)[c]				
		Bactria			Fungi	
		Staphylococous aureus NCLM-2602	*Bacillus subtillis* NCLM-2458	*Escherichia coli* NCLM-2809	*Aspergillus niger* NCLM-617	*Rhizopus otyzae* NCLM-1299
Benzaldehyde	**6a** (90)	3	2	3	2	1
4-Hydroxy-benzaldehyde	**6b** (93)	1	3	2	3	2
3-Hydroxy-benzaldehyde	**6c** (92)	2	3	2	1	1
2-Hydroxy-benzaldehyde	**6d** (89)	3	2	1	2	2
4-Fluorobenzaldehyde	**6e** (94)	3	2	3	2	3
3-Fluorobenzaldehyde	**6f** (91)	2	3	2	3	2
2,4-Difluoro-benzaldehyde	**6g** (90)	2	1	1	1	2
4-Cyanobenzaldehyde	**6h** (88)	3	2	2	2	1
4-Nitrobenzaldehyde	**6i** (90)	2	2	1	1	2
4-Isopropyl-benzaldehyde	**6j** (95)	1	3	2	2	3
4-Methoxy-benzaldehyde	**6k** (92)	3	2	3	3	1
3-Nitrobenzaldehyde	**6l** (87)	2	1	2	2	2
4-Bromobenzaldehyde	**6m**(88)	2	2	2	2	2
4-Hydroxy-3-methoxy benzaldehyde	**6n** (90)	3	2	3	3	3
2,4,6-Trimethoxy-benzaldehyde	**6o** (94)	5	8	5	4	4
1H-Indol-3-carboxaldehyde	**6p** (92)	2	2	3	4	3
Standard Antibiotic[d]	–	10	8	9	8	9

[a] These results are average results of four experiments.
[b] Isolated yields of **6** after 3 h.
[c] These compounds were used at concentration of 100 μg/mL.
[d] Streptomycin for bacteria and Nystain for fungi were used at concentration of 30 μg.

activity against *Staphylococococous aureus* (inhibition 5 mm, standard showed 10 mm) and *Bacillus subtillis* (inhibition 8 mm, standard showed 8 mm). Among the other compounds **6a**, **6e**, **6k** and **6n** shown moderate activity against *Escherichia coli* and the compounds **6b**, **6c**, **6f**, **6j** and **6p** showed moderate activity against *Bacillus subtillis* bacteria. Compounds **6n** and **6p** showed moderate activity against *Aspergillus Niger* and *Rhizopus Otyzae* fungi.

In conclusion, we have synthesised a series of novel thiazolidinone derivatives using [bmIm]OH as a catalyst as well as solvent for the key step of formation of iminothiazolidinone and its Knovengel condensation with aromatic aldehydes. These compounds have been screened for potential antibacterial and antifungal activities. The results from our biological activity studies showed that compound **6o** having 2,4,6-trimethoxy group on benzilidene moiety shows good activity against all tested bacteria and fungi.

Acknowledgments

We are gratefully acknowledged DST (No. SR/FTP/CS-114/2007) New Delhi, India for financial assistance. M.S.S. thanks to DST for scholarship.

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[23] The solution 2-fluoro-4-morpholin-4-yl-phenylamine (**3**) (1 mmol) and ethyl bromoacetate (1.1 mmol) in [bmIm]OH (2 mmol) was stirred at rt. After 6 h cold water was added and extracted with ethyl acetate (3× 10 mL), washed with brine and dried over anhydrous sodium sulfate and concentrated. The crude product was purified by silica gel column chromatography using petroleum ether: ethyl acetate (20:1) eluent to get pure iminothiazolidin-4-one (**5**). Aqueous layer was re-extracted with ether (3× 10 mL) to remove organic impurities and dried under vacuum at 90 °C to get pure ionic liquid.
[24] A mixture iminothiazolidin-4-one (**5**) (1 mmol) and aldehyde (1.1 mmol) in [bmIm]OH (2 mmol) was stirred at rt. After 3 h cold water was added and residue was filtered dried and recrystalized from hot ethanol to get pure 5-benzylidene-3-(3-fluoro-4-yl-morpholin-4-yl-phenylimino)-thiazolidin-4-one (**6**). Aqueous layer was re-extracted with ether (3× 10 mL) to remove organic impurities and dried under vacuum at 90 °C to get pure ionic liquid.
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[26] Analytical data: *3-Ethyl-2-(3-fluoro-4-morpholin-4-yl-phenylimino)thiazolidin-4-one* (**5**): Reddish solid; ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.16 (t, 3H, J = 6.9 Hz), 2.97 (t, 4H, J = 3.4 Hz), 3.72–3.79 (m, 6H), 4.02 (s, 2H), 6.70–6.82 (m, 2H), 6.97–7.06 (m, 1H); MS (*m*/*z*): 324.5 [M^++1]; IR (KBr): 1709, 1630. *(5E)-3-Ethyl-2-(3-fluoro-4-morpholinophenylimino)-5-(4-methoxybenzylidene)thiazolidin-4-one* (**6k**): Yellow solid; mp: 138–140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.34 (t, 3H, J = 7.0 Hz), 3.10–3.14 (m, 4H), 3.83 (s, 3H), 3.90–4.00 (m, 4H), 4.03 (q, 2H, J = 7.0 Hz), 6.75–6.82 (m, 2H), 6.94 (d, 2H, J = 8.8 Hz), 6.98–7.10 (m, 1H), 7.41 (d, 2H, J = 8.8 Hz), 7.71 (s, 1H); MS (*m*/*z*) 442.5 [M^++1]; IR (KBr): 2968, 2852, 2821, 1705, 1637, 1504, 1377, 1338, 1268, 1116, 1043, 923. *(5E)-3-Ethyl-2-(3-fluoro-4-morpholinophenylimino)-5-(4-hydroxy-3-methoxybenzylidene)thiazolidin-4-one* (**6n**): Yellow solid; mp: 176–178 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): (1.34 (t, 3H, J = 7.0 Hz), 1.59 (bs, 1H, exchangeable with D_2O), 3.11 (t, 4H, J = 4.4 Hz), 3.83 (s, 3H), 3.89 (t, 4H, J = 4.4 Hz), 4.03 (q, 2H, J = 7.0 Hz), 6.74–6.82 (m, 2H), 6.90–7.00 (m, 3H), 7.41 (d, 1H, J = 8.7 Hz), 7.70 (s, 1H); MS (*m*/*z*): 458.5 [M^++1]; IR (KBr): 3541, 2969, 2854, 2824, 1710, 1639, 1509, 1380, 1339, 1270, 1115, 1043, 923. *(5E)-3-Ethyl-2-(3-fluoro-4-morpholinophenylimino)-5-(2, 4, 6-trimethoxybenzylidene)thiazolidin-4-one* (**6o**): Yellow solid; mp: 133–135 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.34 (t, 3H, J = 7.0 Hz), 3.10 (t, 4H, J = 4.6 Hz), 3.89 (s, 9H), 3.89 (t, 4H, J = 4.6 Hz), 4.02 (q, 4H, J = 7.0 Hz), 6.07 (s, 2H), 6.72–6.94 (m, 3H), 7.98 (s, 1H); MS (*m*/*z*): 502.5 [M^++1]; IR (KBr): 2954, 2902, 2853, 2820, 2360, 2333, 1655, 1640, 1620, 1550,1369, 1118, 915. *(5E)-5-((1H-indol-3-yl) methylene)-3-ethyl-2-(3-fluoro-4-morpholinophenylimino)thiazolidin-4-one* (**6p**): Yellow solid; mp: 137–139 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.36 (t, 3H, J = 7.0 Hz), 3.11 (t, 4H, J = 4.4 Hz), 3.90 (t, 4H, J = 4.4 Hz), 4.05 (q, 2H, J = 7.0 Hz), 6.78–6.83 (m, 2H), 6.96 (t, 1H, J = 9.0 Hz), 7.28–7.32 (m, 2H), 7.42 (d, 1H, J = 7.6 Hz), 7.44 (m, d, 1H, J = 2.8 Hz), 7.85 (d, 1H, J = 7.6 Hz), 8.11 (s, 1H), 8.62 (bs, 1H, exchangeable with D_2O); MS (*m*/*z*): 451.5 [M^++1]; IR (KBr): 3403, 3174, 2955, 2891, 2837, 2700, 2360, 2251, 1701, 1633, 1602, 1114, 923.