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ARTICLE TYPE

Poly(*N*-bromo-*N*-ethyl-benzene-1,3-disulfonamide) and *N,N,N′,N′*-tetrabromobenzene-1,3-disulfonamide as new efficient reagents for one-pot synthesis of furano and pyrano pyrimidinones (thiones)

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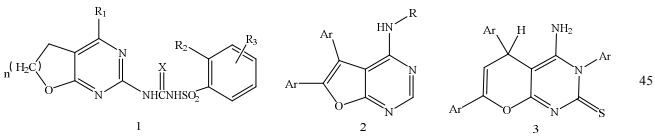
In this study, one-pot diastereoselective three-component reaction of urea/thiourea, 2,3-dihydrofuran/3,4-dihydro-2*H*-pyran with aromatic aldehydes have been developed for synthesis of furano and pyrano pyrimidinones (thiones) using poly(*N*-bromo-*N*-ethyl-benzene-1,3-disulfonamide) [PBBS] and *N,N,N′,N′*-tetrabromobenzene-1,3-disulfonamide [TBBDA].

Introduction

Multi-component reactions (MCRs) are important tools for the rapid and effective synthesis of a wide variety of organic molecules.[1] These reactions convert more than two starting materials directly into their products by one-pot reactions. Further, they are performed without need to isolate any intermediate during their processes; this reduces time and saves both energy and raw material.[2]

In recent years, fused ring pyrimidinones (thiones) have attracted intense interest due to their useful biological and pharmacological properties, such as being antitumor, antiallergic, antibacterial, antihypertensive, cardiotonic, vasodilator, bronchiodilator and hepatoprotective agents. They have antimalarial, antifungal, analgesics, anti-HIV and herbicidal properties in some cases.[3-9]

For example, some pyrimidine sulfonamide derivatives of the general structure **1** (Scheme 1) have been developed as powerful herbicides.[10] Several 4,5,6-trisubstituted furo[2,3-*d*]pyrimidin-4-amines **2** (Scheme 1) have been detected as ACK1 (Activated Cdc42-associated tyrosine Kinase 1) inhibitors. Some findings suggest that ACK1 is a potential target for developing anti-cancer therapeutics.[11] Furthermore, the results revealed that 5-amino-2,4-di(2-thienyl)-4,6-dihydro-6-phenylpyrano[2,3-*d*]pyrimidin-7-thione compounds of the general structure **3** (Scheme 1) containing thione and dithienyl moieties showed antibacterial activity equal to that of gentamycin.[12] Biginelli reactions are ranked as one of the most powerful tools for the facile synthesis of complex heterocyclic scaffolds such as fused ring pyrimidinones (thiones).[13]

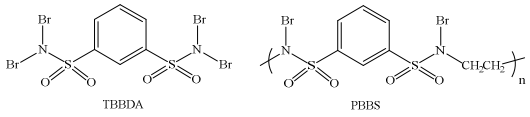


Scheme 1. Some examples of fused ring pyrimidinones (thiones).

Recently, Wu and coworkers reported a novel diastereoselective one-pot three-component reaction containing urea/thiourea, various aldehydes and alkenes for the synthesis of pyrimidinone (thione) derivatives using TMS-Cl.[14] Then, these compounds have been synthesized in the presence of *L*-proline/TFA,[15] *p*-TSA,[16] antimony trichloride[17] and [Hnmp]HSO_4.[18]

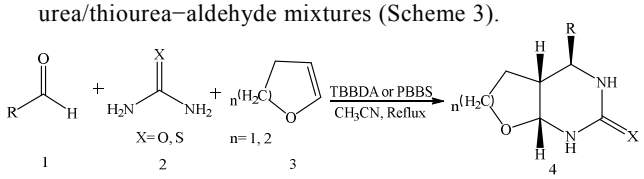
Although several methods are available for the preparation of furano and pyrano pyrimidinones (thiones), some of them suffer from disadvantages such as long reaction time, low yields of products, the use of toxic metal reagents and strongly acidic conditions. Therefore, to avoid these limitations, the discovery of a new, easily available reagent for the preparation of these compounds is still desirable.

Poly(*N*-bromo-*N*-ethyl-benzene-1,3-disulfonamide) [PBBS] and *N,N,N′,N′*-tetrabromobenzene-1,3-disulfonamide [TBBDA] are effective reagents[19] for several organic transformations.[20-26] They react under heterogeneous conditions, are conveniently handled and after completion of the reaction, the sulfonamide was recovered, rebrominated and used for several times (Scheme 2).



Scheme 2. The structure of TBBDA and PBBS.

In continuation of our studies in the application of poly(*N*-bromo-*N*-ethyl-benzene-1,3-disulfonamide) [PBBS] and *N,N,N′,N′*-tetrabromobenzene-1,3-disulfonamide [TBBDA], in organic synthesis,[19-26] herein we report a simple and efficient method for the preparation of pyrano and furano pyrimidinone (thione) derivatives from one-pot three-component reactions of cyclic enol ethers with urea/thiourea−aldehyde mixtures (Scheme 3).



Scheme 3. Diastereoselective three-component reactions of cyclic enol ethers with urea/thiourea−aldehyde mixtures.

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Results and discussion

Initially, we decided to explore the role of TBBDA and PBBS as reagents for the three-component reaction of 4-chlorobenzaldehyde (1a, 1 mmol), urea (2, 1 mmol) and 3,4-dihydro-2*H*-pyran (3, 1 mmol) (Table 1). In the absence of reagent, no desired product was observed, even after prolonged reaction time (Table 1, entry 1). Since the synthesis of 4-(4-chlorophenyl)octahydro-2*H*-pyrano[2,3-*d*]pyrimidin-2-one failed in the absence of reagent, the effect of the reagent was also investigated in various conditions, and the results are presented in Table 1, entries 2-10. The best results were achieved when the reaction was carried out in CH_3CN (5 mL) in the presence of TBBDA (0.1 g, 0.18 mmol) or PBBS (0.1 g) at 82 ^oC (Table 1, entry 3).

Table 1. Optimization of reaction conditions for the synthesis of pyrano pyrimidinone 4a[a]

Entry	Solvent	TBBDA (mol%)/ PBBS (g)	Temp (°C)	Time (h)	Yield (%)[b] TBBDA/PBBS
1	CH_3CN	0	82	12	c
2	CH_3CN	9 /0.05	82	6	88/78
3	CH_3CN	18 /0.1	82	2	92/90
4	CH_3CN	30 /0.15	82	3	92/90
5	$CHCl_3$	18 /0.1	62	8	36/23
6	Toluene	18 /0.1	110	8	29/15
7	EtOH	18 /0.1	78	8	75/72
8	CH_3OH	18 /0.1	65	8	72/68
9	$EtOH/H_2O$	18 /0.1	Reflux	8	58/47
10	CH_3CN/DMF	18 /0.1	Reflux	8	91/90

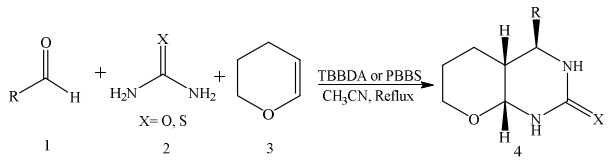
[a] Reaction conditions: 4-chlorobenzaldehyde (1.0 mmol), urea (1.0 mmol), 3,4-dihydro-2*H*-pyran (1.0 mmol) in solvent (5 mL).

[b] Isolated yield.

[c] Desired product not formed.

After optimization of the reaction conditions, in order to study the generality of the procedure, various aromatic aldehydes, urea/thiourea and 3,4-dihydro-2*H*-pyran were submitted to these reaction conditions and provide corresponding 4-aryloctahydro-2*H*-pyrano[2,3-*d*]pyrimidin-2-ones or 4-aryloctahydro-2*H*-pyrano[2,3-*d*]pyrimidin-2-thiones in good to high yields (Table 2).

Table 2. Synthesis of pyrano pyrimidinones (thiones)[a]



1 2 3 4

Entry	Aldehyde	X	Product	Time(h)/Yield(%)[b] TBBDA	PBBS
1	4-Chlorobenzaldehyde	O	4a	2/92	2/90
2	4-Chlorobenzaldehyde	S	4b	3/89	3/81
3	4-Biphenylcarbaldehyde	O	4c	2/89	3/82
4	4-Biphenylcarbaldehyde	S	4d	3/85	5/80
5	2-Naphthaldehyde	O	4e	2/90	3/83
6	2-Naphthaldehyde	S	4f	2/82	3/79
7	4-Nitrobenzaldehyde	O	4g[c]	2/95	2/90

[a] Reaction conditions: aryl aldehyde (1.0 mmol), urea or thiourea (1.0 mmol), reagent (0.18 mmol) and 3,4-dihydro-2*H*-pyran (1.0 mmol) in CH_3CN (5 mL).

[b] Isolated yield.

[c] 1:1 Diastereomeric mixture obtained.

It was shown that the aromatic aldehydes with electron-withdrawing groups reacted faster than the electron-donating groups (Table 2, entries 1, 2 and 7). Replacing urea with thiourea produced the corresponding thio-

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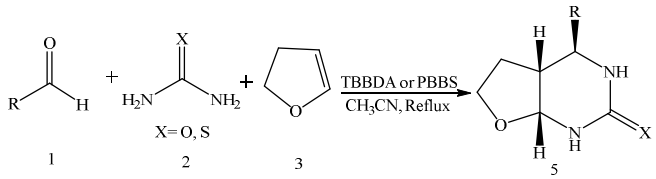
derivatives in good yields (Table 2, entries 2, 4 and 6). Comparatively, thiourea shows lower reactivity than urea. The reason for low yields in producing the desired products with thiourea is probably due to the strong coordinating ability of sulfur often leads to the belief that sulfur will hinder reagent activity.[27]

Table 3. Synthesis of furano pyrimidinones (thiones)[a]



1 2 3 5

Entry	Aldehyde	X	Product	Time(h)/Yield(%)[b]	
				TBBDA	PBBS
1	4-Methylbenzaldehyde	O	5a	2/92	3/85
2	4-Methylbenzaldehyde	S	5b	3/90	3/80
3	2-Hydroxy-3-methoxybenzaldehyde	O	5c	2/91	3/84
4	2-Hydroxy-3-methoxybenzaldehyde	S	5d	3/89	3/82
5	2-Chlorobenzaldehyde	O	5e	2/94	2/84
6	2-Chlorobenzaldehyde	S	5f	3/90	3/85

[a] Reaction conditions: aryl aldehyde (1.0 mmol), urea or thiourea (1.0 mmol), reagent (0.18 mmol) and 2,3-dihydrofuran (1.0 mmol)) in CH_3CN (5 mL).

[b] Isolated yield.

We obtained the desierd products in good to high yields under this condition reaction (Table 3). Comparison of yield and time for the reaction was shown that aromatic aldehydes carrying either electron donating (Table 3, entries 1-4) or electron-withdrawing substituents (Table 3, entries 5 and 6) reacted in good to high yields.

We have proposed a possible mechanism for this Biginelli type reaction which is based on the mechanism suggested by Overman and Wolfe (Scheme 4).[28] Since PBBS and TBBDA contain bromine atoms which are attached to nitrogen atoms, it is probable that they release Br^+ *in situ* which can act an electrophilic specie.[19-26] It accelerates the formation of the *N*-acyliminium ion intermediate **A** from an aldehyde and urea in presence of these reagents. The nucleophilic attack of cyclic enol ether **3** on intermediate **A** generates an oxonium ion intermediate **B**, which undergoes cyclization either in an *exo* and/or *endo* fashion as shown in Scheme **4**, leading to *exo* and/or *endo* intermediate. The severe steric interaction between the tetrahydropyrylium or dihydrofuranium cycle and urea or thiourea group disfavors the reaction by *endo* intermediate and the cyclization occurs by attack of the NH_2 group in an *exo* fashion. The reaction is diastereoselective in nature as only the *cis*-isomer was observed. In previous reports,[14-18] the NOE and NOESY experiments and by the X-ray crystallographic analysis of this compounds provided a straight evidence of the *cis* fused ring juncture. But aromatic aldehydes containing a nitro group led to diastereomeric mixtures (Table 2, entry 7). The portion of isomers was determined from their ^{1}H NMR spectrum. In case of 4-chlorobenzaldehyde (1a) no diastereomeric mixture was formed (Table 2, entry 1). So it was concluded that the electronic nature and position of the substituents on the aromatic ring is very important on these reaction (Scheme 4).[17]

To test this type of MCR, the scope of the reaction was investigated with a series of aromatic aldehydes, urea/thiourea and 2,3-dihydrofuran in an effort to build up similar 4-arylhexahydrofuro[2,3-*d*]pyrimidin-2(1*H*)-ones or 4-arylhexahydrofuro[2,3-*d*]pyrimidin-2(1*H*)-thiones (Table 3).

To investigate the role of HOBr in activating the reaction, hydrogen bromide was added to a solution of sodium hypochlorite in water.[29] When the reaction was carried out in this condition only a trace amount of corresponding products was observed. Also, using a catalytic amount of aqueous 48% HBr instead of TBBDA gave lower yields (15%). This result indicates that the generation of the protic acids HOBr or HBr may not be the only factor responsible for the reagent activity of TBBDA. It is possible that the positive bromonium moiety also has some role in facilitating the process.

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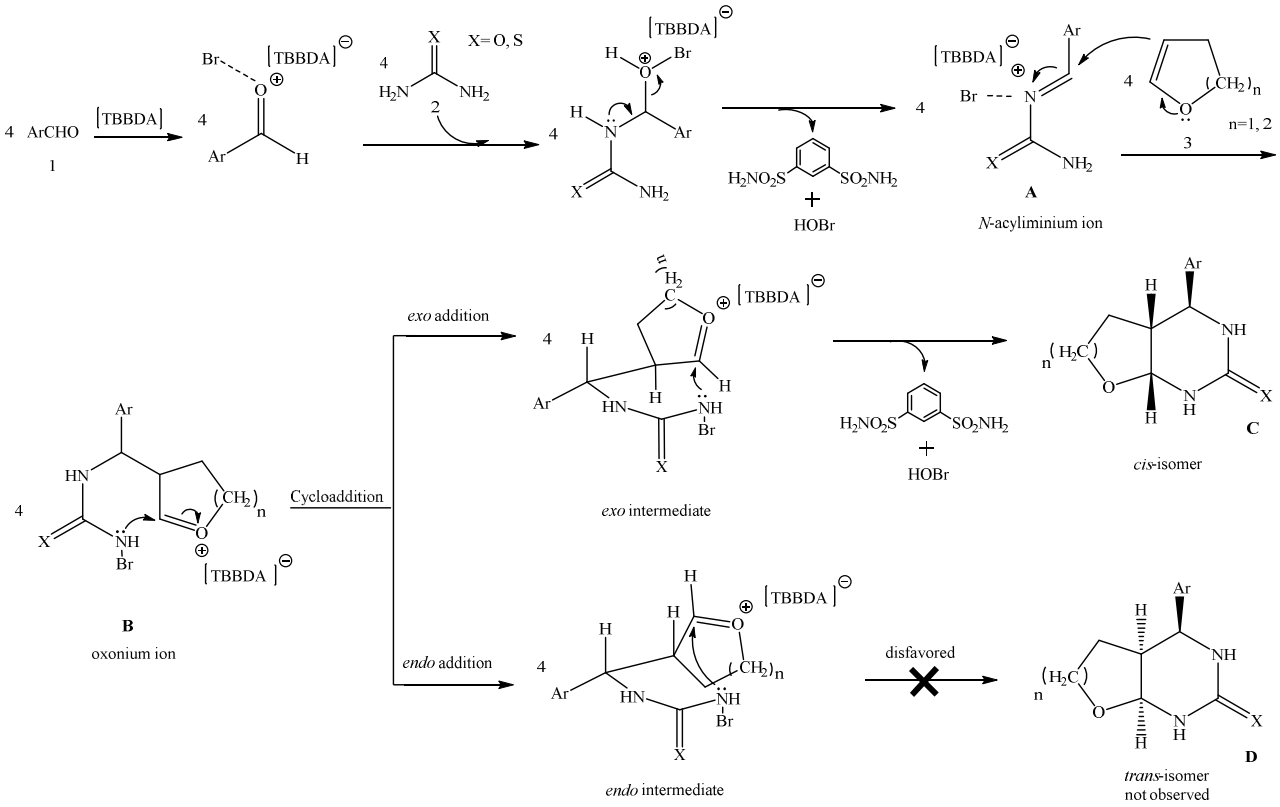

Scheme 4. Suggested mechanism for the synthesis of pyrano and furano pyrimidinones (thiones)

To demonstrate the efficiency of the described method in comparison with formerly reported procedures in the literature, we compared the results obtained in the preparation of 4-(4-chlorophenyl)octahydro-2*H*-pyrano[2,3-*d*]pyrimidin-2-one with those of other methods (Table 4). The results clearly indicate that use of TBBDA is an efficient method for the synthesis of furano and pyrano pyrimidinones (thiones). We observed significant decrease of reaction time, product purity and thus cost efficiency.

Table 4. Compared performance of various methods for the synthesis of pyrano pyrimidinone 4a

Entry	Catalyst/(mol%)	Time (h)	Yield (%)	Ref.
1	TMSCl/100	10	92	14
2	*L*-proline/15 TFA/6	7	85	15
3	$SbCl_3$/10	3.5-7	91	17
4	TBBDA/18	2	92	This work

Conclusions

In conclusion, a simple and highly efficient synthesis of furano and pyrano pyrimidinones (thiones) by a three-component condensation of aromatic aldehydes, urea/thiourea with 2,3-dihydrofuran (DHF)/3,4-dihydro-2*H*-pyran (DHP) using poly(*N*-bromo-*N*-ethyl-benzene-1,3-disulfonamide) [PBBS] and *N,N,N′,N′*-tetrabromobenzene-1,3-disulfonamide [TBBDA] in a one-pot manner was developed. This method offers several significant advantages, such as being inexpensive reagents, high yield, high atom economy, ease of product isolation, environmental friendliness (non-corrosive reagent) which make it a useful and attractive process for the rapid synthesis of furano and pyrano pyrimidinones (thiones).

Experimental

Mass spectra were recorded on a Shimadzu QP 1100 BX Mass Spectrometer (University of Tehran, Iran). ^{1}H and ^{13}C-NMR spectra were recorded on Bruker Advance 400 FT NMR spectrometers (undertaken at University of Mazandaran, Iran) at 400MHz and 100MHz in DMSO-d_6, respectively. Chemical shifts are reported in ppm (δ), relative to the internal standard of tetramethylsilane (TMS). Chemical shift values are reported in parts per million relative to TMS as internal reference, unless

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otherwise stated; s (singlet), d (doublet), t (triplet), m (multiplet); J in Hertz (Hz). Infrared (IR) spectroscopy was performed on a Perkin Elmer GX FT-IR spectrometer in KBr pellets. All starting materials were obtained from commercial sources and used without purification.

General procedure for the synthesis of furano and pyrano pyrimidinones (thiones):

TBBDA (0.1 g, 0.18 mmol) or PBBS (0.1 g) was added to a solution of aromatic aldehyde **1** (1 mmol), urea or thiourea **2** (1 mmol), 2,3-dihydrofuran or 3,4-dihydro-(2*H*)-pyran **3** (1 mmol) in CH_3CN (5 mL) and the reaction mixture was magnetically stirred and refluxed till the reaction was completed (monitored by thin-layer chromatography TLC (3:2, n-hexane/acetone)). The products were precipitated directly. The crude product was isolated by filtration through a Buechner funnel. Then, CH_2Cl_2 (5 mL) was added, and the precipitated sulfonamide was removed by filtration. The residue so obtained was purified by simple crystallization using ethanol to give pure product.

Spectral data:

4-(4-Chlorophenyl)octahydro-2*H*-pyrano[2,3-*d*]pyrimidin-2-one (4a): White solid; Mp: 235-236 (Lit.[15] 239-241 °C); IR (KBr): υ 3307, 3212, 3097, 2945, 2863, 1701, 1595, 1490, 1298, 1087, 1029, 762 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.19–1.24 (m, 2H), 1.52–1.59 (m, 1H), 1.69–1.80 (m, 2H), 3.44 (dd, *J* = 10, 11.6 Hz, 1H), 3.88 (d, *J* = 8 Hz, 1H), 4.42 (dd, *J* = 2.4, 4.4 Hz, 1H), 4.56 (d, *J* = 10.8 Hz, 1H), 6.68 (s, 1H), 7.30 (d, *J* = 3.2 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.7, 23.3, 38.1, 52.4, 66.2, 80.7, 128.8, 129.9, 132.5, 141.0, 155.1.

4-(4-Chlorophenyl)octahydro-2*H*-pyrano[2,3-*d*]pyrimidine-2-thione (4b): White solid; Mp: 268-270 (Lit.[15] 260-263 °C); IR (KBr): υ 3186, 3042, 2962, 2835, 1670, 1572, 1534, 1490, 1203, 1035, 1029, 746 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.23 (d, *J* = 14.8 Hz, 2H), 1.59–1.65 (m, 1H), 1.69–1.75 (m, 1H), 1.86 (t, *J* = 4.4 Hz, 1H), 3.46 (t, *J* = 10.2 Hz, 1H), 3.86 (d, *J* = 11.2 Hz, 1H), 3.96 (dd, *J* = 2.4, 4 Hz, 1H), 4.53 (d, *J* = 10.4 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 8.47 (s, 1H), 8.87 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.8, 22.9, 36.4, 53.6, 66.1, 78.7, 128.8, 130.0, 132.8, 139.6, 176.9.

4-([1,1'-Biphenyl]-4-yl)octahydro-2*H*-pyrano[2,3-*d*]pyrimidin-2-one (4c): White solid; Mp: 220-223 °C; IR (KBr): υ 3329, 3276, 3077, 2946, 2870, 1677, 1649, 1508, 1384, 1082, 1034, 766 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.21–1.32 (m, 2H), 1.53–1.60 (m, 1H), 1.75–1.85 (m, 2H), 3.90 (d, *J* = 10.4 Hz, 1H), 4.44 (s, 1H), 4.59 (d, *J* = 9.2 Hz, 1H), 6.61 (s, 1H), 7.29 (s, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.41–7.47 (m, 5H), 7.66 (d, *J* = 6.4 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.3, 22.9, 37.7, 52.3, 65.8, 80.3, 126.5, 126.6, 127.4, 128.1, 128.9, 139.5, 139.8, 140.8, 154.6; MS: m/z = 308 (M^+, 17%), 249 (54%), 208 (25%), 182 (48%), 152 (37%), 107 (30%), 84 (50%), 69 (65%), 55 (62%), 43 (100%).

4-([1,1'-Biphenyl]-4-yl)octahydro-2*H*-pyrano[2,3-*d*]pyrimidine-2-thione (4d): White solid; Mp: 244-246 °C; IR (KBr): υ 3154, 3079, 2942, 2857, 1655, 1603, 1570, 1536, 1203, 1068, 1034, 769 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.27–1.38 (m, 2H), 1.54–1.65 (m, 1H), 1.74–1.91 (m, 2H), 3.43–3.49 (m, 1H), 3.86 (d, *J* = 10.8 Hz, 1H), 4.41 (s, 1H), 4.52–4.59 (m, 1H), 7.35–7.47 (m, 5H), 7.66 (d, *J* = 7.2 Hz, 4H), 8.43 (s, 1H), 8.84 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.4, 22.6, 36.0, 53.6, 65.6, 78.3, 126.6, 127.5, 128.1, 128.9, 130.2, 130.7, 139.6, 139.7, 176.5; MS: m/z = 324 (M^+, 92%), 265 (40%), 249 (53%), 181 (100%), 165 (42%), 152 (53%), 113 (23%), 76 (90%), 59 (40%), 43 (62%).

4-(Naphthalen-2-yl)octahydro-2*H*-pyrano[2,3-*d*]pyrimidine-2-one (4e): White solid; Mp: 258-259 °C; IR (KBr): υ 3311, 3200, 3079, 2943, 2894, 1671, 1603, 1494, 1374, 1076, 745 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.22–1.25 (m, 2H), 1.51–1.57 (m, 1H), 1.78–1.95 (m, 2H), 3.38–3.48 (m, 1H), 3.91 (d, *J* = 9.2 Hz, 1H), 4.44 (d, *J* = 8.8 Hz, 1H), 4.71 (d, *J* = 10.8 Hz, 1H), 6.72 (m, 1H), 7.33 (s, 1H), 7.43–7.51 (m, 3H), 7.85–7.91 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.0, 24.5, 39.2, 54.4, 67.4, 81.9, 125.7, 126.4, 126.7, 127.0, 128.0, 128.2, 128.5, 133.1, 133.2, 139.4, 155.3; MS: m/z = 282 (M^+, 22%), 279 (100%), 164 (20%), 159 (45%), 149 (25%), 131 (28%), 92 (15%), 63 (7%), 43 (5%).

4-(Naphthalen-2-yl)octahydro-2*H*-pyrano[2,3-*d*]pyrimidine-2-thione (4f): White solid; Mp: 275-277 °C; IR (KBr): υ 3358, 3262, 3177, 2925, 2855, 1619, 1537, 1211, 1034, 748 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.32 (m, 5H), 2.49–2.53 (m, 1H), 3.29–3.34 (m, 1H), 3.39–3.43 (m, 1H), 4.38–4.51 (m, 1H), 7.40–7.56 (m, 3H), 7.78–7.82 (m, 1H), 7.87–7.89 (d, *J* = 7.6 Hz, 3H), 8.30–8.33 (m, 1H), 8.64 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.0, 25.0, 30.2, 60.7, 66.4, 97.7, 124.5, 125.2, 125.8, 126.1, 127.5, 127.9, 128.0, 132.3, 132.4, 132.8, 176.1; MS: m/z = 298 (M^+, 100%), 239 (42%), 194 (9%), 179 (15%), 165 (17%), 155 (63%), 128 (18%), 76 (20%), 59 (20%), 43 (23%).

4-(4-Nitrophenyl)octahydro-2*H*-pyrano[2,3-*d*]pyrimidin-2-one (4g): White solid (1:1 diastereomeric mixture) ; Mp: 267-268 (Lit.[15] 260-265 °C); IR (KBr): υ 3315, 3219, 3086, 2939, 2860, 1696, 1606, 1520, 1348, 1273, 1033, 755 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.60–0.62 (m, 1H), 1.23 (m, 2H), 1.44–1.47 (m, 1H), 1.55–1.62 (m, 2H), 1.78–1.91 (m, 4H), 3.14 (t, *J* = 11.2 Hz, 1H), 3.46 (t, *J* = 11.2 Hz, 1H), 3.74 (d, *J* = 11.6 Hz, 1H), 3.90 (d, *J* = 9.2 Hz, 1H), 4.00 (d, *J* = 9.2 Hz, 1H), 4.44 (s, 1H), 4.51 (s, 1H), 4.72 (d, *J* = 10.8 Hz, 1H), 6.83 (s, 1H), 7.13 (s, 1H), 7.15 (s, 1H), 7.40 (s, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 8.24 (t, *J* = 8.8 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.7, 23.2, 24.9, 25.7, 39.3, 40.2, 52.7, 55.1, 65.4, 66.2, 80.6, 81.7, 123.8, 124.0, 128.8, 129.4, 147.2, 147.4, 149.6, 150.0, 154.9, 155.0.

4-(*p*-Tolyl)hexahydrofuro[2,3-*d*]pyrimidin-2(1*H*)-one (5a): White solid; Mp: 211-214 °C; IR (KBr): υ 3294, 3218, 3091, 2933, 2900, 1695, 1661, 1502, 1371, 1284, 1035, 768 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.61 (m, 1H), 1.89 (m, 1H), 2.62 (m, 4H), 3.63 (m, 1H), 3.89 (m, 1H), 4.03 (m, 1H), 4.77 (m, 1H), 6.73 (s, 1H), 7.15 (m, 3H),

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7.21 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.3, 28.6, 42.7, 55.6, 64.9, 84.6, 128.8, 130.5, 138.2, 140.2, 156.9; MS: m/z = 232 (M^+, 33%), 187 (52%), 146 (13%), 120 (100%), 118 (32%), 91 (32%), 70 (78%), 56 (10%), 42 (37%).

4-(*p*-Tolyl)hexahydrofuro[2,3-*d*]pyrimidin-2(1*H*)-thione (5b): White solid; Mp: 227-229 °C; IR (KBr): υ 3207, 2950, 2881, 1612, 1543, 1518, 1313, 1203, 1050, 811, 633 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.64 (m, 1H), 2.04 (m, 1H), 2.27 (s, 3H), 2.37 (m, 1H), 3.70 (d, J = 5.6 Hz, 1H), 3.89 (d, J = 6 Hz, 1H), 4.09 (m, 1H), 4.69 (m, 1H), 7.16 (m, 4H), 8.57 (s, 1H), 8.63 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.1, 27.6, 42.7, 55.0, 64.5, 81.5, 127.4, 129.5, 137.3, 138.1, 177.3; MS: m/z = 248 (M^+, 100%), 203 (14%), 173 (14%), 145 (28%), 118 (73%), 91 (37%), 76 (40%), 60 (23%), 43 (53%).

4-(2-Hydroxy-3-methoxyphenyl)hexahydrofuro[2,3-*d*]pyrimidin-2(1*H*)-one (5c): White solid; Mp: 229-231 °C; IR (KBr): υ 3419, 3324, 3218, 2935, 1667, 1591, 1505, 1269, 1201, 1077, 766 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.54–1.55 (m, 1H), 2.18 (m, 1H), 3.54 (m, 2H), 3.70 (s, 3H), 4.03 (m, 1H), 4.62 (m, 1H), 5.22 (m, 1H), 6.69 (m, 1H), 6.78–6.85 (m, 3H), 7.12 (s, 1H), 7.41 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.5, 40.0, 46.7, 55.4, 58.1, 79.0, 111.5, 120.0, 120.6, 127.5, 139.5, 148.3, 154.2; MS: m/z = 264 (M^+, 78%), 233 (37%), 219 (100%), 204 (95%), 176 (60%), 150 (48%), 106 (43%), 91 (78%), 77 (40%), 56 (38%).

4-(2-Hydroxy-3-methoxyphenyl)hexahydrofuro[2,3-*d*]pyrimidin-2(1*H*)-thione (5d): White solid; Mp: 274-276 °C; IR (KBr): υ 3405, 3195, 2930, 1588, 1556, 1504, 1485, 1268, 1181, 1079, 980 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.34–1.48 (m, 1H), 2.20 (m, 1H), 3.52–3.53 (m, 2H), 3.72 (s, 3H), 4.18 (m, 1H), 4.66 (m, 1H), 5.20 (m, 1H), 6.70–6.72 (m, 1H), 6.83–6.90 (m, 3H), 9.01 (s, 1H), 9.12 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.7, 29.0, 47.2, 55.6, 59.7, 76.9, 101.7, 111.8, 120.7, 125.3, 139.3, 148.2, 175.5; MS: m/z = 280 (M^+, 100%), 249 (15%), 235 (37%), 205 (17%), 190 (17%), 176 (15%), 155 (22%), 91 (17%), 77 (22%), 56 (23%).

4-(2-Chlorophenyl)hexahydrofuro[2,3-*d*]pyrimidin-2(1*H*)-one (5e): White solid; Mp: 223-225 °C; IR (KBr): υ 3320, 3070, 2956, 2926, 2875, 1658, 1548, 1442, 1233, 1035, 756 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.53 (m, 1H), 1.75–1.82 (m, 1H), 1.92–2.07 (m, 1H), 3.59–3.68 (m, 2H), 5.36–5.42 (m, 1H), 5.54–5.61 (m, 1H), 6.36–6.50 (m, 1H), 6.58–6.78 (m, 1H), 7.31–7.63 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.4, 30.8, 50.7, 65.4, 82.5, 127.9, 128.5, 129.4, 129.7, 130.7, 135.8, 159.7; MS: m/z = 252 (M^+, 12%), 207 (69%), 193 (89%), 140 (100%), 129 (35%), 102 (27%), 70 (83%), 60 (57%), 44 (77%).

4-(2-Chlorophenyl)hexahydrofuro[2,3-*d*]pyrimidin-2(1*H*)-thione (5f): White solid; Mp: 248-251 °C; IR (KBr): υ 3219, 2949, 2887, 1617, 1542, 1521, 1477, 1316, 1204, 1034, 757 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.70 (m, 1H), 2.72 (m, 1H), 2.48 (m, 1H), 3.63–3.67 (m, 1H), 3.76–3.89 (m, 1H), 4.55–4.60 (m, 1H), 4.69 (m, 1H), 7.27–7.46 (m, 4H), 8.64 (s, 1H), 8.71 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.2, 40.1, 51.6, 64.6, 80.8, 127.7, 128.1, 129.6, 130.7, 135.8, 137.8, 177.1; MS: m/z = 268 (M^+, 18%), 222 (12%), 193 (10%), 163 (100%), 139 (100%), 112 (31%), 102 (36%), 76 (87%), 60 (62%), 43 (89%).

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