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ORIGINAL ARTICLE

Design and effective synthesis of novel furo[2,3-d] pyrimidine derivatives containing ethylene ether spacers

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KEYWORDS

Alkyl isocyanide;
Furo[2,3-d]pyrimidine;
Ethylene ether spacer;
Arylidenebarbituric acid;
Antibacterial activity

Abstract [1 + 4] Cycloaddition reaction of ethylene ether-based *N*,*N*-dimethybenzylidenebarbituric acid with alkyl isocyanide in DMF produced novel high substituted furo[2,3-d]pyrimidine derivatives containing ether spacers under mild reaction conditions. The structures of the products were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. Good antibacterial activity was found in compound **5c**.

1. Introduction

It is well known that fused pyrimidine systems represent a very interesting class of compounds because of their diverse chemistry [1]. Also, they have many important biological properties such as antitumor and antibacterial [2–4], antimalarial [5] and antifolate activities [6]. Moreover, they are used as potential radiation protection agent [7]. Among these systems, furo [2,3-d]pyrimidine ring system is of biological interest; thus, these derivatives have been reported as the inhibitors of dihydrofolatereductase, thymidylate synthase, antitumor agents, antiprotozoan agents, antibacterial [8–10] and anti-HCMV (human cytomegalovirus) [11]. Also, some furo-pyrimidines were shown to be potent VEGFR2 (vascular endothelial growth factor receptor 2), EGFR (epidermal growth factor receptor) [12] and kinase [13–15] inhibitors.

Synthesis of furo-pyrimidines has received little attention and only few procedures have been reported in the literature [16–26], most of which rely on multi-step reactions with low yields. The existence of a lipophilic group in the furo-pyrimidine structure has been shown to improve the biological activity of these compounds [27,28]. Based on the above information, in the present investigation, a series of novel furo-pyrimidine derivatives containing hydrophobic ethylene ether spacers was designed and synthesized by the reaction of ethylene glycol-substituted benzylidenebarbituric acid with isocyanides.

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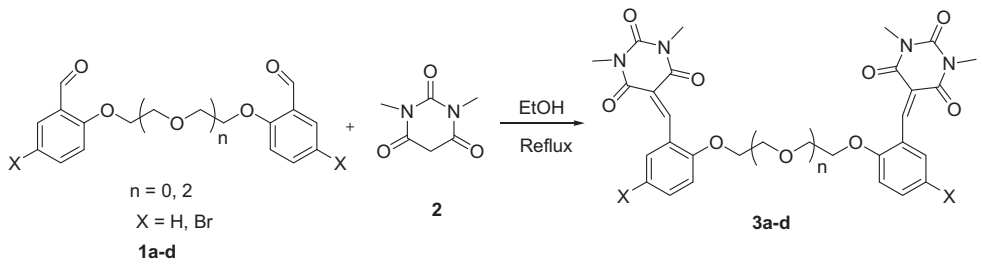


Scheme 1 Synthesis of benzylidenebarbituric derivatives containing ethylene ether spacers.

2. Experimental

2.1. General

Commercially available materials were used without further purification. Melting points were determined on an *Electrothermal 9100* apparatus and were uncorrected. IR spectra were obtained on an *ABB* FT-IR *FTLA 2000* spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on *Bruker*spectrometers at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. $CDCl_3$ and DMSO-d_6 were applied as solvents.

2.2. General procedure for the synthesis of benzylidenebarbituric acid derivatives containing ethylene ether spacers *3a–d*

A mixture of ethylene ether based dialdehyde derivatives **1a–d** (5 mmol) and barbituric acid derivatives **2** (10 mmol) in ethanol (10 mL) was heated at reflux for 4–5 h. Upon cooling, solid materials were precipitated from the solution. These precipitates were filtered off, washed with hot water, and recrystallized from EtOH to afford pure products **3a–d** [29].

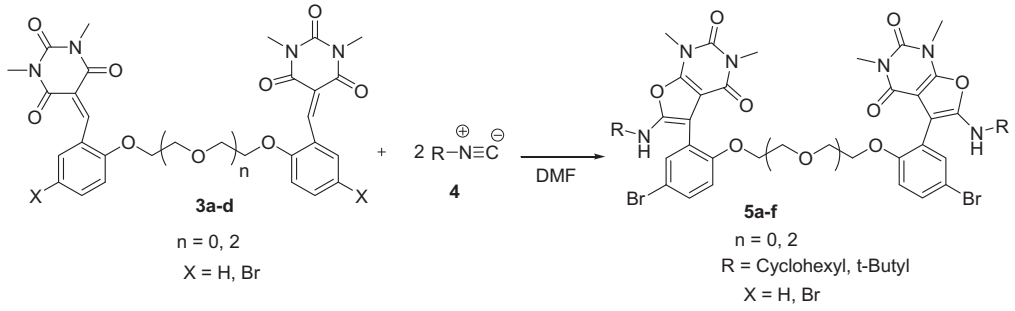
2.3. General procedure for the synthesis of furo-[2,3-d] pyrimidine derivatives containing ethylene glycol spacers *5a–f*

To the magnetically stirred benzylidenebarbituric derivatives (1 mmol) in DMF (10 mL), alkyl isocyanide (2 mmol) was added via a syringe and heated for 24-30 h at 50 °C. After the completion of the reaction (monitored by TLC), the solution was evaporated and diluted with H_2O and the precipitated solid product was recrystallized from water/acetone in several times.

1,2-Bis(*2-*(*6-*(*cyclohexylamino*)*-1,3-dimethylfuro[2,3-d]pyrimidine-2,4*(*1H,3H*)*-dione*)*phenoxy*)*ethane* ***5a***: Yield 53%. M.p. = 130 °C. IR (KBr, cm^{-1}): 3370, 1698, 1638. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.268–1.76 (m, 20H, 10CH_2), 3.18, 3.23, 3.18 and 3.30 (*s*, 12H, 4N–CH_3), 3.45–3.47 (m, 2H, NH), 3.77–3.79 (m, 2H, CH–N), 4.29 (t, J = 6.8 Hz, 2H, CH_2–O), 4.49 (t, J = 6.8 Hz, 2H, CH_2–O), 6.86–6.95 (m, 2H, H-arom.), 7.05 (t, J = 6.4 Hz, 2H, H-arom), 7.30–7.33 (m, 4H, H-arom. H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.3, 24.6, 25.5, 32.4, 32.6, 32.7, 48.8, 48.9, 66.4, 88.5, 110.4, 112.8, 120.9, 121.3, 121.4, 121.5, 121.6, 128.5, 129.8, 129.9, 130.7, 136.0, 155.3 and 155.8. Anal. Calc. for $C_{42}H_{48}N_6O_8$ (764.35): C, 65.95; H, 6.33; N, 10.99. Found: C, 66.46; H, 6.48; N, 11.36.

1,2-Bis(*4-bromo-2-*(*6-*(*cyclohexylamino*)*-1,3-dimethylfuro[2,3-d]pyrimidine-2,4*(*1H,3H*)*-dione*)*phenoxy*)*ethane* ***5b***: Yield 57%. M.p. = 73–78 °C. IR (KBr, cm^{-1}): 3364, 1679, 1621. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.14–1.93 (m, 20H, 10CH_2), 3.32–3.39 (m, 18H, 4N–CH_3, 2CH_2O, 2NH), 3.73–3.75 (m, 2H, CH–N), 6.67 (d, J = 8.4 Hz, 2H, H-arom), 7.15–7.19 (m, 2H, H-arom), 7.41 (d, J = 2.4 Hz, 2H, H-arom). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.4, 24.5, 25.2, 31.7, 32.2, 49.9, 77.2, 87.6, 112.4, 118.8, 127.2, 129.6, 129.7, 129.8, 3131.9, 153.4, 162.7. Anal. Calc. for $C_{42}H_{46}Br_2N_6O_8$ (920.17): C, 54.67; H, 5.03; N, 9.11. Found: C, 54.98; H, 5.33; N, 8.72.

1,2-Bis(*4-bromo-2-*(*6-*(*tert-butylamino*)*-1,3-dimethylfuro[2,3-d]pyrimidine-2,4*(*1H,3H*)*-dione*)*phenoxy*)*ethane* ***5c***: Yield 62%. M.p. = 218–222 °C. IR (KBr, cm^{-1}): 3344, 1681, 1632. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (s, 9H, *t*-but), 1.28 (s, 9H, *t*-but), 2.87 (*s*, 6H, 2N–CH_3), 2.94 (*s*, 6H, 2N–CH_3), 3.32 (s, 2H, NH), 4.33 (s, 4H, 2CH_2–O), 6.96 (d, J = 8.4, 2H, H-arom), 7.51 (br s, 2H, H-arom), 7.54 (dd, J = 8.4, 1.6 Hz, 2H, H-arom). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.1, 28.2, 28.3, 28.6, 51.5, 67.2, 112.8, 120.9, 121.3, 128.7, 130.8, 131.3, 133.9, 134.2, 161.7, 162.6. Anal. Calc. for $C_{38}H_{42}Br_2N_6O_8$ (868.14): C, 52.43; H, 4.86; N, 9.65. Found: C, 52.64; H, 4.73; N, 9.23.

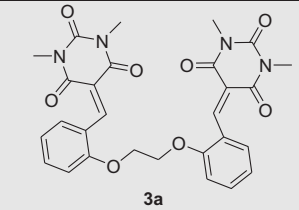
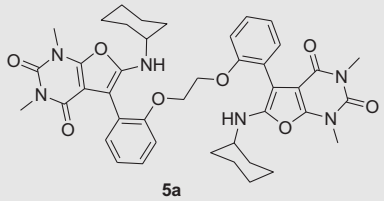
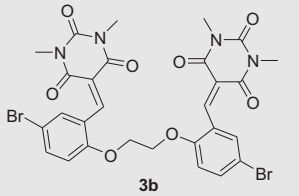
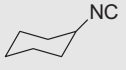
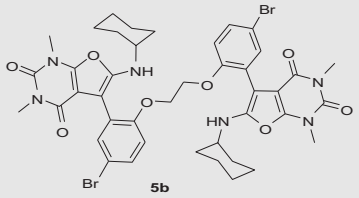
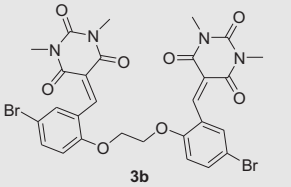
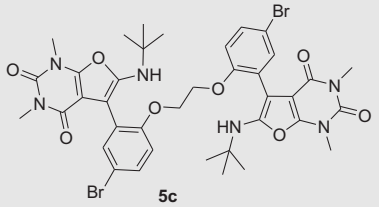
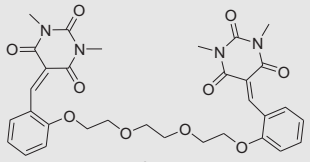
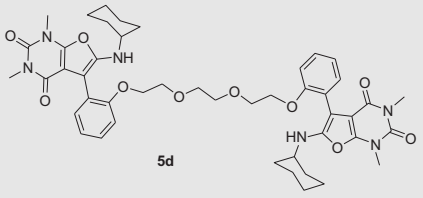
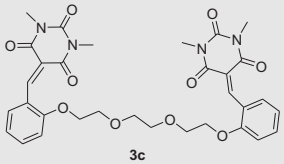
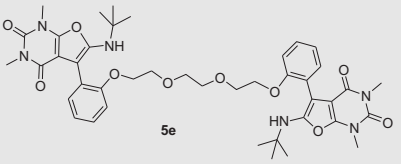
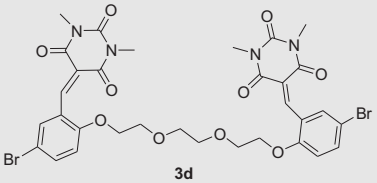
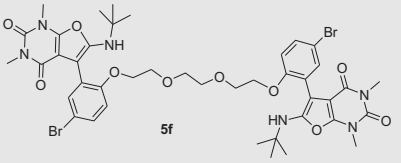


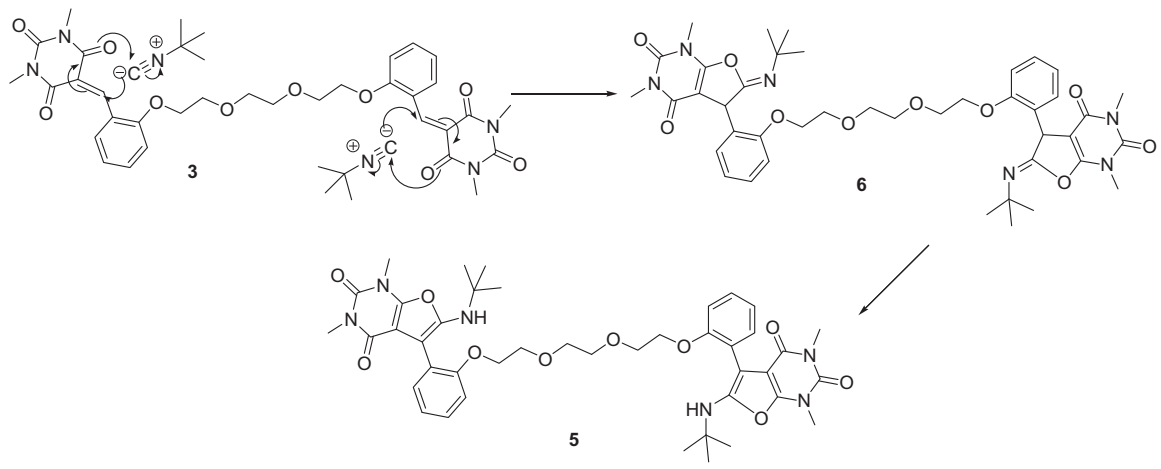
Scheme 2 Synthesis of furo-[2,3-d]pyrimidine derivatives containing ethylene ether spacers.

1,2-Bis(2-(2-(6-(cyclohexylamino)-1,3-dimethylfuro[2,3-d]pyrimidine-2,4(1H,3H)-dione)phenoxy)ethoxy)ethane ***5d***: Yield 46%. M.p. = 75–80 °C. IR (KBr, cm^{-1}): 3344, 1678. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.08–1.97 (m, 20H, $10CH_2$), 3.23 (m, 2H, CH–N), 3.31 (*s*, 6H, $2N–CH_3$), 3.37 (m, 2H, NH), 3.64 (*s*, 6H, $2N–CH_3$), 3.71–3.81 (m, 8H, $4CH_2–O$), 4.14–4.20 (m, 4H, $2CH_2–O$), 6.87 (*d*, *J* = 8.0 Hz, 2H, H-arom.), 7.0–7.04 (m, 4H, H-arom), 7.46 (*t*, *J* = 8.0 Hz, 2H, H-arom). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.7, 24.9, 25.0, 25.4, 27.9, 32.7, 32.8, 48.4, 48.5, 68.0, 69.4, 70.6, 70.8, 112.2, 112.3, 113.5, 120.7, 121.9, 128.1, 129.9, 131.0, 132.3, 134.3, 150.8, 156.8, 162.6. Anal. Calc. for $C_{46}H_{56}N_6O_{10}$ (852.41): C, 64.77; H, 6.62; N, 9.85. Found: C, 64.36; H, 6.86; N, 9.41.

1,2-Bis(2-(2-(6-(tert-butylamino)-1,3-dimethylfuro[2,3-d]pyrimidine-2,4(1H,3H)-dione)phenoxy)ethoxy)ethane ***5e***: Yield 50%. M.p. = 90–95 °C. IR (KBr, cm^{-1}): 3344, 1670 and 1630. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.22 (s, 18H, 2*t*-but), 3.29 (*s*, 6H, $2N–CH_3$), 3.47 (*s*, 6H, $2N–CH_3$), 3.60 (s, 2H, NH), 3.68 (t, *J* = 4.4 Hz, 4H, $2CH_2O$), 3.73–3.75 (m, 4H, $2CH_2–O$), 4.05–4.09 (m, 4H, $2CH_2–O$), 6.88 (d, *J* = 8.4 Hz, 2H, H-arom.), 6.99 (*t*, *J* = 7.4 Hz, 2H, H-arom). 7.19–7.21 (m, 2H, H-arom), 7.33–7.38 (m, 2H, H-arom). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.6, 29.3, 30.0, 54.0, 68.2, 69.6, 70.6, 96.0, 111.2, 112.7, 121.1, 128.8, 131.1, 132.8, 149.2, 150.6, 154.9, 155.9, 158.0. Anal. Calc. for $C_{42}H_{56}N_6O_{10}$ (800.37): C, 62.99; H, 6.54; N, 10.49. Found: C, 63.14; H, 6.66; N, 10.68.

Table 1 Synthesis of furo-[2,3-d]pyrimidine derivatives containing ethylene ether spacers.

Entry	benxylidenebarbituric acid **3**	isocyanide **4**	product **5**	Yield (%)
1	 **3a**	 **4a**	 **5a**	53
2	 **3b**	 **4a**	 **5b**	57
3	 **3b**	 **4b**	 **5c**	62
4	 **3c**	 **4a**	 **5d**	46
5	 **3c**	 **4b**	 **5e**	50
6	 **3d**	 **4b**	 **5f**	38



Scheme 3 Proposed mechanism.

1,2-Bis(2-(4-bromo-2-(6-(tert-butylamino)-1,3-dimethylfuro[2,3-d]pyrimidine-2,4(1H,3H)-dione)phenoxy)ethoxy)ethane ***5f***: Yield 38%. M.p. = 204–206 °C. IR (KBr, cm^{-1}): 3427, 1707 and 1665. ^1H NMR (400 MHz, DMSO-d_6) δ: 0.99 (s, 18H, 2*t*-but), 3.18 (*s*, 6H, 2N–CH_3), 3.40 (*s*, 6H, 2N–CH_3), 3.52 (br s, 4H, 2CH_2–O), 3.65 (br s, 4H, 2CH_2–O), 4.01 (br s, 4H, 2CH_2–O), 3.11 (s, 2H, NH), 7.04 (d, J = 8.8 Hz, 2H, H-arom), 7.43–7.45 (*m*, 2H, H-arom), 7.45 (d, J = 2.0 Hz, 2H, H-arom). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.7, 28.2, 29.1, 29.8, 53.2, 67.9, 68.7, 69.6, 111.4, 114.0, 122.0, 130.1, 134.0, 148.8, 149.9, 154.8, 157.2. Anal. Calc. for $C_{42}H_{50}Br_2N_6O_{10}$ (956.2): C, 52.62; H, 5.26; N, 8.77. Found: C, 52.94; H, 5.44; N, 9.01.

2.4. Antibacterial activity determination

In Vitro antibacterial activity of the 1,2-bis(4-bromo-2-(6-(tert-butylamino)-1,3-dimethylfuro[2,3-d]pyrimidine-2,4(1H,3H)-di one)phenoxy)ethane ***5c*** was investigated in different concentrations (6.25, 12.5, 25 and 50 mg/ml) against four pathogenic bacterial strains, two Gram-positive (*Staphylococcus aureus* and *Bacillus cereus*) and two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) by the agar disc diffusion method. Mueller-Hinton sterile agar plates (MHA) were seeded with bacterial strains (10^8 CFU/ml). Sterile 6-mm diameter filter paper discs were impregnated with different concentrations of the **5c** and were placed on to MHA medium [33]. After 18–24 h of incubation at 37 °C, the diameter of the clear zone around the disc was measured and expressed in millimetres as its antibacterial activity. Control experiments were carried out under similar conditions using Ceftriaxone, Tetracycline, Amoxycillin and Doxycycline for antibacterial activity as standard drugs. Each test was performed in triplicate.

3. Results and discussion

In connection with our previous work on the reaction of isocyanides with electron-deficient heterodienes (arylidene and alkylidene Meldrum's acid) [30–32], benzylidenebarbituric acid derivatives containing ethylene ether spacers were obtained from the reaction of dialdehyde 1 and *N*,*N*-dimethyl barbituric acid [29] (Scheme 1).

Then, treatment of 1,2-bis(2-(2-((tetrahydro-1,3-dimethyl-2,4,6-tri-oxopyrimidin-5(6H)-ylidene)methyl)phenoxy) ethoxy) ethane **3c** and cyclohexylisocyanide **4a** was selected as a model reaction in DMF at room temperature (Scheme 2).

The desired product **5d** was isolated in 46% yield (Table, Entry 4). Encouraged by this result, we turned our attention to other substituted **5** and isocyanides. Thus, all the ethylene ether based benzylidenebarbituric acid **3** and alkyl isocyanides **4** in DMF at room temperature underwent a smooth 1:2 cycloaddition reaction to give new furo[2,3-*d*]pyrimidine derivatives **5a–f** in 38–62% yields (Table 1, Scheme 2).

The structures of compounds **5a–f** were deduced from elemental analysis, IR, ^1H and ^{13}C NMR spectra. For example, the IR spectrum of compound **5e** had an absorption band cor-

Table 2 Antibacterial activity of **5c** against indicator bacterial strains.

Comp.	Microorganism	Inhibition zone in mm			
		6.25(mg/ml)	12.5(mg/ml)	25(mg/ml)	50(mg/ml)
5C	*S. aureus*	10 ± 0.577	15 ± 0.288	16 ± 0.763	20 ± 0.5
	E. coli	0	0	10 ± 0.577	15 ± 0.763
	P. aeruginosa	8 ± 0.288	11 ± 0.5	13 ± 0.288	17 ± 0.5
	B. cereus	8 ± 0.577	8 ± 0.577	9 ± 0.288	11 ± 0.288

±Standard deviation.

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Table 3 Antibacterial activity of the different antibiotics against indicator bacterial strains.

Microorganism	Inhibition zone in mm			
	Ceftriaxone	Amoxycillin	Doxycycline	Tetracycline
S. aureus	170 ± 0.577	16 ± 0.288	25 ± 0.5	20 ± 0.5
E. coli	22 ± 0.577	11 ± 0.288	0 ± 0	0 ± 0
P. aeruginosa	21 ± 0.288	0 ± 0	0 ± 0	0 ± 0
B. cereus	0 ± 0	0 ± 0	22 ± 0.288	15 ± 0.288

±Standard deviation.

responding to amine NH bond (3344 cm^{-1}), as well as bands characteristic of carbonyl functions (1670 and 1630).

The ^1H NMR spectrum of **5e** exhibited three single sharp lines readily recognized as arising from two tert-butyl (δ = 1.22 ppm) and two sets of N-methyl groups (δ = 3.29 and 3.47 ppm). It also showed a triplet (δ = 3.68) and two multiple signal (δ = 3.73–3.75 and δ = 4.05–4.09) for the methylene protons and singlet signal at δ = 3.60 ppm for the –NH moiety.

The synthesis of ethylene ether-based furo-pyrimidines **5** can be rationalized by initial formation of a conjugated electron-deficient heterodyne **3** by a Knoevenagel condensation of the *N*, *N*-dimethylbarbituric acid **2** and dialdehyde **1**. Then the [4 + 1] cycloaddition reaction of the electron-deficient heterodiene moiety of **3** (ethylene ether-based benzylidenebarbituric acid) with isocyanide **4** produced an iminolactone intermediate **6**. The subsequent isomerization of iminolactone **6** leads to formation of product **5** (see Scheme 3).

Antibacterial potential of **5c** was tested against bacterial strains and the results are presented in Table 2. The verification of antibacterial activity data revealed that **5c** has good bactericidal properties against *S. aureus*, *P. aeruginosa*, *E. coli*, and *B. cereus* bacterial strains. The antibacterial activity increased with increase in concentration of **5c**. The results regarding the antibacterial activity of the different antibiotics are indicated in Table 3.

The inhibition zone numbers are the average of three time independent experiments.

In conclusion reaction of ethylene ether-based benzylidenebarbituric acid derivatives with alky isocyanide in DMF without needing a catalyst, provides a convenient and efficient synthesis of furo[2,3-d]pyrimidine derivatives containing ethylene ether spacers. Having neutral condition, room temperature, easy procedure and reactions could make this technique a suitable synthesis method for new functionalized derivatives of furo-pyrimidines.1,2-Bis(4-bromo-2-(6-(tert-butylamino)-1, 3-dimethylfuro[2,3-d]pyrimidine-2,4(1H,3H) dione) phenoxy) ethane ***5c*** was found to possess good antibacterial activities.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jscs.2016.05.005.

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