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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Regioselective synthesis and antibacterial evaluation of novel bis-pyrimidine derivatives via a three-component reaction

Nosrat O. Mahmoodi · Sajede Shoja · Bahman Sharifzadeh · Mehdi Rassa

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Abstract A series of novel bis-2-phenylpyrimidines with alkyl linkages have been prepared by a three-component cyclo-condensation of benzamidine hydrochloride, β-keto-ester, and dihaloalkanes. The easy work-up of the products, rapid reaction, and mild conditions are notable features of this protocol. The reaction was efficiently catalyzed in one-pot by K_2CO_3 as a base in *N*,*N*-dimethylformamide under optimized temperature (70 °C) conditions providing the title compounds in moderate to high yields. The antibacterial activities of the selected products were evaluated against some strains of Gram-positive and Gram-negative bacteria. Biological data indicated that some products exhibit promising activities.

Keywords Three-component reaction · Antibacterial activity · Bis-pyrimidine · Benzamidine hydrochloride · β-ketoester

Introduction

The pyrimidine moiety turned out to be an important pharmacophor, interacting with the synthesis and function of nucleic acid like the cyctostaticum fluorouracil (Rosemeyer, 2004; Goette, 1981) or the anti-HIV drug zidovudine (Darbyshire *et al.*, 2004) or potent antioxidant agents. Short-acting barbiturates like thiopental sodium (pentothal) (Dordoni *et al.*, 2004) are frequently used as general anesthetics, while methylphenobarbital (Eadie and Hooper, 2002) even now is in use as antiepileptic.

A survey of literature in the recent past reveals that some pyrimidines are building blocks for pharmaceutical agents (Deshmukh *et al.*, 2009). They exhibit a wide spectrum of pharmacophore as it acts as microbicidal (Sedaghati *et al.*, 2012), antihypertensive (Winter *et al.*, 1962), anti-tumor and anticancer agents (Desai *et al.*, 2011; Becan and Wagner, 2013) and DNA replication in eukaryotic cells (Sawa and Masai, 2008). It can be suggested that the bis-pyrimidine compounds would consider as bis-drugs, and are estimated to be capable of double therapeutic behavior.

Influence and pharmacological properties of alkyl linkages in the mono, and bis-compounds have been reported (Maletic *et al.*, 2011; Levi *et al.*, 1989; Perrey *et al.*, 2000; Tanabe *et al.*, 2011). For example, recently the relationship between alkyl chain length and the antifungal (Sortino *et al.*, 2011), antimalarial (Fattorusso *et al.*, 2011), antitubercular (Gao *et al.*, 2013) and antibacterial (Xu *et al.*, 2009) activity have been described. In addition to these, role of alkyl chain in activity of ligands for α_1-adrenoceptor subtypes is studied (Romeo *et al.*, 2011). Also the effect of alkyl chain length on plasticizer and biodegradation properties was examined (Erythropel *et al.*, 2013).

Results and discussion

Chemistry

The most click procedure for the preparation of pyrimidinones has been reported by condensation of β-dicarbonyl compounds with the amidine or other analogs of them via

N. O. Mahmoodi (✉) · S. Shoja · B. Sharifzadeh
Department of Organic Chemistry, Faculty of Sciences, University of Guilan, PO Box 41335-1914, Rasht, Iran
e-mail: mahmoodi@guilan.ac.ir; nosmahmoodi@gmail.com

M. Rassa
Department of Biology, Faculty of Sciences, University of Guilan, PO Box 41335-1914, Rasht, Iran

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base catalyst (Spivey *et al.*, 2003). Literatures researching indicate that structural evaluations, properties, and synthetic routes toward bis-pyrimidines have not been reported.

Following our interest in synthesis of bis-intelligent compounds (Mahmoodi and Khodaee, 2004; Mahmoodi *et al.*, 2010, 2012; Rineh *et al.*, 2007; Kiyani *et al.*, 2009a, b; Ghavidast *et al.*, 2010; Zare *et al.*, 2011; Khodaee *et al.*, 2013), here we report synthesis of bis-pyrimidines capable of serving as bis-drugs. The reports that describing some lipophilicity bis-heterocyclic compounds compared to their mono-heterocyclic analogues will present superior medicinal and pharmacological activities (El-sharief and Moussa, 2009) prompted us to design and synthesis bis-pyrimidines **6a–i** contained alkyl linkages (Scheme 1). In general, lipophilicity is one of the most important parameter because it is mainly involved in pharmacokinetic processes such as absorption, distribution, metabolism, excretion, and toxicity and in ligand–target interactions (El-Baih *et al.*, 2006). Lipophilicity is the molecular factor of choice in several quantitative structure–activity relationships of diverse classes of compounds (Mosmann, 1983).

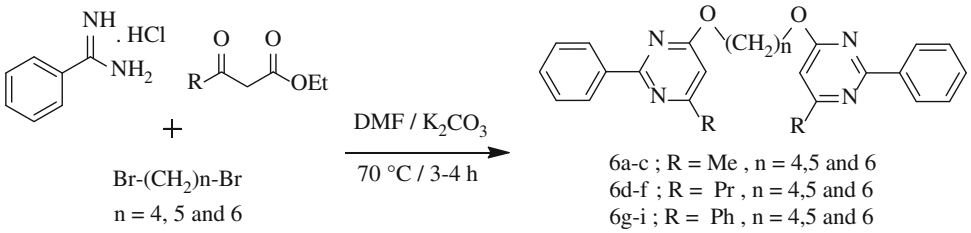
Intermolecular condensation of β-ketoester with benzamidine hydrochloride give intermediate (**2**) which subsequently eliminates H_2O to form intermediate (**3**) followed by intramolecular nucleophilic attack to the carbonyl group leading to the cyclic product (**4**) which subsequently undergoes EtOH elimination give the pyrimidinole ring of (**5**). The later on tautomerization gives a pyrimidinone ring (**5′**), and further reaction between (**5′**) via appropriate dihaloalkane in the presence of base in one-pot affords target product (**6**) (Scheme 2).

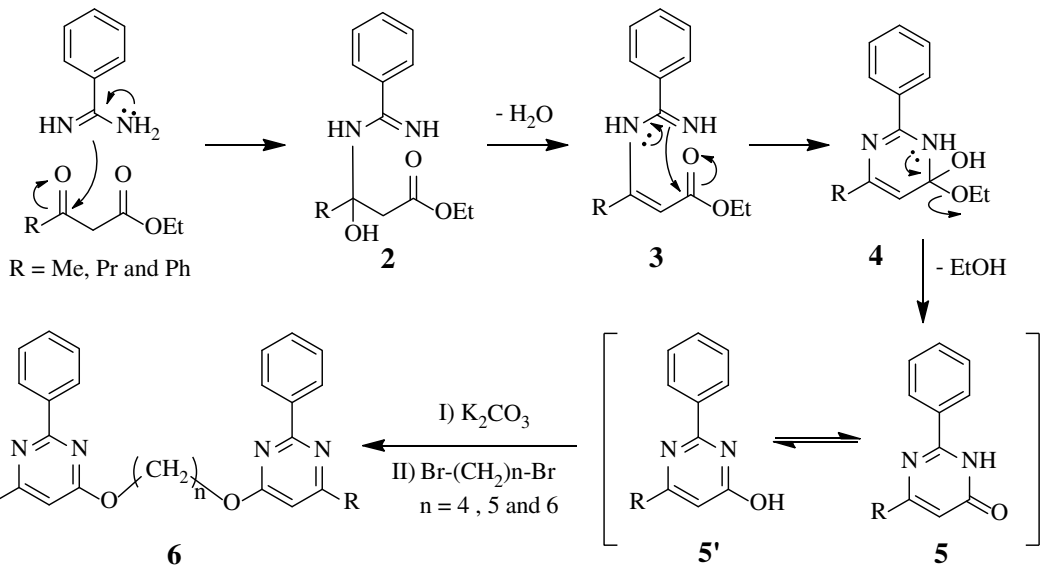
All of the compounds described in Scheme 1 were characterized by spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR) and elemental analysis.

The IR spectra of bis-pyrimidines derivatives **6a–i** revealed the presence of etheric C–O stretching vibration bands at υ 1,241–1,269 cm^{-1}, absorption bands in the 1,621–1,670 cm^{-1} region corresponding to endocyclic C=N stretching bands due to the ring closure, and peaks in the regions 1,467–1,491 and 1,592–1,620 cm^{-1} which indicate the presence of aromatic C=C groups.

The ^{1}H NMR spectra of bis-pyrimidines **6a–i** showed a sharp singlet at region δ 6–8 ppm due to the pyrimidine rings protons. The etheric –OCH_2 protons demonstrate a signal at δ 4.0–4.5 ppm as triplet for all of the compounds. Protons bound to the aromatic rings were observed within the expected chemical shift regions and exhibited the expected integral values.

Scheme1 Synthesis of bis-pyrimidines (**6a–i**)





Scheme 2 Proposed reaction mechanism for synthesis of (**6a–i**)

The ^{13}C NMR spectra of bis-pyrimidines **6a–i** showed signals at 161.1–172.3 ppm assigned to quaternary carbons (C2, C4, C6) of the pyrimidine ring. C5 Carbon of pyrimidine displayed a signal at 99.9–108.2 ppm for all of the compounds. The etheric carbons of bis-pyrimidines appeared as a signal in the region at 61.7–68.8 ppm in all of the compounds. The signals due to the aromatic and aliphatic carbon groups resonate at their usual positions (see the "Experimental" section).

Pharmacological screening

The in vitro antibacterial activities of compounds **6a–i** were evaluated against Gram-positive and Gram-negative bacteria using the cultures of five different standard microorganisms: *Escherichia coli* (*E. coli*) ATCC 25922 and *Salmonella enterica* (*S. enterica*) ATCC 13312 as Gram-negative models, and *Staphylococcus aureus* (*S. aureus*) ATCC 29213, *Bacillus subtilis* (*B. subtilis*) ATCC 29213 and *Micrococcus luteus* (*M. luteus*) ATCC 29213 as a Gram-positive model.

The results revealed that most of compounds **6a–i** exhibit strong activities toward *M. luteus*, *B. subtilis* (Gram-positive bacterium), and *S. enterica* (a Gram-negative bacterium). All of the compounds listed in Table 1 exhibit weak antimicrobial activities against *S. aureus* (a Gram-positive bacterium). Also the results indicate that compounds **6e**, **6f**, and **6i** have moderate growth-inhibiting activity against *E. coli*.

In fact, the weakness in some of the results in Table 1 is the biological point of view due to the following factors; (a) The target compound is not capable to penetrating to the membranous wall of bacteria; (b) Formation of an enzyme in bacteria that eliminate the drug compound; (c) Bacteria causing alter the part of structure itself, that drug compound must be affect on it.

Structure–activity relationships

All of the synthetic derivatives prepared in the course of this study have been evaluated for antibacterial activity against five different standard microorganisms. Results are reported in Table 1. In these bis-compounds, talk about this topic is a bit complicated. This issue is examined from two directions: influence of the modification of the substituents on pyrimidine ring; and influence of the variation of the length of the alkyl chain.

In general, it can be said that the alkyl linkage with higher "*n*" lead to longer distance between the phenyl groups, and better results can be seen; because of less steric hindrance. However, the effect of the other substituents on pyrimidine ring should not be ignored. For example **6f** showed strong activity against *M. luteus* and *B. subtilis*, while **6c** and **6i** exhibit undesirable result against these bacteria.

In other hand, the smaller size of drug compounds, because the more solubility in phospholipid, lead to greater penetration power to the membranous wall of the bacteria, and thus more favorable effect is observed. Of course the kind of bacteria is very decisive. For example **6a** and **6g** demonstrate strong activities against *M. luteus* and *B. subtilis*, while those activities against the *S. enterica* are not favorable. The activity of **6d** against these bacteria is not desirable too.

Table 1 Antimicrobial activity of the compounds (**6a–i**)

Entry	Compound	Conc. of compound in DMSO µg/0.1 mL	Antimicrobial activity (zone of inhibition in mm)				
			Gram-negative		Gram-positive		
			Escherichia coli	*Salmonella enterica*	*Staphylococcus aureus*	*Bacillus subtilis*	*Micrococcus luteus*
1	**6a**	12	–	9	–	16	–
2	**6b**	12	–	16	–	9	15
3	**6c**	12	–	13	–	10	–
4	**6d**	12	–	10	–	13	12
5	**6e**	12	10	–	–	13	14
6	**6f**	12	8	–	10	22	16
7	**6g**	12	–	–	–	16	18
8	**6h**	12	–	14	–	14	13
9	**6i**	12	13	12	–	11	12
10	Erythromycin	15	16	8	21	12	10
11	Tetracycline	30	12	7	23	14	16
12	DMSO	–	–	–	–	–	–

Experimental

Materials and equipments

Chemicals materials were purchased from Fluka, Merck, and Aldrich. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were determined on a Shimadzo IR-470 spectrometer. All ^{1}H NMR and ^{13}C NMR data were recorded in $CDCl_3$ using a Bruker Avance 400 and 100-MHz spectrometer. Chemical shifts are reported in ppm (δ) using deuterated solvents as internal references. Elemental analysis was made by a Carlo-Erba EA1110 CNNO-S analyzer and agreed with the calculated values.

*General procedure for the synthesis of 1,4-bis((6-alkyl or phenyl-2-phenylpyrimidin-4-yl)oxy) alkane derivatives (**6a–i**)*

A 25 mL round bottom flask was charged with benzamidine hydrochloride (31.7 mg, 0.203 mmol), β-ketoester derivatives (0.184 mmol), powdered K_2CO_3 (63.7 mg, 0.461 mmol), and a stir bar. The flask was sealed and charged with DMF (1.5 mL) followed by dihaloalkane (0.23 mmol). With vigorous stirring, the reaction mixture was heated to 70 °C for 2–4 h, and reaction progress was monitored by TLC. Upon completion of the reaction, the reaction mixture was diluted with EtOAc (10 mL), and washed with sat. aq $NaHCO_3$ (10 mL) and brine (10 mL). The combined aqueous phases were back-extracted with EtOAc (5 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuum to afford the title compound as near colorless oil that slowly solidified upon standing.

*1,4-Bis((6-methyl-2-phenylpyrimidin-4-yl)oxy)butane (**6a**)* Pale orange oil; yield 88 %; IR (ν_{max}/cm^{-1}): 3396, 2949, 2872, 1663, 1603, 1505, 1467, 1389, 1257, 882, 773, 680, 608; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.38 (d, 4H, Ar–H, $J = 8.0$ Hz), 7.75 (t, 4H, Ar–H, $J = 7.4$ Hz), 7.55 (t, 2H, Ar–H, $J = 7.8$ Hz), 6.20 (s, 2H, H5 of pyrimidine), 4.51 (t, 4H, –OCH_2–, $J = 10.4$ Hz), 2.55 (s, 6H, substituted-CH_3), 1.55 (t, 4H, –CH_2–, $J = 14.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 169.79 (C4 of pyrimidine), 166.97 (C6 of pyrimidine), 163.82 (C2 of pyrimidine), 128.63–133.26 (Ar–C), 100.61 (C5 of pyrimidine), 68.75 (OCH_2), 29.81 (CH_2), 28.10 (substituted-CH_3). Molecular weight: 426.52, Anal. calcd. for $C_{26}H_{26}N_4O_2$: C, 73.22; H, 6.14; N, 13.14 %. Found C, 73.18; H, 6.19; N, 13.17 %.

*1,5-Bis((6-methyl-2-phenylpyrimidin-4-yl)oxy)pentane (**6b**)* Yellow oli; yield 85 %; IR (ν_{max}/cm^{-1}): 3408, 2054, 2883, 1659, 1598, 1516, 1474, 1390, 1241, 879, 771, 672, 623; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.13 (d, 4H, Ar–H, $J = 8.8$ Hz), 7.74 (t, 4H, Ar–H, $J = 9.4$ Hz), 7.55 (t, 2H, Ar–H, $J = 7.8$ Hz), 6.17 (s, 2H, H5 of pyrimidine), 4.20 (t, 4H, –OCH_2–, $J = 11.6$ Hz), 2.50 (s, 6H, substituted-CH_3), 1.61–1.70 (m, 4H, –CH_2–), 1.39–1.49 (m, 2H, –CH_2–); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 169.92 (C4 of pyrimidine), 167.57 (C6 of pyrimidine), 166.75 (C2 of pyrimidine), 128.87–137.44 (Ar–C), 107.25 (C5 of pyrimidine), 61.74 (OCH_2), 29.93 (CH_2), 28.91 (substituted-CH_3), 24.33 (CH_2). Molecular weight: 440.55, Anal. calcd. for $C_{27}H_{28}N_4O_2$: C, 73.61; H, 6.41; N, 12.72 %. Found C, 73.62; H, 6.47; N, 12.70 %.

*1,6-Bis((6-methyl-2-phenylpyrimidin-4-yl)oxy)hexane (**6c**)* Orange oil; yield 89 %; IR (ν_{max}/cm^{-1}): 3411, 2962, 2890, 1668, 1602, 1514, 1491, 1420, 1244, 893, 776, 679, 628; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.44 (d, 4H, Ar–H, $J = 9.2$ Hz), 7.69 (t, 4H, Ar–H, $J = 7.4$ Hz), 7.55 (t, 2H, Ar–H, $J = 7.8$ Hz), 6.19 (s, 2H, H5 of pyrimidine), 4.29 (t, 4H, –OCH_2–, $J = 11.2$ Hz), 2.16 (s, 6H, substituted-CH_3), 1.61–1.70 (m, 4H, –CH_2–), 1.45 (t, 4H, –CH_2–, $J = 12.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 169.95 (C4 of pyrimidine), 167.67 (C6 of pyrimidine), 163.82 (C2 of pyrimidine), 127.40–137.78 (Ar–C), 104.64 (C5 of pyrimidine), 64.14 (OCH_2), 29.30 (CH_2), 24.11 (substituted-CH_3), 21.73 (CH_2), Molecular weight: 454.57, Anal. calcd. for $C_{28}H_{30}N_4O_2$: C, 73.98; H, 6.65; N, 12.33 %. Found C, 73.96; H, 6.66; N, 12.34 %.

*1,4-Bis((2-phenyl-6-propylpyrimidin-4-yl)oxy)butane (**6d**)* Deep yellow oil; yield 79 %; IR (ν_{max}/cm^{-1}): 3407, 2958, 2877, 1658, 1612, 1503, 1476, 1401, 1269, 891, 786, 684, 623; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.44 (d, 4H, Ar–H, $J = 9.2$ Hz), 7.58–7.79 (m, 6H, Ar–H), 6.02 (s, 2H, H5 of pyrimidine), 4.02 (t, 4H, –OCH_2–, $J = 11.0$ Hz), 2.53 (t, 4H, –CH_2–, $J = 12.8$ Hz), 1.49–1.87 (m, 8H, –CH_2–), 0.86 (t, 6H, –CH_3 of substituted Pr, $J = 14.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 172.31 (C4 of pyrimidine), 172.06 (C6 of pyrimidine), 168.24 (C2 of pyrimidine), 129.12–134.18 (Ar–C), 102.57 (C5 of pyrimidine), 67.83 (OCH_2), 43.48 (CH_2), 27.21 (CH_2), 22.14 (CH_2), 19.43 (CH_3 of substituted Pr); Molecular weight: 482.63, Anal. calcd. for $C_{30}H_{34}N_4O_2$: C, 74.66; H, 7.10; N, 11.61 %. Found C, 74.64; H, 7.12; N, 11.65 %.

*1,5-Bis((2-phenyl-6-propylpyrimidin-4-yl)oxy)pentane (**6e**)* Yellow oil; yield 76 %; IR (ν_{max}/cm^{-1}): 3405, 2942, 2879, 1670, 1620, 1501, 1479, 1421, 1269, 902, 790, 674, 623; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.65 (d, 4H, Ar–H, $J = 9.2$ Hz), 7.76 (t, 4H, Ar–H, $J = 8.0$ Hz), 7.56 (t, 2H, Ar–H, $J = 8.2$ Hz), 6.09 (s, 2H, H5 of pyrimidine), 4.02 (t, 4H, –OCH_2–, $J = 10.2$ Hz), 2.70 (t, 4H, –CH_2–, $J = 12.6$ Hz), 1.33–1.82 (m, 10H, –CH_2–), 0.95 (t, 6H,

–CH_3 of substituted Pr, J = 14.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 168.15 (C4 of pyrimidine), 167.23 (C6 of pyrimidine), 162.29 (C2 of pyrimidine), 129.67–135.98 (Ar–C), 99.98 (C5 of pyrimidine), 65.91 (OCH_2), 44.66 (CH_2), 29.31 (CH_2), 22.13 (CH_2), 21.04 (CH_2), 12.19 (CH_3 of substituted Pr); Molecular weight: 496.65, Anal. calcd. for $C_{31}H_{36}N_4O_2$: C, 74.97; H, 7.31; N, 11.28 %. Found C, 74.96; H, 7.32; N, 11.26 %.

1,6-Bis((2-phenyl-6-propylpyrimidin-4-yl)oxy)hexane ***(6f)*** Pale orange oil; yield 81 %; IR (ν_{max}/cm^{-1}): 3419, 2951, 2921, 1646, 1596, 1509, 1480, 1400, 1259, 788, 669, 617; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.66 (d, 4H, Ar–H, J = 8.8 Hz), 7.62–7.79 (m, 6H, Ar–H), 6.09 (s, 2H, H5 of pyrimidine), 4.03 (t, 4H, –OCH_2–, J = 12.4 Hz), 2.73 (t, 4H, –CH_2–, J = 14.0 Hz), 1.88–1.96 (m, 4H, –CH_2–), 1.38–1.50 (m, 8H, –CH_2–), 0.95 (t, 6H, –CH_3 of substituted Pr, J = 14.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 171.93 (C4 of pyrimidine), 169.98 (C6 of pyrimidine), 164.13 (C2 of pyrimidine), 129.09–133.28 (Ar–C), 100.33 (C5 of pyrimidine), 68.89 (OCH_2), 45.02 (CH_2), 29.87 (CH_2), 28.93 (CH_2), 25.46 (CH_2), 18.75 (CH_3 of substituted Pr); Molecular Weight: 510.68, Anal. calcd. for $C_{32}H_{38}N_4O_2$: C, 75.26; H, 7.50; N, 10.97 %. Found C, 75.24; H, 7.54; N, 10.95 %.

1,4-Bis((2,6-diphenylpyrimidin-4-yl)oxy)butane ***(6g)*** Cream oil; yield 71 %; IR (ν_{max}/cm^{-1}): 3336, 2962, 2591, 1657, 1609, 1504, 1479, 1250, 783, 675, 628; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.00 (d, 4H, Ar–H, J = 7.6 Hz), 7.83 (d, 4H, Ar–H, J = 8.8 Hz), 7.56–7.63 (m, 8H, Ar–H), 7.37–7.44 (m, 6H, Ar–H and H5 of pyrimidine), 4.06 (t, 4H, –OCH_2–, J = 10.8 Hz), 2.07–2.12 (m, 4H, –CH_2–); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 170.19 (C4 of pyrimidine), 168.10 (C6 of pyrimidine), 167.22 (C2 of pyrimidine), 128.17–137.38 (Ar–C), 100.91 (C5 of pyrimidine), 62.04 (OCH_2), 29.42 (CH_2); Molecular weight: 550.66, Anal. calcd. for $C_{36}H_{30}N_4O_2$: C, 78.52; H, 5.49; N, 10.17 %. Found C, 78.50; H, 5.44; N, 10.16 %.

1,5-Bis((2,6-diphenylpyrimidin-4-yl)oxy)pentane ***(6h)*** Pale yellow oil; yield 69 %; IR (ν_{max}/cm^{-1}): 3393, 2942, 2874, 1651, 1592, 1509, 1480, 1247, 886, 778, 679, 603; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 8.00 (d, 4H, Ar–H, J = 7.6 Hz), 7.82 (d, 4H, Ar–H, J = 8.8 Hz), 7.52–7.56 (m, 8H, Ar–H), 7.36–7.43 (m, 6H, Ar–H and H5 of pyrimidine), 4.07 (t, 4H, –OCH_2–, J = 10.2 Hz), 1.82–1.91 (m, 4H, –CH_2–), 1.59–1.67 (m, 2H, –CH_2–); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 170.12 (C4 of pyrimidine), 168.03 (C6 of pyrimidine), 161.14 (C2 of pyrimidine), 128.97–137.93 (Ar–C), 108.22 (C5 of pyrimidine), 65.09 (OCH_2), 36.18 (CH_2), 29.26 (CH_2); Molecular weight: 564.69, Anal. calcd. for $C_{37}H_{32}N_4O_2$: C, 78.70; H, 5.71; N, 9.92 %. Found C, 78.68; H, 5.70; N, 9.91 %.

1,6-Bis((2,6-diphenylpyrimidin-4-yl)oxy)hexane ***(6i)*** Cream oil; yield 74 %; IR (ν_{max}/cm^{-1}): 3390, 2958, 2881, 1667, 1610, 1503, 1472, 1265, 898, 768, 686, 615; ^{1}H NMR (400 MHz, $CDCl_3$) (δ/ppm): 7.99 (d, 4H, Ar–H, J = 6.4 Hz), 7.83 (d, 4H, Ar–H, J = 8.8 Hz), 7.38–7.59 (m, 14H, Ar–H and H5 of pyrimidine), 4.06 (t, 4H, –OCH_2–, J = 11.6 Hz), 2.06–2.12 (m, 4H, –CH_2–), 1.66–1.72 (m, 4H, –CH_2–); ^{13}C NMR (100 MHz, $CDCl_3$) (δ/ppm): 170.09 (C4 of pyrimidine), 166.98 (C6 of pyrimidine), 162.54 (C2 of pyrimidine), 128.79–138.97 (Ar–C), 106.11 (C5 of pyrimidine), 62.51 (OCH_2), 37.88 (CH_2), 22.75 (CH_2); Molecular weight: 578.72, Anal. calcd. for $C_{38}H_{34}N_4O_2$: C, 78.87; H, 5.92; N, 9.68 %. Found C, 78.86; H, 5.91; N, 9.67 %.

Antibacterial activity

A sterilized glass tube (5 mm diameter) was used aseptically to make wells on plates. The antibacterial activity of compounds was assayed biologically using the Agar well-diffusion method. A colony of each standard test organism was sub-cultured in order to obtain fresh bacteria on the nutrient agar plates at 37 °C for 18 h. To preparations of suspensions of microorganisms (0.5 McFarland), one to two colonies from each plate was dissolved in isotonic saline solution. Then Mueller–Hinton agar (Merck) plates were prepared according to manufacturers' instructions in order to evaluate the antibacterial activities of compounds. The sterile Mueller–Hinton agar plates were inoculated with the bacteria.

0.01 g of test samples was dissolved in 1 mL dimethyl sulfoxide (DMSO) to obtain a stock solution. A concentration of 1 mg/mL or 100 µg/0.1 mL of each sample was prepared. 0.1 mL of prepared samples was dropped into each respective labeled well aseptically. The inoculated plates were left on the table for 1 h to allow the each sample to diffuse into the agar. For comparison, erythromycin and tetracycline were used as a positive control and DMSO as a negative control. Test organism growth may be affected by the inhibitory action of the test compound and so, a clear zone around the disk appeared as an indication of the inhibition of the test organism growth. The results of our tests were presented as the inhibition zones, given in millimeters (mm). Measurements were obtained after 24 h for bacteria.

Conclusion

In conclusion, this three-component, one-pot protocol for first time provides a regioselective, fast, and practical

method for the preparation of novel 1,4-bis((6-alkyl or phenyl-2-phenylpyrimidin-4-yl)oxy)alkane from a variety of benzamidine hydrochloride, β-ketoester, and dihaloalkanes in good yields. This allows the rapid assessment of pharmacological activities of these novel bis-pyrimidine derivatives. The simplicity, high atom economy, easy execution, simple workup, and good yields, together with the use of inexpensive starting materials and an environmentally friendly procedure, are features of this procedure. Most of the compounds prepared as part of this study exhibited good antibacterial activity against *M. luteus*, *B. subtilis* and *S. enterica*.

Supporting information

This file demonstrates the FT-IR, ^{1}H NMR, and ^{13}C NMR spectra of compounds **6a–i**.

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