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ORIGINAL PAPER

Synthesis of benzohetero[3, 2-*a*]pyrimidines using cyclic β-keto lactone as a building block

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Abstract A novel method for the synthesis of 3-(2-substituted ethyl)-2-methylbenzohetero[3,2-*a*]pyrimidines in high yield (80–85%) was achieved, which involves a dihydrofuranone intermediate, readily obtained from β-ketolactone to 2-aminobenzoheterocycles. The major advantage of the methodology is the high yield and product purity.

Keywords Biselectrophilic reactions · Fused pyrimidine · 4,5-Dihydro-furan-2(3*H*)-one · Ammonium acetate · Heterocycles

Introduction

Fused pyrimidines have shown antipsychotic [1], antihypertensive [2] and potent in vivo central nervous activities [3]. They have also been used as tranquilizers [4], α-2-antagonists [5, 6] and exhibit high affinity for α-2-adrenoceptor with high selectivity vs. the α-receptor. Similarly, benzo[3,2-*c*]pyrimidines and thiazolo[3,2-*c*]pyrimidines have shown central dopamine and serotonin antagonistic activity [7]. These compounds have been used as neuroleptics (especially atypical) antidepressants, sedatives, hypnotics, cerebral protestants and muscle relaxants [8] and antiallergic bronchodilators [9]. Benzimidazolo[3,2-*c*] pyrimidines have been used as antihistamines [10]. Several of these compounds exhibit antitumor cytotoxic activity and other biological activities [11–15]. Fused pyrimidines with a 3-(2-chloroethyl) side chain are important compounds in medicinal chemistry [16–18].

In a previous report [19] α-formyl-γ-butyrolactone was condensed with 2-aminoheterocycles to introduce the 3-(2-chloroethyl) side chain in fused heterocycles. Now, we wish to report about the incorporation of both a methyl group at the 2-position along with a 3-(2-chloroethyl) side chain in fused heterocycles, which we attempted by the condensation of α-acetyl-γ-butyrolactone with 2-aminoheterocycles. Reports [20–22] about the condensation of α-acetyl-γ-butyrolactone with 2-aminobenzothiazoles and 2-aminopyridines led to the synthesis of fused heterocycles as a mixture of two products [21]. These reports inspired us to develop a new route towards the synthesis of benzohetero[3,2-*a*]pyrimidines. As part of our continued interest [23, 24] in the synthesis of novel heterocyclic compounds, we have recently reported the synthesis of chromenes, quinolines and pyrazolo[3,4-*b*]pyridines via multi-component reactions. In this communication, we report about the condensation of amines with ketones for the synthesis of new benzohetero[3,2-*a*]pyrimidines having a 2-methyl-3-(2-chloroethyl) side chain using cyclic β-ketolactone and 2-aminoheterocycles. Cyclic β-ketolactone reacts similarly to biselectrophile in ring-switching reactions [25, 26], and 2-aminoheterocycles act as bisnucleophiles.

Results and discussion

2-Aminoheterocycles **1a**–**1d** were condensed with α-acetyl-γ-butyrolactone (**2**) either by refluxing in toluene in the presence of a catalytic amount of *PTSA* or by heating in ammonium acetate to obtain the target compounds. It was observed that **1a**–**1c** upon reaction with **2** in toluene using

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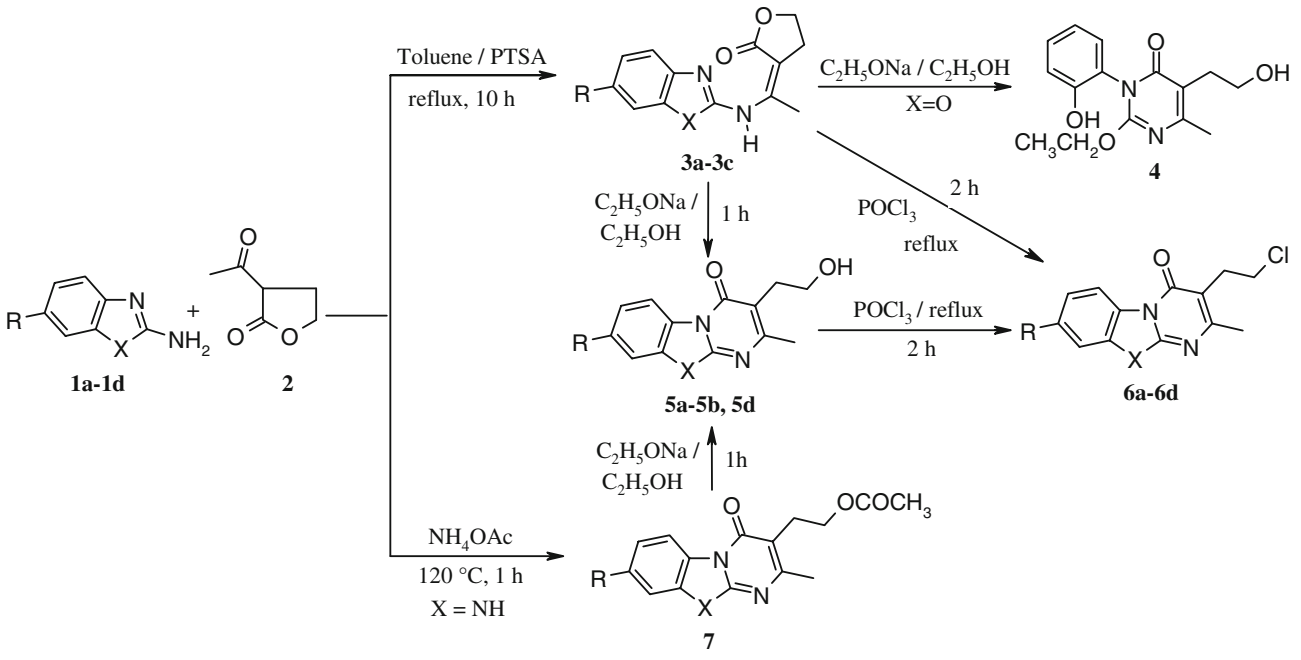
catalytic amounts of *PTSA* at reflux temperature furnished the thermodynamically favored (*Z*)-2-aminoethylidene heterodihydrofuranone intermediates **3a**–**3c** in 80–85% yield. Here, *PTSA* acts as a selective catalyst, protonating the oxygen of the keto carbonyl of lactone and initiating the subsequent attack of the amino moiety to yield the enamine intermediates **3a**–**3c**. The use of other acids, such as sulfuric, hydrochloric or acetic acid, or neat reaction conditions lead to inseparable mixtures of products.

The structures of **3a**–**3c** were confirmed by spectroscopic and analytical methods. Just to give an example, the IR of dihydrofuranone **3a** shows peaks at 2,910 and 1,700 cm^{-1} for NH and CO. The unexpected decrease of lactone C=O by 40–45 cm^{-1} can be explained by intermolecular hydrogen bonding [27] between NH and CO, which stabilizes the (*Z*)-isomer. In addition the (*E*)-isomer would suffer from steric repulsion between the methyl and the carbonyl group at the allyl system.

The ^{1}H NMR of **3a** in *DMSO-d*$_6$ shows a singlet at 2.52 ppm for methyl protons. The triplet at 2.85 ppm and 3.95 ppm $J = 7$ Hz is observed for $-CH_2CH_2O$ group. Aromatic protons are observed between 7.30 and 7.95 ppm. The D_2O exchangeable NH proton shows a broad singlet at 11.10 ppm. This structure was also confirmed by ^{13}C NMR analysis, which is given in the experimental part, and the elemental analysis is in agreement with the structure proposed. Upon reaction with sodium ethoxide in ethanol, the dihydrofuranones **3a** and **3b** are cyclized to fused pyrimidones **5a** and **5b**, having a 2-hydroxyethyl side chain in 80–85% yield. Interestingly, it was observed that under the same reactions conditions compound **3c** produced unexpected uracil **4** in 73% yield, which results from ring closure followed by subsequent ring opening. IR, ^{1}H NMR and elemental analysis methods were used to deduce the structures of **4**, **5a** and **5b** (given in the experimental part). For example, the IR of compound **4** showed bands at 3,340, 3,200 cm^{-1} for hydroxyethyl and phenolic OH, the amide CO is observed at 1,660 cm^{-1}. The ^{1}H NMR of **4** in *DMSO-d*$_6$ shows triplet-quartet at 1.19 and 4.31 ppm $J = 7$ Hz for the ethoxy group; two triplets at 2.63 and 4.62 ppm are $J = 7$ Hz observed for the $-CH_2CH_2O-$ group. The broad singlet at 3.52 and 9.84 ppm was observed for hydroxyethyl and phenolic OH. Compounds **3a**–**3c**, **5a**–**5b** and **5d** when refluxed with $POCl_3$ gave the expected benzohetero [3,2-*a*]pyrimidones **6a**–**6d** with a 2-chloroethyl side chain in 80–82% yield (Schemes 1, 2, 3).



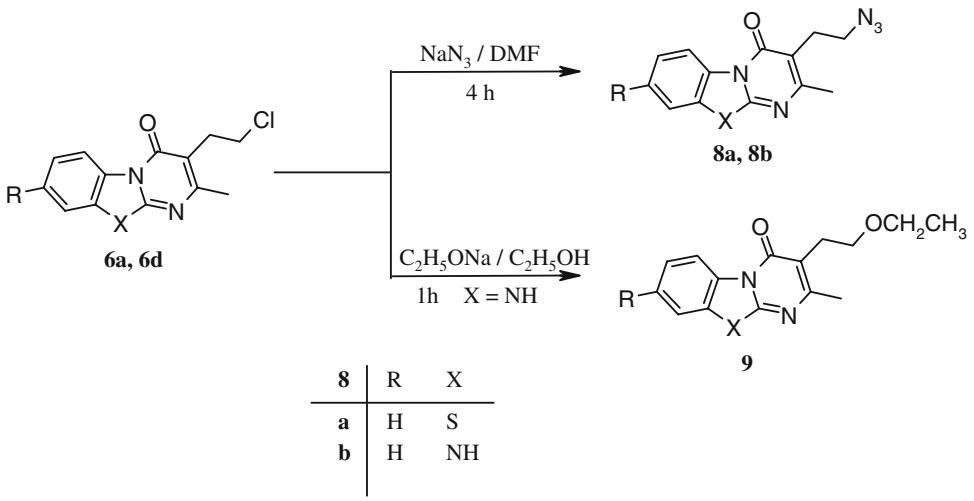
1	R	X
a	H	S
b	OCH_3	S
c	H	O
d	H	NH

3	R	X
a	H	S
b	OCH_3	S
c	H	O

5,6	R	X
a	H	S
b	OCH_3	S
c	H	O
d	H	NH

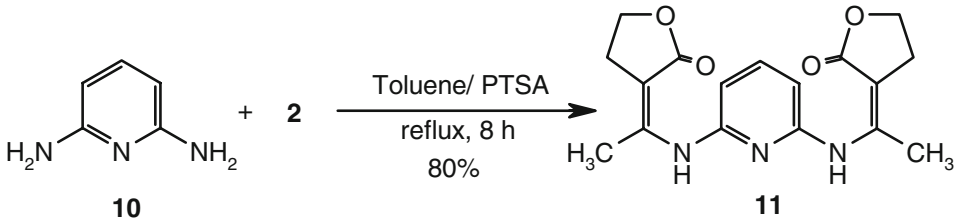
Scheme 1

Scheme 2



8	R	X
a	H	S
b	H	NH

Scheme 3



The S_N^2 displacement of chlorine in **6a** and **6d** with NaN_3/*DMF* at 70–80 °C furnished azido derivatives **8a** and **8b**. Ethyl ether **9** was obtained by refluxing **6d** with sodium ethoxide in ethanol. The formation of **8a**, **8b** and **9** indicated the presence of chloroethyl side chain in **6a**, **6d**, while formation of **6a**–**6d** confirmed the dihydrofuranone structures of **3a**–**3c**. Previously, [16] we have reported these types of reactions in ammonium acetate. But the same strategy does not work for the reactions of **1a**–**1d** with cyclic *β*-ketolactone **2**. We observed that **1a**–**1c** forms salt with ammonium acetate, reducing electron donating tendency of the amino group. On the other hand, 2-aminobenzimidazole **1d** can react with lactone **2**, furnishing benzimidazolo[3,2-*a*]pyrimidine **7**, which has an ethyl acetoxy side chain. It was observed that the 2-hydroxyethyl group gets acetylated in ammonium acetate. This type of phenomenon, though uncommon in the literature, was observed in some cases [19]. When **7** was refluxed in basic medium, compound **5d** with a free alcohol moiety resulted, which could be converted to compound **6d** bearing a chloroethyl side chain upon heating under reflux in phosphorous oxychloride.

The reaction of **2** with 2,6-diaminopyridine (**10**) under similar conditions gave 2, 6-dihydrofuranone intermediate **11** in 80% yields.

Conclusion

Reaction of cyclic *β*-ketolactones and 2-aminoheterocycles in toluene with *PTSA* as a catalyst led to thermodynamically stable (*Z*)-2-aminoethylidene benzo[*d*]thiazol/benzo[*d*]oxazoldihydrofuranone intermediates in 80–85% yield, which gives facile ring closure bezohetero[3,2-*a*]pyrimidin-4(1*H*)-ones having a 2-chloroethyl/2-hydroxyethyl side chain in 80–85%. The new route was useful to obtain fused pyrimidines with improved yields as a single product.

Experimental

Melting points were determined on a *Gallenkamp* melting-point apparatus in open capillary tubes. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian *XL*-300 spectrometer (300 MHz). Chemical shifts were reported in ppm from internal tetramethylsilane standard and are given in *δ*-units. ^{1}H NMR and ^{13}C NMR spectra are scanned using $CDCl_3$ or *DMSO*-d_6. Infrared spectra were taken with a Shimadzu FTIR-408 with potassium bromide pellets. Elemental analyses are performed on a Hosli CH-Analyzer and are within ±0.3 of theoretical values. All reactions were monitored by thin layer chromatography, carried out

on 0.2-mm silica gel 60 F_{254} (Merck) plates using UV light (254 and 366 nm) for detection. Starting materials were obtained from commercial suppliers and used without further purification. Common reagent-grade chemicals were either commercially available and were used without further purification or prepared by standard literature procedures.

*General procedure for the synthesis of Z-2-aminoethylidene Dihydrofuranones **3a–3c** and **11***

A mixture of 0.01 mol 2-aminoheterocycles **1a–1c/10** and 1.28 g α-acetyl-γ-butyrolactone, **2** (0.01 mol, 1.10 cm^3) and a catalytic amount (0.020 g) of *p*-toluenesulfonic acid in 20 cm^3 toluene was refluxed for 8–10 h. (*TLC* Check). After complete conversion the solvent was removed in vacuo. The residue was stirred in 30 cm^3 cold water. The solid was collected by filtration, washed with water, dried and recrystallized from a proper solvent.

(Z)-3-(1-(Benzo[d]thiazolo-2-ylamino)ethylidene) dihydrofuran-2(3H)-one (**3a**, $C_{13}H_{12}N_2O_2S$)
Yield 2.13 g (82%), mp 179 °C (*DMF*); R_f 0.42 (toluene/acetone 9:1); IR (KBr): $\bar{\nu}$ = 2,910, 1,700, 1,640, 1,540, 1,490 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO-d_6*): δ = 2.52 (s, 3H, CH_3), 2.85 (t, *J* = 7 Hz, 2H, CH_2), 4.40 (t, *J* = 7 Hz, 2H, CH_2), 7.30 (dt, *J* = 7.3 & 2.7 Hz, 1H, C_5–H), 7.41 (dt, *J* = 8.3 & 2.5 Hz, 1H, C_6–H), 7.72 (dd, *J* = 8.3 & 2.8 Hz, 1H, C_4–H), 7.95 (dd, *J* = 8.3 & 2.3 Hz, 1H, C_7–H), 11.10 (bs, 1H, NH) ppm; ^{13}C NMR (300 MHz, *DMSO-d_6*): δ = 19.2 (CH_3), 25.2 (CH_2), 67.0 (OCH_2), 104.1, 112.7, 123.3, 124.8, 125.6, 129.0, 123.9, 133.7, 144.3, 163.3 ppm.

(Z)-3-(1-(6-Methoxybenzo[d]thiazolo-2-ylamino) ethylidene)dihydrofuran-2(3H)-one (**3b**, $C_{14}H_{14}N_2O_3S$)
Yield 2.46 g (85%), mp 206 °C (*DMF*); R_f 0.32 (toluene/acetone 9:1); IR (KBr): $\bar{\nu}$ = 2,950, 1,690, 1,650, 1,600, 1,550, 1,510, 1,700, 1,430 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO-d_6*): δ = 2.56 (s, 3H, CH_3), 2.94 (t, *J* = 7 Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.42 (t, *J* = 7 Hz, 2H, CH_2O), 7.03 (dd, *J* = 8.3 & 2.3 Hz, 1H, C_5–H), 7.54 (m, 2H, C_4–H, C_7–H), 10.95 (bs, 1H, NH) ppm; ^{13}C NMR (300 MHz, *DMSO-d_6*): δ = 15.5 (CH_3), 23.9 (CH_2), 69.2 (OCH_2), 55.9 (OCH_3), 101.1, 105.0, 113.2, 122.8, 125.5, 141.3, 152.2, 156.8, 170.0, 174.5 ppm.

(Z)-3-(1-(Benzo[d]oxazol-2-ylamino) ethylidene)-dihydrofuran-2 (3H)-one (**3c**, $C_{13}H_{12}N_2O_3$)
Yield 1.85 g (76%), mp 187 °C (ethanol); R_f 0.40 (toluene/acetone 8:2); IR (KBr): $\bar{\nu}$ = 1,700, 1,650, 1,580, 1,510, 1,450 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO-d_6*): δ = 2.51 (s, 3H, CH_3), 2.96 (t, *J* = 7 Hz, 2H, CH_2), 4.40 (t, *J* = 7 Hz, 2H, CH_2O), 7.22–7.83 (m, 4H, Ar–H), 11.06 (bs, 1H, NH) ppm; ^{13}C NMR (300 MHz, *DMSO-d_6*): δ = 17.2 (CH_3), 24.3 (CH_2), 67.2 (OCH_2), 103.1, 110.7, 119.2, 123.9, 124.9, 141.5, 150.0, 152.5, 154.2, 166.3 ppm.

(3Z)-3-{1-[(6-{[(1Z)-1-(2-Oxodihydrofuran-3(2H)-ylidene)ethyl]amino}-pyridin-2-yl)amino]ethylidene} dihydrofuran-2 (3H)-one (**11**, $C_{17}H_{19}N_3O_4$)
Yield 2.63 g (80%), mp 233 °C (*DMF*); R_f 0.21 (toluene/acetone 9:1); IR (KBr): $\bar{\nu}$ = 1,700, 1,650, 1,570, 1,500, 1,450, 1,420 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO-d_6*): δ = 2.51 (s, 6H, CH_3), 2.93 (t, *J* = 7.1 Hz, 4H, $2CH_2$), 4.34 (t, *J* = 7 Hz, 4H, $2CH_2O$), 6.70 (d, *J* = 8.1 Hz, 1H, C_4–H), 7.71 (d, *J* = 8 Hz, 2H, C_3–H, C_5–H), 10.49 (bs, 2H, 2NH) ppm.

*General procedure for the synthesis of (2-hydoxyethyl)pyrimidines **4**, **5a** and **5b***

To a solution of 0.01 mmol compound **3a–3b** or **3d** dissolved in 30 cm^3 absolute ethanol was added a solution of sodium ethoxide (0.23 g freshly cut sodium metal dissolved in 10 cm^3 absolute ethanol) and the reaction mixture refluxed for 1 h. The solvent was removed under reduced pressure, the residue was stirred in 100 cm^3 cold water and acidified with 2 N hydrochloric acid. The precipitated solid product was collected by filtration, washed with cold water, dried and recrystallized from a proper solvent.

1-(2-Hydropheny)-2-ethoxy-4-methyl-5-(2-hydroxyethyl)pyrimidin-6(1H)-one (**4**, $C_{15}H_{18}N_2O_4$)
Yield 2.08 g (72%), mp 204 °C (acetonitrile); R_f 0.13 (toluene/acetone 9:1); IR (KBr): $\bar{\nu}$ = 3,340 (OH), 3,200, 2,900, 1,660, 1,600, 1,540, 1,450 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO-d_6*): δ = 1.19 (t, *J* = 7 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.63 (t, *J* = 7 Hz, 2H, CH_2), 3.52 (s, 1H, OH), 4.32 (q, *J* = 7 Hz, 2H, CH_2), 4.62 (t, *J* = 7 Hz, 2H, CH_2O), 6.91 (dt, *J* = 7.3 & 2.3 Hz, 1H, C_4–H), 7.03 (dd, *J* = 8.3 & 2.6 Hz, 1H, C_6–H), 7.11 (dd, *J* = 8.3 & 2.8 Hz, 1H, C_3–H), 7.32 (dt, *J* = 8.3 & 2.8 Hz, 1H, C_5–H), 9.84 (bs, 1H, OH) ppm.

3-(2-Hydroxyethyl)-2-methyl-1,3-benzthiazolo[3,2-a] pyrimidin-4(1H)-one (**5a**, $C_{13}H_{12}N_2O_3S$)
Yield 2.15 g (78%), mp 189 °C (acetonitrile); R_f 0.15 (toluene/acetone 7:3); IR (KBr): $\bar{\nu}$ = 3,260, 2,911, 1,660, 1,590, 1,510, 1,460 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO-d_6*): δ = 2.32 (s, 3H, CH_3), 2.82 (t, *J* = 7 Hz 2H, CH_2), 3.44 (t, *J* = 7 Hz, 2H, CH_2O), 4.65 (bs, 1H, OH), 7.62 (m, 2H, C_7–H, C_8–H), 8.06 (dd, *J* = 8.3 & 2.7 Hz, 1H, C_6–H), 8.32 (dd, *J* = 8.3 & 2.8 Hz, 1H, C_9H) ppm; ^{13}C NMR (300 MHz, *DMSO-d_6*): δ = 19.9 (CH_3), 26.6 (CH_2), 65.3 (OCH_2), 105.0, 113.2, 126.3, 128.4, 133.6, 135.0, 136.9, 138.7, 163.0, 173.5 ppm.

3-(2-Hydroxyethyl)-2-methyl-8-methoxy-1,3-benzothiazolo [3,2-a]pyrimid- in-4(1H)-one (**5b**, $C_{14}H_{14}N_2O_3S$)
Yield 2.37 g (82%), mp 195 °C (ethanol); R_f 0.12 (toluene/acetone 8:2); IR (KBr): $\bar{\nu}$ = 3,400, 2,910, 1,660, 1,600, 1,560, 1,500, 1,470, 1,430 cm^{-1}; ^1H NMR (300 MHz, *DMSO-d*$_6$): δ = 2.37 (s, 3H, CH_3), 2.70 (t, J = 7 Hz, 2H, CH_2O), 3.35 (t, J = 7 Hz, 2H, CH_2O), 3.83 (s, 3H, OCH_3), 4.72 (bs, 1H, OH), 7.13 (d, J = 8.2 Hz, 1H, C_6–H), 7.75 (d, J = 2.7 Hz, 1H, C_9–H), 8.80 (dd, J = 8.3 & 2.8 Hz, 1H, C_7–H) ppm; ^{13}C NMR (300 MHz, *DMSO-d*$_6$): δ = 20.9 (CH_3), 28.1 (CH_2), 55.9 (OCH_3), 59.5 (OCH_2), 111.3, 114.4, 116.1, 122.9, 129.5, 131.1, 153.0, 156.6, 160.3, 163.5 ppm.

Procedure for the synthesis of 3-(2-Hydoxyethyl)-2-methylbenzimidazolo[3,2-a] pyrimidin-4(1H)-one (**5d**, $C_{13}H_{13}N_3O_2$)

Benzimidazolo[3,2-*a*]pyrimidine **7** (0.01 mol) was refluxed in a solution of sodium ethoxide (0.23 g sodium metal dissolved in 10 cm^3 ethanol) in 20 cm^3 ethanol for 1 h. The solvent was removed under reduced pressure. The residue obtained was stirred in 30 cm^3 cold water. The solid precipitate was collected by filtration, washed with water, dried, and recrystallized from a proper solvent.

Yield 1.83 g (80%), mp 286 °C (*DMF*); R_f 0.16 (toluene/methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,100, 1,670, 1,640, 1,610, 1,580, 1,540, 1,490, 1,460 cm^{-1}; ^1H NMR (300 MHz, *DMSO-d*$_6$): δ = 2.04 (s, 3H, CH_3), 2.72 (t, J = 7 Hz, 2H, CH_2), 3.36 (t, J = 7 Hz, 2H, CH_2O), 4.65 (bs, 1H, OH), 7.22 (dt, J = 8.3 & 2.8 Hz, 1H, C_8–H), 7.30 (dt, J = 8.3 & 2.7 Hz, 1H, C_7–H), 7.50 (dd, J = 8.3 & 2.8 Hz, 1H, C_6–H), 8.41 (dd, J = 7.3 & 2.9 Hz, 1H, C_9–H), 12.60 (bs, 1H, NH) ppm; ^{13}C NMR (300 MHz, *DMSO-d*$_6$): δ = 21.3 (CH_3), 29.1 (CH_2), 57.5 (OCH_2), 116.3, 119.4, 122.1, 122.9, 125.2, 128.1, 138.4, 156.6, 164.0 ppm.

General procedure for the synthesis of 3-(2-chloroethyl)-2-methylhetero[3,2-a] pyrimidin-4(1H)-one ***6a–6d***

Dihydrofuranone **3a–3c**, **5a–5b**, or **5d** (0.01 mol) was refluxed in 30 cm^3 phosphorous oxychloride for 2 h. The excess of phosphorous oxychloride was removed under reduced pressure. Ice-cold water (100 cm^3) was added to the reaction mixture, which was followed by neutralization with 6 g solid sodium carbonate and further stirring for 2 h. The precipitated product was collected by filtration, washed with water, dried, and recrystallized.

3-(2-Chloroethyl)-2-methyl-1,3-benzthiazolo[3,2-a] pyrimidin-4(1H)-one (**6a**, $C_{13}H_{11}N_2OSCl$)
Yield 2.08 g (75%), mp 141 °C (ligroin) [Lit[21] mp 144 °C]; R_f 0.50 (toluene/acetone 9:1); IR (KBr): $\bar{\nu}$ = 1,670, 1,590, 1,500, 1,440 cm^{-1}; ^1H NMR (300 MHz, *DMSO-d*$_6$): δ = 2.52 (s, 3H, CH_3), 3.15 (t, J = 7 Hz 2H, CH_2), 3.85 (t, J = 7 Hz, 2H, CH_2Cl), 7.52 (dt, J = 8.2 & 2.8 Hz, 1H, C_7–H), 7.76 (dt, J = 8.3 & 2.2 Hz, 1H, C_8–H), 8.06 (dd, J = 8.3 & 2.7 Hz, 1H, C_6–H), 8.30 (dd, J = 8.3 & 2.8 Hz, 1H, C_9H) ppm; ^{13}C NMR (300 MHz, *DMSO-d*$_6$): δ = 20.9 (CH_3), 23.2 (CH_2), 41.9 (OCH_2), 116.1, 121.6, 124.7, 125.8, 129.6, 130.1, 137.2, 153.0, 155.0, 163.3 ppm.

3-(2-Chloroethyl)-2-methyl-8-methoxy-1,3-benzothiazolo [3,2-a]pyrimidin-4(1H)-one (**6b**, C_{14} $H_{13}Cl_2N_2O_2S$)
Yield 2.75 g (80%), mp 178 °C (ligroin); R_f 0.16 (toluene/acetone 9:1); IR (KBr): $\bar{\nu}$ = 2,910, 1,660, 1,600, 1,570, 1,510, 1,480, 1,440 cm^{-1}; ^1H NMR (300 MHz, *DMSO-d*$_6$): δ = 2.42 (s, 3H, CH_3), 3.15 (t, J = 7 Hz, 2H, CH_2), 3.76 (t, J = 7 Hz, 2H, CH_2Cl), 3.83 (s, 3H, OCH_3), 6.92 (d, J = 8.3 Hz, 1H, C_6–H), 7.13 (d, J = 2.3 Hz, 1H, C_9–H), 8.80 (dd, J = 8.3 & 2.2 Hz, 1H, C_7–H) ppm; ^{13}C NMR (300 MHz, *DMSO-d*$_6$): δ = 18.4 (CH_3), 25.9 (CH_2), 63.2 (OCH_3), 45.5 (OCH_2), 118.1, 126.6, 122.7, 128.8, 127.6, 133.1, 139.2, 156.0, 159.0, 169.2 ppm.

3-(2-Chloroethyl)-2-methyl-1,3-benzoxazolo [3,2-a]pyrimidin-4(1H)-one (**6c**, $C_{13}H_{11}ClN_2O_2$)
Yield 2.06 g (79%), mp 140 °C (ligroin); R_f 0.19 (toluene/methanol 9:1); IR (KBr): $\bar{\nu}$ = 1,680, 1,640, 1,600, 1,530 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3H, CH_3), 3.22 (t, J = 7 Hz, 2H, CH_2), 3.83 (t, J = 7 Hz, 2H, CH_2Cl), 7.21 (dt, J = 8.2 & 2.8 Hz, 1H, C_7–H), 7.36 (dt, J = 8.3 & 2.2 Hz, 1H, C_8–H), 8.08 (dd, J = 8.3 & 2.7 Hz, 1H, C_6–H), 8.26 (dd, J = 8.3 & 2.8 Hz, 1H, C_9H) ppm; ^{13}C NMR (300 MHz, *DMSO-d*$_6$): δ = 19.2 (CH_3), 24.3 (CH_2), 65.2 (OCH_2), 106.1, 118.7, 119.2, 126.9, 133.9, 148.5, 155.0, 156.5, 158.2, 168.0 ppm.

3-(2-Chloroethyl)-2-methyl-1,3-benzoimidazolo [3,2-a]pyrimidin-4(1H)-one (**6d**, $C_{13}H_{12}ClN_3O$)
Yield 1.95 g (75%), mp 230 °C (*DMF* ethanol); R_f 0.23 (toluene/methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,100, 1,660, 1,630, 1,610, 1,570, 1,520, 1,500, 1,470, 1,440 cm^{-1}; ^1H NMR (300 MHz, *DMSO-d*$_6$): δ = 2.40 (s, 3H, CH_3), 3.01 (t, J = 7 Hz, 2H, CH_2), 3.92 (t, J = 7 Hz, 2H, CH_2Cl), 7.32 (dt, J = 8.3 & 2.2 Hz, 1H, C_7–H), 7.50 (dt, J = 8.3 & 2.2 Hz, 1H, C_8–H), 7.62 (dd, J = 8.3 & 2.2 Hz, 1H, C_6–H), 8.43 (dd, J = 8.3 & 2.3 Hz, 1H, C_9–H), 12.61 (bs, 1H, NH) ppm; ^{13}C NMR (300 MHz, *DMSO-d*$_6$): δ = 21.7 (CH_3), 23.2 (CH_2), 41.9 (OCH_2), 116.1, 116.4, 119.0, 122.0, 122.9, 125.6, 138.4, 153.0, 157.6, 163.0 ppm.

Procedure for the synthesis of 3-(2-Acetoxyethyl)-2-methylbenzimidazolo- [3,2-a] pyrimidin-4(1H)-one (**7**, $C_{15}H_{15}N_3O_3$)

A 100-cm^3 round-bottom flask containing a mixture of 1.32 g 2-aminobenzimidazole **1d** (0.01 mol), 1.28 g α-acetyl-γ-butyrolactone (**2**) (0.01 mol, 1.10 cm^3), and 2.95 g ammonium acetate (0.05 mol) was heated at 120 °C for 1 h. Cold water (30 cm^3) was added to the viscous reaction mixture and stirred for 30 min to remove excess of ammonium acetate. The precipitated solid product was collected by filtration, washed with water, dried, and re-crystallized. Yield 2.28 g (80%), mp 232 °C (*DMF*); R_f 0.52 (toluene/acetone 9:1); IR (KBr): $\bar{\nu}$ = 3,100, 1,730, 1,670, 1,610, 1,570, 1,530, 1,490, 1,460 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO-d_6*): δ = 2.04 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.67 (t, J = 7 Hz, 2H, CH_2), 4.22 (t, J = 7 Hz, 2H, CH_2O), 7.22 (dt, J = 8.3 & 2.8 Hz, 1H, C_8–H), 7.30 (dt, J = 8.3 & 2.8 Hz, 1H, C_7–H), 7.5(dd, J = 8.3 & 2.8 Hz, 1H, C_6–H), 8.41(dd, J = 7.3 & 2.7 Hz, 1H, C_9–H), 12.60 (bs, 1H, NH) ppm; ^{13}C NMR (300 MHz, *DMSO-d_6*): δ = 20.7 (CH_3), 21.3 (CH_3), 24.8 (CH_2), 61.5 (OCH_2), 115.1, 116.5, 120.0, 123.0, 125.2, 125.5, 138.4, 153.0, 157.6, 161.0, 170.3 ppm.

General procedure for the synthesis of 3-(2-azidoethyl)-2-methyl-1,3-benzthiazolo[3,2-a] pyrimidin-4 (1H)-one ***8a–8b***

Compound **6a–6b** (0.01 mol) was stirred with 1.95 g sodium azide (0.03 mmol) in 30 cm^3 *DMF* and 5 cm^3 water at 60–70 °C for 4 h. The product was precipitated by adding 100 cm^3 cold water in the reaction mixture. The precipitated solid was collected by filtration, washed with cold water, and recrystallized from a proper solvent.

3-(2-Azidoethyl)-2-methyl-1,3-benzthiazolo[3,2-a] pyrimidin-4(1H)-one (**8a**, $C_{13}H_{11}N_5OS$)
Yield 2.28 g (80%), mp 94 °C, (Cyclohexane); R_f 0.45 (toluene/acetone 9:1); IR (KBr): $\bar{\nu}$ = 2,110 (N_3), 1,670 (CO), 1,590, 1,577, 1,550, 1,514 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO-d_6*): δ = 2.32 (s, 3H, CH_3), 2.82 (t, J = 8.3 Hz 2H, CH_2N_3), 3.44 (t, J = 8.3 Hz, 2H, CH_2), 7.63 (m, 2H, C_7–H, C_8–H), 8.06 (dd, J = 8.3 & 2.6 Hz, 1H, C_6–H), 8.30 (dd, J = 8.3 & 2.6 Hz, 1H, C_9H) ppm; ^{13}C NMR (300 MHz, *DMSO-d_6*): δ = 20.2 (CH_3), 26.2 (CH_2), 59.0 (OCH_2), 108.1, 121.7, 127.3, 135.8, 138.6, 141.0, 143.9, 147.7, 155.3 ppm.

3-(2-Azidoethyl)-2-methyl-1,3-benzimidazolo[3,2-a] pyrimidin-4(1H)-one (**8b**, $C_{13}H_{12}N_6O$)
Yield 2.27 g (85%), mp 234 °C (*DMF* ethanol); R_f 0.18 (toluene/acetone 9:1); IR (KBr): $\bar{\nu}$ = 3,220 (NH), 2,100 (N_3), 1,670 (CO), 1,647 (NH), 1,583, 1,553 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO-d_6*): δ = 2.04 (s, 3H, CH_3), 2.72 (t, J = 7 Hz, 2H, CH_2N_3), 3.36 (t, J = 7 Hz, 2H, CH_2), 7.22 (dd, J = 8.3 & 2.8 Hz, 1H, C_6–H), 7.60 (dd, J = 8.3 & 2.8 Hz, 1H, C_9–H), 8.82 (dt, J = 8.3 & 2.8 Hz, 1H, C_7–H), 8. 94 (dt, J = 8.2 & 2.3 Hz, 1H, C_8–H), 12.60 (bs, 1H, NH) ppm; ^{13}C NMR (300 MHz, *DMSO-d_6*): δ = 17.9 (CH_3), 28.1 (CH_2), 58.0 (OCH_2), 110.1, 122.7, 129.4, 136.5, 139.5, 143.2, 145.3, 148.8, 154.2 ppm.

Procedure for the synthesis of 3-(2-Ethoxyethyl)-2-methyl-1,3-benzimidazolo[3,2-a] pyrimidin-4(1H)-one (**9**, $C_{15}H_{17}N_3O_2$)

A suspension of 2.46 g **6d** (0.01 mol) in 30 cm^3 ethanol was refluxed in a solution of sodium ethoxide (0.23 g sodium dissolved in 10 cm^3 ethanol) for 1 h. The solvent was removed under reduced pressure. The residue was stirred in 100 cm^3 water and then acidified with 2 N hydrochloric acid. The precipitated solid was collected by filtration, dried, and recrystallized. Yield 2.11 g (78%), mp 225 °C (ethanol); IR (KBr): $\bar{\nu}$ = 3,100 (NH), 1,630 (CO), 1,600, 1,520, 1,500, 1,470, 1,450 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO-d_6*): δ = 1.13 (t, J = 7 Hz, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.83 (t, J = 7 Hz, 2H, CH_2), 3.41 (t, J = 7 Hz, 2H, CH_2), 3.50 (q, J = 7 Hz, 2H, CH_2), 7.23 (dt, J = 8.3 & 2.7 Hz, 1H, C_7–H), 7.31 (dt, J = 8.3 & 2.7 Hz, 1H, C_8–H), 7.45 (dd, J = 8.3 & 2.7 Hz, 1H, C_6–H), 8.40 (dd, J = 8.3 & 2.8 Hz, 1 H, C_9–H), 12.60 (s, 1H, NH) ppm; ^{13}C NMR (300 MHz, *DMSO-d_6*): δ = 15.5 (CH_3), 21.3 (CH_3), 25.9 (CH_2), 67.7 (OCH_2), 68.3 (OCH_2), 116.1, 116.5, 119.0, 122.0, 123.3, 125.2, 138.4, 147.2, 148.8, 166.3 ppm.

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