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Research article

One-pot multi-component synthesis of new bis-pyridopyrimidine and bis-pyrimidoquinolone derivatives

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ABSTRACT

A variety of bis-heterocycles such as bis(pyrimido[4,5-*b*]quinolone), bis(chromeno[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine), bis(pyrido[2,3-*d*:6,5-*d*′]dipyrimidine), and bis(benzo[*g*]pyrimido[4,5-*b*]quinolone) derivatives were synthesized *via* one-pot, multi-component reaction of various 6-aminouracils or 6-aminothiouracils, terephthalaldehyde, and CH-acids such as 4-hydroxycoumarin, dimedone, 2-hydroxy-1,4-naphthoquinone, barbituric acid, and thiobarbituric acid in EtOH as a solvent at reflux. The mild conditions, fast rate of reaction, absence of catalyst, different functional group compatibility, simple operation and work-up involving no chromatographic process, are worth mentioning.

1. Introduction

Multi-component reactions (MCRs) have regarded as essential tools for the preparation of biologically active heterocyclic compounds because of their productivity, convergence, simple procedures, and easy execution [1]. The development of MCRs and their applications for the one-pot synthesis of various useful heterocyclic compounds are of remarkable interest in the running research articles [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13].

Heterocyclic scaffolds are widely distributed in nature and used in structure-based drug design [14]. Therefore, considerable attention has been paid to develop novel approaches to the synthesis of heterocycles [15, 16, 17, 18, 19, 20, 21, 22]. Among them pyridopyrimidine derivatives have attracted wide attention due to their broad biological activities including anticancer [23], antiviral [24], antiallergic [25], anti-HIV [26], anti-inflammatory [27], and antifolate [28] properties; and pyrimidoquinoline derivatives are of importance because of their interesting and diverse pharmacological properties; such as, antimicrobial, anti-inflammatory, anticancer [29], antiallergic [30], anti-HIV, antimalarial [31], and antibacterial [32] activities. Some biologically important pyridopyrimidines [33] and pyrimidoquinolines [34] are shown in Figure 1.

Also some bis-heterocyclic compounds exhibit a wide range of biological and pharmacological activities and have received extensive attention in recent decades [35, 36]. In 2013 Nefzi and Murru prepared a new library of oxazol-thiazole bis-heterocycles by a solution and solid-phase parallel synthesis methodology in good to excellent yields.[38] Also in 2016 Montano et al. reported synthesis of novel unsymmetrical bis-heterocycles containing the imidazo[2,1-*b*]thiazole or the benzo[*d*]imidazo[2,1-*b*]thiazole frameworks bound with quinolone, chromone, or julolidine *via* an acid-free Groebke-Blackburn-Bienayme reaction (GBBR) under microwave-heating conditions in good to excellent yields [36].

As part of our continuing interest in the preparation of novel heterocyclic compounds and due to importance of pyridopyrimidine and pyrimidoquinoline derivatives as substructures in a wide range of drug-like compounds, herein we developed synthesis of new bis-pyridopyrimidines and bis-pyrimidoquinolones by one-pot, multi-component reaction of diverse 6-aminouracils, terephthalaldehyde, and CH-acids in EtOH as a solvent at reflux without a catalyst.

2. Experimental

2.1. Reagent and apparatus

The diverse 6-aminouracils, 6-aminothiouracil, terephthalaldehyde, 4-hydroxycoumarin, dimedone, 2-hydroxy-1,4-naphthoquinone, barbituric acid, thiobarbituric acid, and solvents were purchased from Sigma-Aldrich chemical company and were used as received without further purification. Melting points were measured with an electrothermal 9100 apparatus. Infrared (IR) spectra were obtained on a Bruker Tensor 27 spectrometer. Mass spectra recorded with an Agilent 5975C VL MSD with Triple-Axis Detector operating at an ionization potential of 70 eV.

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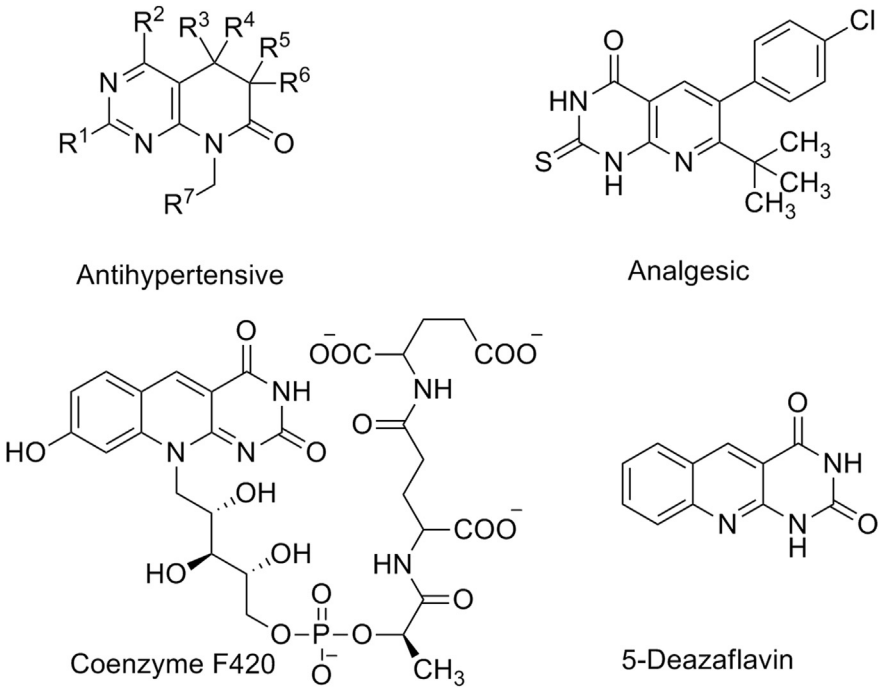


Figure 1. Some biologically important pyridopyrimidines and pyrimidoquinolines.

Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker DRX-300 Avance instrument (300 MHz for ^{1}H, 68.8 and 125 MHz for ^{13}C) with DMSO as solvent. Chemical shifts are given in parts per million (ppm), and coupling constant (*J*) are reported in hertz (Hz).

2.2. General procedure for the synthesis of product 4a

A mixture of 6-aminothiouracil (2 mmol, 0.286 g), terephthalaldehyde (1 mmol, 0.134 g), 2-hydroxy-1,4-naphthoquinone (2 mmol, 0.348 g) and 10 mL EtOH in a 50 mL flask was stirred at reflux for 5 min. Upon completion as monitored by TLC (ethyl acetate/n-hexane, 1:1), the reaction mixture was cooled to room temperature and filtered to give the crude product. The resulting solid product was washed with EtOH to give pure product **4a** in 76% yields.

2.3. Spectral data

2.3.1. 7,7'-(1,4-Phenylene)bis(10-thioxo-9,10,11,12-tetrahydro-6H-chromeno[3',4':5,6]pyrido[2,3-d]pyrimidine-6,8(7H)-dione) (4a)

White solid: M.p.: 300–302 °C, yield: 0.510 g (76%). IR (KBr) (ν_{max}/cm^{-1}): 3340, 3220, 1680, 1650, 1220. MS (EI, 70 eV): *m/z* (%) = 378 (19), 266 (24), 155 (100), 120 (39), 82 (88), 57 (38). ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.52 (2H, s, 2CH), 6.74–7.79 (12H, m, Ar), 12.13 (2H, s, 2NH), 12.45 (2H, s, 2NH), 13.49 (2H, s, 2NH). ^{13}C NMR (62.8 MHz, DMSO-d_6): δ 35.8 (CH), 92.2 (CC = ONH), 106.3 (CC = OO), 117.5, 118.4, 125.0, 125.6, 127.7, 133.7, 136.7, 153.3, 155.7, 164.6, 165.9 (C=O), 166.5 (C=O), 174.1 (C=S).

2.3.2. 7,7'-(1,4-Phenylene)bis(11,12-dihydro-6H-chromeno[3',4':5,6]pyrido[2,3-d]pyrimidine-6,8,10(7H,9H)-trione) (4b)

White solid: M.p.: 305–307 °C, yield: 0.435 g (68%). %). IR (KBr) (ν_{max}/cm^{-1}): 3320, 3200, 1687, 1650, 1215. MS (EI, 70 eV): *m/z* (%) = 251 (5), 162 (74), 120 (100), 92 (88), 63 (30). ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.46 (2H, s, 2CH), 6.60–7.80 (12H, m, Ar), 10.72 (2H, s, 2NH), 11.02 (2H, s, 2NH), 14.05 (2H, s, 2NH). ^{13}C NMR (62.8 MHz, DMSO-d_6): δ 35.7 (CH), 87.5 (CC = ONH), 106.6 (CC = OO), 117.5, 118.6, 125.0, 125.6, 127.6, 133.6, 137.2, 150.7, 153.3, 156.8, 164.8 (C=O), 166.8 (C=O), 168.3 (C=O).

2.3.3. 7,7'-(1,4-Phenylene)bis(9,11-dimethyl-11,12-dihydro-6H-chromeno[3',4':5,6]pyrido[2,3-d]pyrimidine-6,8,10(7H,9H)-trione) (4c)

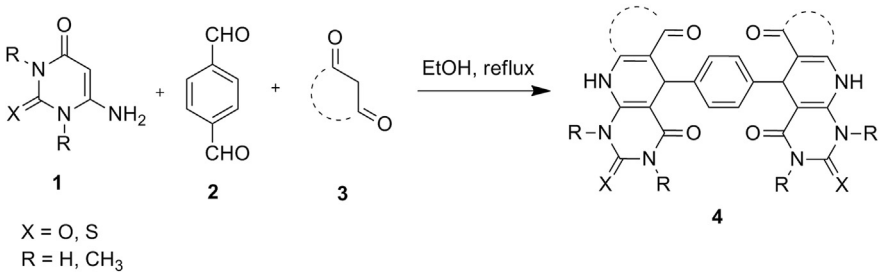
White solid: M.p.: 304–306 °C, yield: 0.508 g (73%). IR (KBr) (ν_{max}/cm^{-1}): 3426, 3328, 3212, 1704, 1653, 1618, 1199. MS (EI, 70 eV): *m/z* (%) = 404 (40), 292 (20), 180 (26), 155 (97), 120 (100), 82 (74), 57 (39). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.10 (6H, s, 2NCH$_3$), 3.12 (6H, s, 2NCH$_3$), 3.34 (6H, s, 2NCH$_3$), 3.36 (6H, s, 2NCH$_3$), 5.52 (4H, s, 4CH), 6.93–7.81 (24H, m, Ar), 13.98 (4H, s, 4NH). ^{13}C NMR (62.8 MHz, DMSO-d_6): δ 29.6 (NCH$_3$), 31.9 (NCH$_3$), 31.3 (NCH$_3$), 37.1 (CH), 38.0 (CH), 88.1 (CC = ONCH$_3$), 92.4 (CC = ONCH$_3$), 105.2 (CC = OO), 106.1 (CC = OO), 117.0, 117.5, 118.3, 120.3, 124.6, 125.0, 125.6, 127.2, 127.6, 128.7, 130.8, 132.7, 133.8, 135.9, 137.0, 138.3, 139.8, 147.5, 151.5, 151.9, 153.3, 153.7, 156.5, 165.1 (C=O), 165.5 (C=O), 166.1 C=O), 167.1 (C=O), 167.5 (C=O).

2.3.4. 5,5'-(1,4-Phenylene)bis(8,8-dimethyl-2-thioxo-2,3,7,8,9,10-hexahydropyrimido[4,5-b]quinoline-4,6(1H,5H)-dione) (4d)

White solid: M.p.: 331–333 °C, yield: 0.496 g (79%). %). IR (KBr) (ν_{max}/cm^{-1}): 3300, 1710, 1680, 1230. MS (EI, 70 eV): *m/z* (%) = 378 (100), 295 (16), 266 (46), 240 (24), 143 (45), 97 (29), 83 (63), 69 (94), 57 (52). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.99 (12H, s, 4CH$_3$), 1.05 (12H, s, 4CH$_3$), 2.24–2.39 (16H, m, 4CH$_2$), 5.32 (4H, s, 4CH), 6.57 (4H, s, Ar), 6.91 (4H, s, Ar), 12.01 (4H, s, 4NH), 12.25 (8H, s, 8NH). ^{13}C NMR (62.8 MHz, DMSO-d_6): δ 28.0 (CH$_3$), 28.3 (CH$_3$), 29.3 (C(CH$_3$)$_2$), 30.1 (C(CH$_3$)$_2$), 32.5 (CH), 33.7 (CH), 51.5 (CH$_2$), 93.5 (CC = ONH), 95.5 (CC = ONH), 112.5, 115.3, 127.3, 127.5, 128.4, 128.6, 129.9, 130.7, 137.4, 138.2, 144.1, 144.9, 150.1, 155.2, 161.5 (C=O), 165.4 (C=O), 174.1 (C=S), 174.7 (C=S), 195.8 (C=O).

2.3.5. 5,5'-(1,4-Phenylene)bis(1,3,8,8-tetramethyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H)-trione) (4e)

White solid: M.p.: 273–275 °C, yield: 0.554 g (85%). %). IR (KBr) (ν_{max}/cm^{-1}): 3360, 3190, 1718, 1689, 1240. MS (EI, 70 eV): *m/z* (%) = 378 (21), 266 (23), 155 (86), 127 (16), 82 (100), 57 (50). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.00 (6H, s, 2CH$_3$), 1.07 (6H, s, 2CH$_3$), 2.18–2.41 (8H, m, 4CH$_2$), 3.06 (6H, s, 2NCH$_3$), 3.25 (6H, s, 2NCH$_3$), 5.38 (2H, s, 2CH), 6.92 (2H, s, Ar), 7.25 (2H, s, Ar), 12.80 (2H, s, 2NH). ^{13}C NMR (62.8 MHz, DMSO-d_6): δ 28.5 (CH$_3$), 29.4 (CH$_3$), 30.2 (CH$_3$), 31.7 (NCH$_3$), 32.5

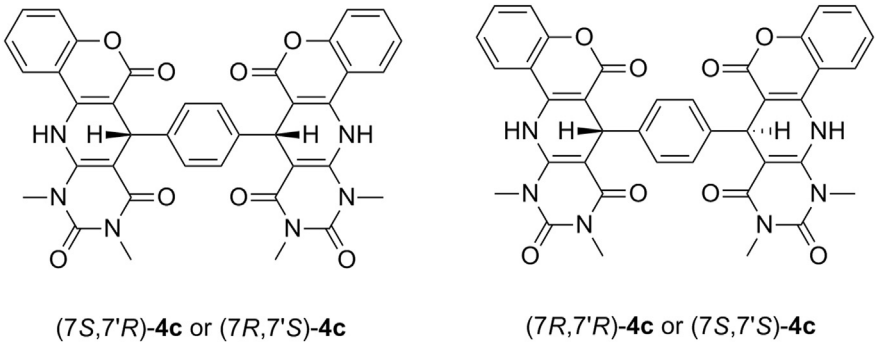


Scheme 1. Synthetic scheme for the product **4**.

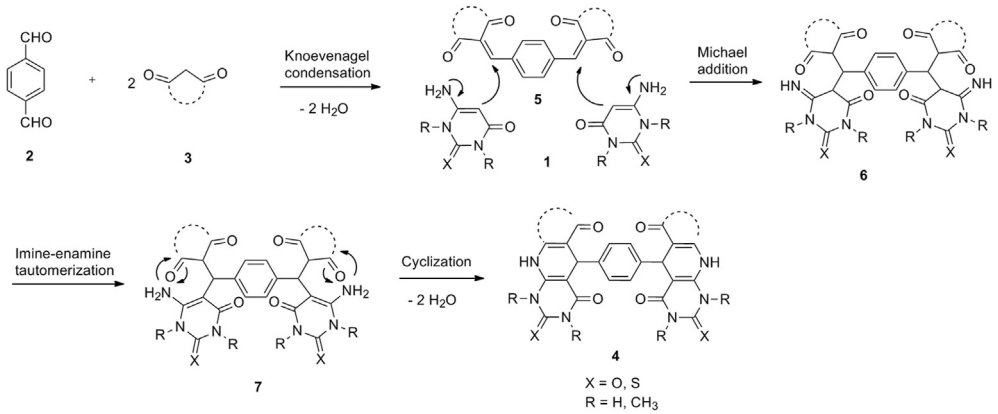
Table 1. One-pot, multi-component synthesis of bis-heterocycles **4a-j**.

Entry	Aminouracil[a]	CH-acid[a]	Product	Time (min)	Yield (%)
1	6-Aminothiouracil	2-Hydroxy-1,4-naphthoquinone	**4a**	5	76
2	6-Aminouracil	4-Hydroxycoumarin	**4b**	5	68
3	6-Amino-1,3-dimethyluracil	4-Hydroxycoumarin	**4c**	5	73
4	6-Aminothiouracil	Dimedone	**4d**	10	79
5	6-Amino-1,3-dimethyluracil	Dimedone	**4e**	10	85
6	6-Aminouracil	Dimedone	**4f**	30	65
7	6-Aminouracil	Thiobarbituric acid	**4g**	5	90
8	6-Aminouracil	Barbituric acid	**4h**	20	70
9	6-Amino-1,3-dimethyluracil	Barbituric acid	**4i**	20	72
10	6-Amino-1,3-dimethyluracil	2-Hydroxy-1,4-naphthoquinone	**4j**	10	69

[a] Various 6-aminouracils (2 mmol), terephthalaldehyde (1 mmol), and CH-acids (2 mmol) were used in EtOH at reflux, without any catalyst.



Scheme 2. The two diastereoisomers of **4c**.



Scheme 3. Proposed mechanism for the formation of product **4**.

(NCH_3), 33.6 ($C(CH_3)_2$), 34.0 (CH), 45.0 (CH_2), 50.9 (CH_2), 89.2 (CC = $ONCH_3$), 115.2, 115.3, 127.1, 127.4, 128.6, 138.0, 151.6, 151.9, 156.0, 161.1 (C=O), 177.3 (C=S), 200.8 (C=O).

2.3.6. 5,5'-(1,4-Phenylene)bis(8,8-dimethyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H)-trione) (4f)

White solid: M.p.: 348–350 °C, yield: 0.408 g (65%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.83 (6H, s, $2CH_3$), 0.86 (6H, s, $2CH_3$), 0.97 (12H, s, $4CH_3$), 1.98–2.40 (16H, m, $8CH_2$), 4.65 (2H, s, 2CH), 4.67 (2H, s, 2CH), 6.16 (2H, s, Ar), 6.95 (6H, s, Ar), 8.69 (4H, s, 4NH), 10.14 (4H, s, 4NH), 10.67 (4H, s, 4NH).

2.3.7. 5,5'-(1,4-Phenylene)bis(8-thioxo-7,8,9,10-tetrahydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6(1H,3H,5H)-trione) (4g)

Orange solid: M.p.: >360 °C, yield: 0.544 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 3172, 1701, 1618, 1209. MS (EI, 70 eV): *m/z* (%) = 407 (2), 379 (3), 279 (6), 183 (7), 149 (38), 111 (34), 85 (61), 57 (100), 43 (92). ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.22 (2H, s, 2CH), 6.65 (2H, s, Ar), 6.96 (2H, s, Ar), 10.84 (2H, s, 2NH), 11.13 (2H, s, 2NH), 12.24 (2H, s, 2NH), 12.47 (2H, s, 2NH), 14.82 (2H, s, 2NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.8 (CH), 87.7 (CC = ONH), 96.7 (CC = ONH), 126.5, 148.2, 149.5, 157.0, 160.0, 167.4 (C=O), 173.6 (C=S).

2.3.8. 5,5'-(1,4-Phenylene)bis(9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone) (4h)

Yellow solid: M.p.: >360 °C, yield: 0.400 g (70%). IR (KBr) (ν_{max}/cm^{-1}): 3396, 3341, 3205, 1745, 1676, 1625, 1212. MS (EI, 70 eV): *m/z* (%) = 127 (12), 99 (5), 84 (6), 68 (36), 89 (5), 45 (33), 43 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.19 (2H, s, 2CH), 5.29 (2H, s, 2CH), 6.60–8.26 (8H, m, Ar), 10.77–11.42 (16H, s, 16NH), 14.22 (4H, s, 4NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 58.8 (CH), 91.0 (CC = ONH), 91.5 (CC = ONH), 118.2, 126.8, 134.4, 147.5, 149.6, 150.3, 150.6, 155.2, 162.2 (C=O), 164.1 (C=O).

2.3.9. 5,5'-(1,4-Phenylene)bis(1,3-dimethyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone) (4i)

Yellow solid: M.p.: 262–264 °C, yield: 0.452 g (72%). IR (KBr) (ν_{max}/cm^{-1}): 3430, 3162, 1686, 1615, 1282. MS (EI, 70 eV): *m/z* (%) = 542 (1), 404 (100), 376 (57), 353 (20), 292 (69), 254 (29), 180 (65), 128 (34), 89 (8), 82 (30), 42 (39). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.04 (6H, s, 2CH3), 3.09 (12H, s, $4CH_3$), 3.21 (6H, s, $2CH_3$), 5.29 (4H, s, 4CH), 6.98 (4H, s, Ar), 7.38 (4H, s, Ar), 10.96 (4H, s, 4NH), 11.17 (4H, s, 4NH), 14.13 (4H, s, 4NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.0 (NCH_3), 28.1 (NCH_3), 29.2 (NCH_3), 30.4 (NCH_3), 32.7 (CH), 88.5 (CC = $ONCH_3$), 90.3 (CC = $ONCH_3$), 126.0, 129.5, 134.0, 136.5, 149.8, 150.0, 155.0, 161.2, 163.9, 167.3.

2.3.10. 5,5'-(1,4-Phenylene)bis(1,3-dimethylbenzo[g]pyrimido[4,5-b]quinoline-2,4,6,11(1H,3H,5H,12H)-tetraone) (4j)

Orange solid: M.p.: 269–271 °C, yield: 0.497 g (69%). IR (KBr) (ν_{max}/cm^{-1}): 3393, 3237, 1703, 1653, 1605, 1254. MS (EI, 70 eV): *m/z* (%) = 720 (M^+, 1), 514 (6), 426 (13), 338 (21), 280 (26), 188 (9), 133 (38), 89 (93), 45 (100). 1H NMR (300 MHz, DMSO-d6): δ 3.09 (6H, s, 2CH3), 3.11 (6H, s, 2CH3), 3.33 (12H, s, 4CH3), 5.77 (4H, s, 4CH), 6.91–8.01 (24H, m, Ar), 13.19 (4H, s, 4NH). ^{13}C NMR (62.8 MHz, DMSO-d_6): δ 29.5 (NCH_3), 31.4 (NCH_3), 31.8 (NCH_3), 35.8 (CH), 36.2 (CH), 87.2 (CC = ONH), 125.0, 127.1, 127.5, 127.9, 129.0, 130.8, 132.0, 133.1, 134.1, 134.9, 135.8, 136.9, 138.2, 151.6, 151.9, 155.8, 160.0 (C=O), 165.0 (C=O), 182.5 (C=O), 187.4 (C=O), 193.0 (C=O).

2.4. Supplementary material

Experimental section, general procedure for the synthesis of product **4a**, structure of all products, copies of ^{1}H, ^{13}C NMR spectrum, IR spectra, and Mass spectra of selected products are provided.

3. Results and discussion

In the current study, synthesis of new functionalized bis-heterocycles (such as bis(pyrimido[4,5-*b*]quinolone), bis(chromeno[3′,4':5,6]pyrido[2,3-*d*]pyrimidine), bis(pyrido[2,3-*d*:6,5-*d'*]dipyrimidine), and bis(benzo[*g*]pyrimido[4,5-*b*]quinolone) derivatives) **4** *via* one-pot, multi-component reaction of various 6-aminouracils or 6-aminothiouracils **1**, terephthalaldehyde **2**, and CH-acids (such as 4-hydroxycoumarin, dimedone, 2-hydroxy-1,4-naphthoquinone, barbituric acid and thiobarbituric acid) **3** in EtOH as a solvent at reflux without any catalyst is described (Scheme 1).

We tested the general scope of this reaction by varying the structure of the 6-aminouracils **1** and CH acids **3**. The reaction was completed after 5–30 min, under the same reaction conditions to give corresponding bis-heterocycles **4** in good to high yields (65–90%). The results are shown in Table 1.

The structures of products **4a-j** were assigned from their IR, mass, ^{1}H NMR, and ^{13}C NMR spectra (see the Supporting Information). The ^{1}H NMR spectrum of **4a** exhibited a singlet at δ 5.52 ppm arising from the CH proton, multiplets for aromatic protons in the range of δ 6.74–7.79 ppm as well as three singlets for the NH protons at δ 12.13, 12.45, and 13.49 ppm. Moreover, the ^{13}C NMR spectrum agreed with the proposed structure **4a**. Resonances due to CH, CC = ONH, CC = OO, C=O, C=O, and C=S groups appeared at δ 35.8, 92.2, 106.3, 165.9, 166.5, and 174.1 ppm, respectively. Also the mass spectrum of **4a** was in agreement with the proposed structure (see the supplementary material).

Compounds **4** have two stereogenic centers, and therefore two diastereoisomers are expected. In some products, one of which is prepared in a highly stereo controlled fashion (for example **4a**). Also the ^{1}H- and ^{13}C NMR spectra of the products **4c**, **4d**, **4f**, **4h**, **4i, 4j** indicated the presence of two diastereoisomers. We were not able to separate these compounds in pure form. However, their NMR data can be extracted from the mixture of the two diastereoisomers and the ^{1}H and ^{13}C NMR spectra of two diastereoisomers are too similar. We did not obtain the good NMR spectra of these samples because of its insolubility in any solvent (All products are very insoluble compounds). The two diastereoisomers of **4c** is shown in Scheme 2.

A proposed mechanism for the synthesis of **4** is shown in Scheme 3. To form the product **4**, it is possible that initially the formation of the adduct **5** occurs through Knoevenagel condensation between terephthalaldehyde **2** (1 mmol) and CH-acid **3** (2 mmol). Then the Knoevenagel adduct **5** undergoes Michael addition with 6-aminouracil **1** (2 mmol) to give **6**. This intermediate is converted into **7** through the imine-enamine tautomerization, followed by *N*-cyclization to prepare product **4**.

4. Conclusion

The present study described a simple route for the synthesis of new bis-pyridopyrimidine and bis-pyrimidoquinolone derivatives by the one-pot, multi-component condensation of 6-aminouracils, terephthalaldehyde, and CH-acids in EtOH as a solvent at reflux. The notable advantages of the present work are easy accessibility of reactants, simplicity of the experimental procedures, high atom economy, absence of catalyst, short reaction time, and good product yields. In addition, various functional groups that exist in these heterocycles lead to the pharmacological/biological activities of them.

Declarations

Author contribution statement

Mohammad Bayat: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Fahimeh Sadat Hosseini: Analyzed and interpreted the data; Wrote the paper.

Milad Masoumi: Performed the experiments.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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