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PII: S0040-4020(17)30336-8

DOI: 10.1016/j.tet.2017.03.079

Reference: TET 28585

To appear in: *Tetrahedron*

Received Date: 7 January 2017

Revised Date: 16 March 2017

Accepted Date: 27 March 2017

Please cite this article as: Qomi HR, Habibi A, Synthesis of a novel functionalized tricyclic pyrimidine-fused 1,5-benzodiazepine library, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.03.079.

Graphical Abstract

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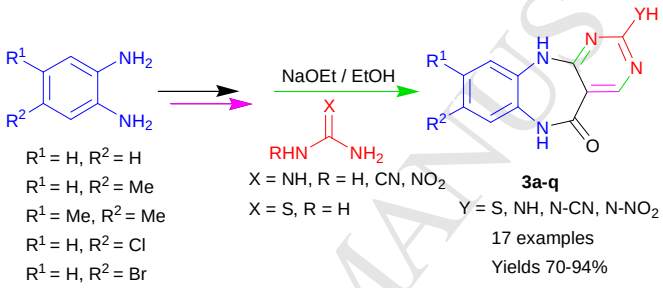

Synthesis of a novel functionalized tricyclic pyrimidine-fused 1,5-benzodiazepine library

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Abstract

A series of novel tricyclic pyrimidine-fused 1,5-benzodiazepines (PFBZDs) was synthesized using an enaminone-based approach. The key step in the synthetic strategy involves the formation of the C=C-NMe_2 structure on vicinal carbonyl groups of the 1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione (BZD). The synthesis of pyrimidine-fused 1,5-benzodiazepines was performed by a simple and efficient method in good to excellent yields under mild and green conditions. The *β*-enaminoamide intermediates were condensed with thiourea and guanidine derivatives to form the corresponding tricyclic PFBZDs. But reaction of aminoguanidine, thiosemicarbazide, 4-phenylthiosemicarbazide and ethane-1,2-diamine with *β*-enaminoamides didn't produce any desired product and led to recovery of the corresponding starting BZD.

Keywords: Pyrimidine-fused heterocycle, Pyrimidine-fused benzodiazepine, β-enaminoamide, 2-Aminopyrimidine, Pyrimidine-2-thiol, Guanidine.

1. Introduction

The development of '*privileged heterocyclic scaffolds*' is a rapidly emerging topic in medicinal chemistry.[1] Fused pyrimidine derivatives are an important class of potential bioactive *N*-heterocyclic scaffolds in modern medicinal chemistry due to their affinity for various biotargets. They display a broad spectrum of pharmaceutical applications such as anti-inflammatory, antioxidant, anticancer, antimicrobial, and antiviral and constitute the backbones of several marketed drugs.[2-6]

Benzodiazepines and their polycyclic derivatives are one of the most explored compound classes as privileged scaffolds in drug discovery. They are used in pharmaceuticals as cytotoxic agents against cancer cell lines[7-10] and anti-HIV-1 agents.[11] It is well documented that the pharmacological activity increases when an additional heterocyclic ring is fused to the heptatomic diazepine nucleus.[12] Because of the biological importance of the polyheterocyclic systems including the 1,5-benzodiazepine moiety[13-15] considerable attention has been directed towards the synthesis of polycyclic 1,5-benzodiazepines, in particular pyrimidine-fused benzodiazepines, as well as the 1,4-isomers.[16] Figure 1 shows some examples of pyrimidine-fused benzodiazepines, which have shown interesting pharmacological properties, such as antihypoxic and antipyretic (**A**); analgesic (**B**); gastric secretion inhibition (**C**); and

immunosuppressive activity (**D**). Compound **D** showed two-fold higher activity than cyclosporine **A** when it was tested in mice.[17]

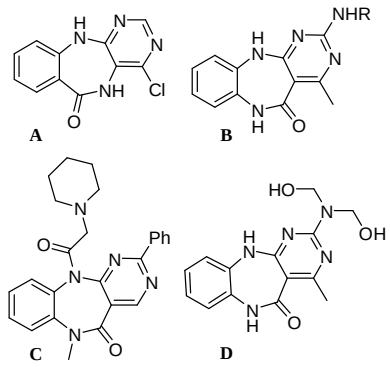


Figure 1. Examples of some bioactive pyrimidine-fused benzodiazepines.

A drug-like molecule could be considered as a congregation of small pieces of chemicals which are linked together and the biological effect of such a complex molecule is due to the contribution of these small fragments which are now working together as a unit. Considering the biological activity of fused-pyrimidine and polycyclic benzodiazepine derivatives, substantial attention has been paid to develop efficient new methodologies to synthesise and screen them against various cancer cell lines.

Heretofore, several fused tricyclic and polycyclic pyrimido 1,5-benzodiazepine derivatives have been reported in the literature, for which in many cases the starting material is a pyrimidine derivative and then the benzodiazepine is created in moderate to good yields in the presence of a catalyst. Among them, Panahi[18-20] *et al.* synthesized the pyrimidine-fused heterocycles (PFHs) *via* one-pot synthesis using three components of barbituric acid and amine with aldehyde or glucose in the presence of an acidic catalyst. Długosz[21] synthesized pyrimido[4,5-*b*][1,5]benzodiazepine derivatives starting with 6-methyl-2-oxo-4-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid and then in four steps the benzodiazepine ring was created with diethyl aniline as catalyst. Bai[22-24] and co-workers synthesized novel tricyclic and tetracyclic pyrimidine-fused benzodiazepines from the reaction of 4,6-dichloro-5-nitropyrimidine and/or 6-chloropyrimidine-4,5-diamine as a starting material with an aromatic amine and aldehyde under transition-metal catalysis and or acid-catalyzed conditions. The group of Roma[25] synthesized a number of 5*H*-pyrimido[4,5-*b*]-[1,5]benzodiazepin-5-ones from the reaction of 4-(dimethylamino)-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one with *N*,*N*-dimethylformamide (DMF) in the presence of phosphorus pentachloride (PCl_5) at room temperature and subsequently react with amidines to form pyrimidines.

β-Enaminones are established as a versatile synthetic intermediate in the synthesis of polyfunctionally substituted heterocycles.[26,27] There are several reports of synthesis of pyrimidine-fused heterocyclic compounds using an enaminone-based approach.[28-30,31-33] In solution, β-enaminones have been reported to condense with thiourea, amidines, and guanidines

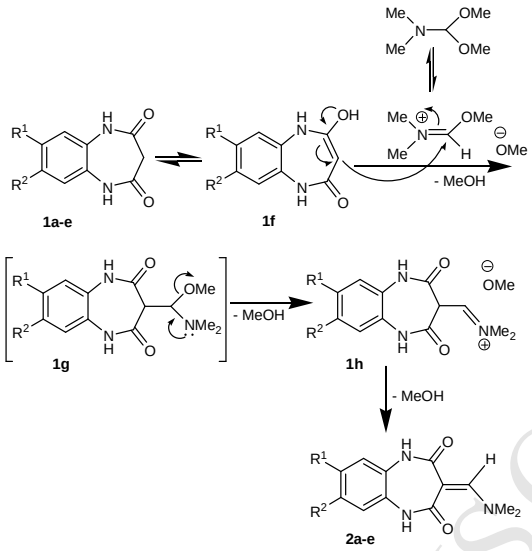
to give 2-mercapto-, 2-alkyl/aryl-, and 2-aminoalkyl/arylpyrimidines, respectively, in moderate to good yields.[34] Using a similar strategy, Farghaly[35] *et al*. developed the synthesis of analogous tetracyclic and pentacyclic PFHs with heterocyclic amines.

We were inspired by the biologically active PFHs, 2-amino pyrimidine,[6,36-38] and pyrimidine-2-thiol moiety.[39,40] A new approach is proposed for the synthesis of a library of various new tricyclic pyrimidine-fused derivatives with the 1,5-BZD core *via* an enaminone-based approach, including 2-aminopyrimidine, pyrimidine-2-yl-cyanamide, *N*-nitro pyrimidine-2-amine, and pyrimidine-2-thiol derivatives (**3a-q**) as precursors of bioactive compounds (Table 2). Unlike the previous reports, in this method pyrimidine was not used as the starting material and instead pyrimidine rings were formed on the BZD scaffold. Also the substituted pyrimidine-fused 1,5-benzodiazepines (PFBZD) were obtained from cheaper and easier to access starting materials by this simple enaminone-based strategy in good to excellent yields under mild conditions and without catalyst.

2. Results and Discussion

In this project, a simple route for the synthesis of a series of novel tricyclic PFBZD derivatives was reported. In the first step, the 1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione (BZD) derivatives (**1a**-**e**) were obtained by the reaction of benzene-1,2-diamines and 1,3-propanedioic acid in the presence of two equivalents of HCl at 80 °C in good yields within 3 hours (Table 1).

In the following step, for the synthesis of key intermediates (**2a**-**e**), the BZDs **1a**-**e** reacted with *N*,*N*-dimethylformamide-dimethylacetal (DMF-DMA) in dry *p*-xylene and/or toluene or under solvent-free condition at reflux for a short time and afforded the corresponding isolable solid product benzodiazepinic β-enaminoamides (**2a**-**e**) in good yields (Table 1). The intermediate 3-((dimethylamino)methylene)-1*H*-benzo[*b*][1,4]diazepine-2,4(3*H*,5*H*)-dione (**2a**) was synthesized from the reaction of **1a** with DMF-DMA under reflux in a sealed tube (Scheme 1). The formamide acetal (DMF-DMA) enters into alkylation mostly via methoxide elimination and generation of a methoxyiminium ion.[41-43] Elemental analysis and spectral data were in complete accordance with the assigned structure **2**. For example, the ^{1}H NMR spectrum of compound **2a** revealed two new singlet signals at δ 2.91 and 7.48 ppm characteristic for the *N*,*N*-dimethylamino group and the exocyclic C=CH protons, respectively. A plausible mechanism for the formation of the β-enaminoamides (**2a**-**e**) is proposed in Scheme 1. The β-enaminoamide derivatives **2a**-**e** were then used as intermediates for the synthesis of the tricyclic PFBZD derivatives.



Scheme 1. A plausible mechanism for the formation of the benzodiazepinic β-enaminoamides.

Table 1. Synthesis of the BZDs **1a**-**e** and the benzodiazepinic β-enaminoamides **2a**-**e**.

Entry	R^1	R^2	Product	Yield (%)
1	H	H	**1a**	64
2	Me	H	**1b**	70
3	Me	Me	**1c**	63
4	Cl	H	**1d**	72
5	Br	H	**1e**	62
6	H	H	**2a**	63
7	Me	H	**2b**	65
8	Me	Me	**2c**	62
9	Cl	H	**2d**	68
10	Br	H	**2e**	55

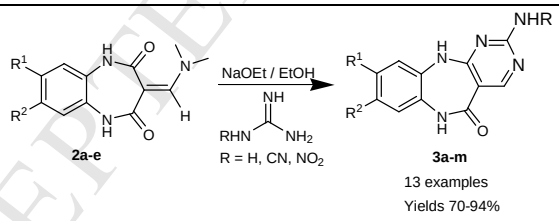
The intermediates (**2a-e**) were condensed with thiourea and guanidine derivatives to form the corresponding tricyclic PFBZD derivatives including 2-aminopyrimidine, pyrimidine-2-yl-cyanamide, *N*-nitro pyrimidine-2-amine, and pyrimidine-2-thiol fused 1,5-benzodiazepine derivatives (**3a-q**). The cyclization reaction of β-enaminoamide **2a** with guanidine nitrate was investigated under reflux in basic conditions which proceeded smoothly to give the desired product **3a** in high yield (Table 2). The scope of this cyclization was then explored with other guanidine derivatives and thiourea which produced the desired 6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-5-ones (**3b-q**) in good to excellent yields (Table 2). All compounds were synthesized by a similar method. The structural confirmation of the initially synthesized starting heterocycles (**1a-e**), benzodiazepinic β-enaminoamide intermediates (**2a-e**), and the final products (**3a-q**) were corroborated using FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and CHN (see Supplementary data). The synthetic route established here provides a basis to obtain functionalized tricyclic PFBZD derivatives, as illustrated in Scheme 2. By investigation of the products of the synthetic route we observed that:

I) Six PFBZD products with non-substituted and symmetrically substituted benzene ring (**3a, 3c, 3f, 3h, 3n, 3p**) were obtained as a single isomeric product. The isolated yields of pure products from reaction of the symmetric substituted β-enaminoamides **2a** and **2c** with guanidine derivatives and thiourea were 70-94%, as depicted in Table 2 and Table 3.

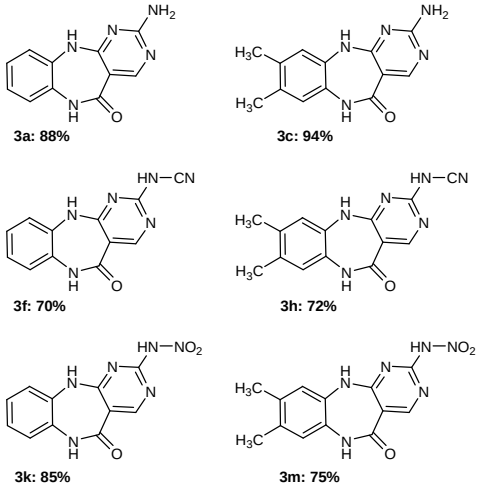
II) Eight PFBZD products containing non-symmetrically substituted benzene rings (**3b**, **3d**, **3e**, **3g**, **3i**, **3j, 3o**, **3q**) were obtained as a mixture of two isomers from the reaction of the non-symmetrically substituted β-enaminoamides **2b**, **2d**, and **2e** with guanidine derivatives and thiourea in good to excellent yield (72-94%). According to the structure of the β-enaminoamides **2b**, **2d**, and **2e**, condensation and cyclization with the reagents can occur with each of two carbonyl groups. Therefore, the two structures for each of the products containing non-symmetrically substituted benzene rings are likely, as depicted in Table 2, Table 3 and Scheme 2.

The work-up of the reactions gave a solid crude product. ^{1}H NMR spectra for each of the products did not show separate chemical shifts for the various protons of the isomers, while ^{13}C NMR spectra easily showed the existence of two isomers due to the appearance of two sets of signals especially in aromatic area (see Supplementary data). Since the two isomers of crude product have similar ^{1}H NMR spectra, calculation of the percent of each isomer in the mixture by ^{1}H NMR was not possible. These crude products decomposed within the range 270 to 350˚C. Thin-layer chromatography (TLC) of the each crude product on silica gel revealed a single spot in various solvent systems. All attempts to separate these isomers in the crude products by preparative TLC and column chromatography failed.

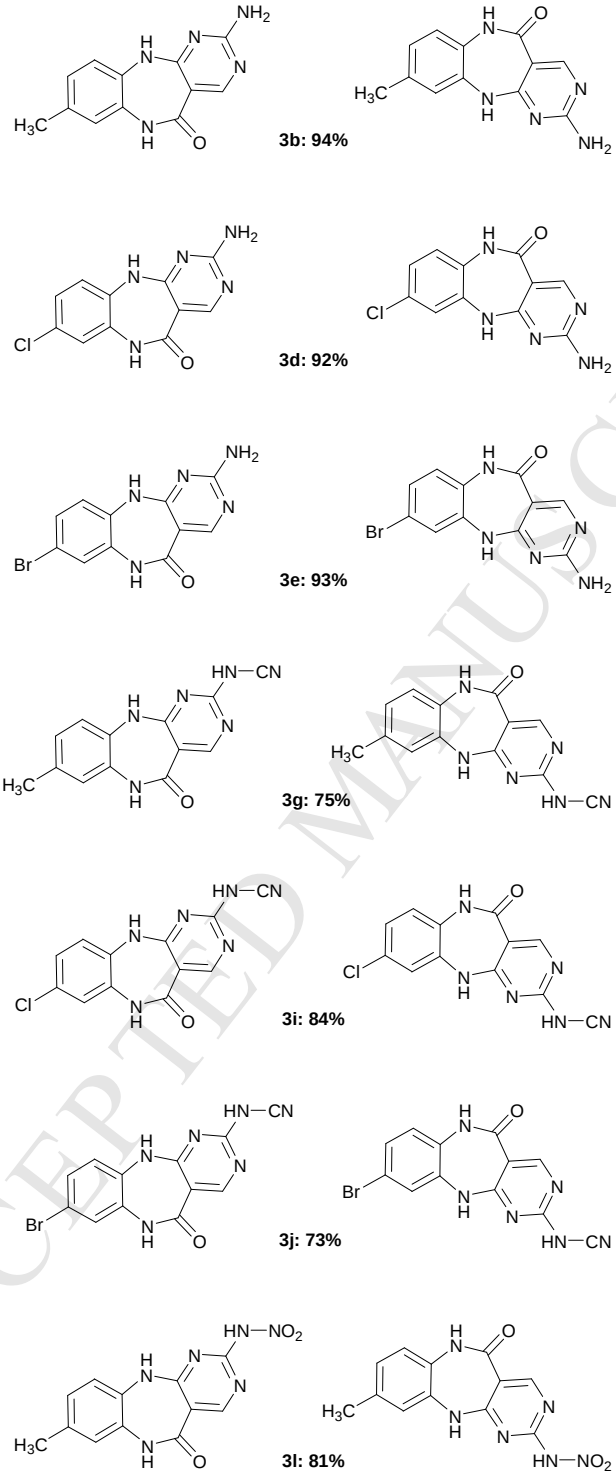
Table 2. The synthesis of functionalized tricyclic pyrimidine-fused 1,5-benzodiazepine (PFBZD) derivatives under optimized conditions[a]



I)	The products from the symmetrically substituted β-enaminoamides[b]

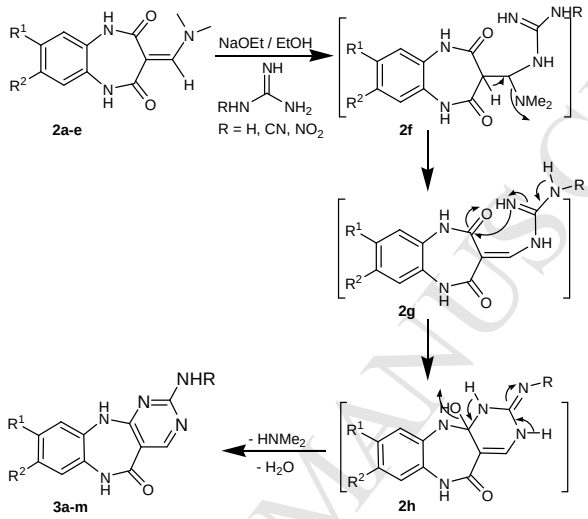


II) The products from the non-symmetrically substituted β-enaminoamides[c]



[a] Reaction conditions: β-enaminoamide (1 mmol), guanidine derivatives (1.1 mmol), sodium ethoxide (1.1 mmol) and absolute ethanol (10 mL), reflux 3-4 h. [b] All yields are pure yields. [c] All yields are crude yields.

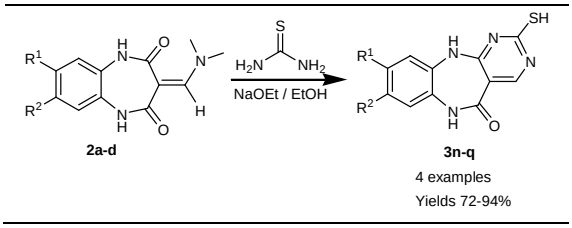
To account for the formation of products **3a-m**, it is suggested that the reaction started with the Michael type addition of the amino group of guanidine derivatives to the activated double bond in β-enaminoamide derivative (**2a-e**), followed by elimination of the dimethylamino group to afford an intermediate adduct (**2g**). Then an intramolecular cyclization and subsequent aromatization *via* loss of water molecule under the reaction conditions would give the desired products **3a-q**, as depicted in Scheme 2.

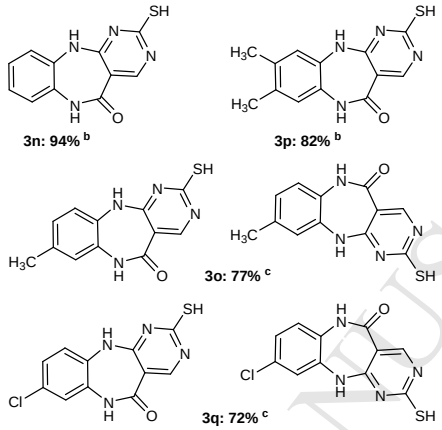


Scheme 2. A plausible reaction mechanism for the synthesis of tricyclic pyrimidine-fused 1,5-benzodiazepine (PFBZD) derivatives **3a-m**. Note: In the case of non-symmetrically substituted compounds on the benzene ring, condensation and cyclization with the reagents can occur with each of two carbonyl groups. Therefore, two structures for each of the products containing non-symmetrically substituted benzene rings are likely, as depicted in Table 2 and Table 3.

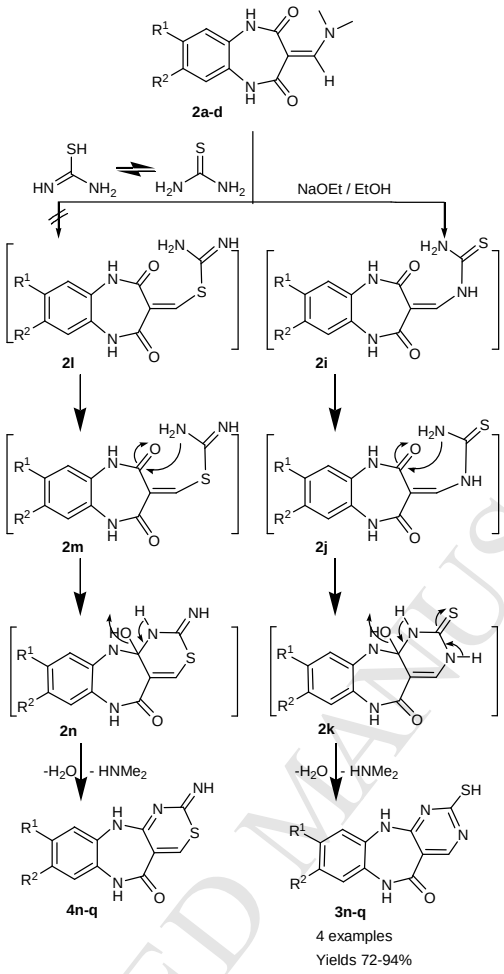
III) In the reaction of thiourea with β-enaminoamides **2a**, **2b**, and **2d**, if the sulfur acts initially as a nucleophile the products **4n-q** would be achieved. While with initial nucleophilic attack by nitrogen, the products **3n-q** could be obtained (Table 3). Although it appears that the nucleophilicity of the sulfur atom is greater than nitrogen, spectral evidence indicates that the expected derivatives **4n-q** were not obtained and rather the novel pyrimidine-2-thiol derivatives **3n-q** were formed, as depicted in Scheme 3.[31,32,44-47] The formation of compounds **3n-q** would involve an initial Michael addition of the amino group of thiourea to the activated double bond in β-enaminoamide derivative (**2a-e**), followed by the same mechanism as described in Scheme 2 to give **3n-q**. Aromatization as a driving force would lead to the formation of products **3n-q**. The structures of the latter products (**3n-q**) were deduced from their elemental analysis and spectral data.

Table 3. The synthesis of tricyclic fused pyrimidine-2-thiol 1,5-benzodiazepine derivatives under optimized conditions[a]



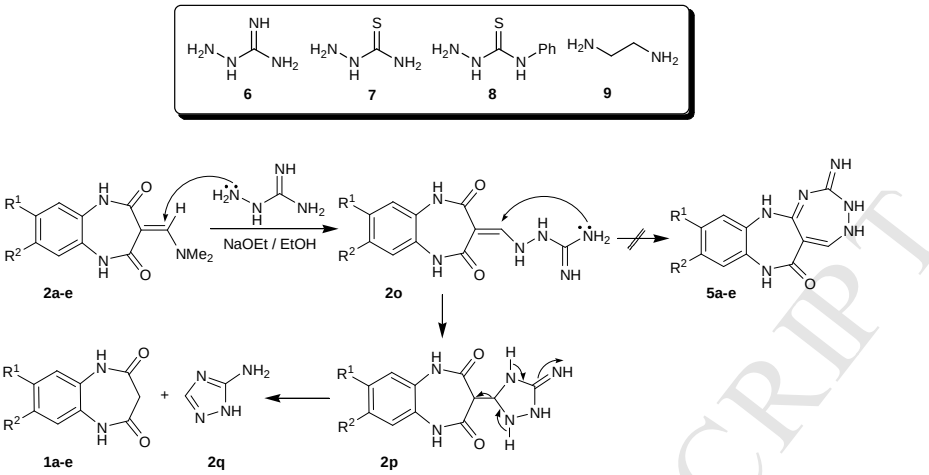


[a] Reaction conditions: β-enaminoamide (1 mmol), thiourea (1.1 mmol), sodium ethoxide (1.1 mmol) and absolute ethanol (10 mL), reflux 3-4 h. [b] The yield of isolated product. [c] The yield of crude product.



Scheme 3. A plausible mechanism for the synthesis of tricyclic fused pyrimidine-2-thiol 1,5-benzodiazepine derivatives **3n-q**.

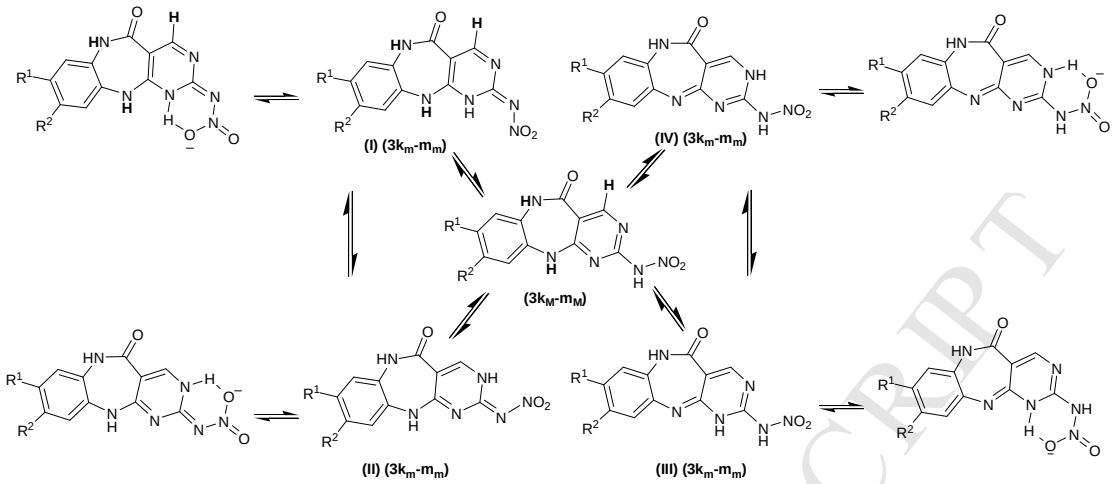
IV) In order to produce new fused seven-membered 1,2,4-triazepine and 1,4-diazepine rings on the BZD scaffold, the reaction of aminoguanidine bicarbonate (**6**), aminothiourea (thiosemicarbazide) (**7**), 3-amino-1-phenylthiourea (4-phenylthiosemicarbazide) (**8**), and ethane-1,2-diamine (**9**) with some β-enaminoamides (**2a-e**) was performed. Surprisingly, results of spectroscopic studies showed that these reactions led to the corresponding starting BZD. The proposed mechanism of these reactions contains a nucleophilic substitution in the first step and in the following an interamolecular Michael addition is performed instead of ring closure and formation of the seven-membered ring. As an example of the possible mechanism, the reaction of β-enaminoamide derivatives with aminoguanidine bicarbonate (**6**) is shown in the Scheme 4, that followed by hydrogen shift and aromatization of the triazole gives the corresponding starting BZD and 2*H*-1,2,4-triazol-3-amine.



Scheme 4. A possible mechanism for formation of the corresponding starting BZD from the reaction of β-enaminoamide derivatives with aminoguanidine bicarbonate.

V) A spectroscopic study of the three compounds **3k-m** showed two products as major and minor species. The major products have the same structure as illustrated in Scheme 2. Four tautomers are possible. A plausible structure for the tautomeric minor product of **3k-m** is proposed in Scheme 5. In the ^{1}H NMR spectra, the ratio of major/minor tautomer for **3k**, **3l**, and **3m** was found to be 72.7/27.3=2.66, 68.5/31.5=2.17, and 59/41=1.44, respectively. Hydrogen of pyrimidine ring in the major tautomer should be appeared in low-field, but it appears in high-field in minor tautomer due to the loss of aromaticity of the pyrimidine ring.

Due to a longer conjugated system connected with the benzene ring, the tautomers (III) and (IV) are more stable and hence more likely. The tautomer (IV) is cross-conjugate, but the isomer (III) has a longer linear conjugated system connected to the benzene ring. Therefore, it is possible that the isomer (III) might be the minor product. Furthermore, while each of the four tautomers has a structure with intramolecular hydrogen bonding between the nitro group oxygen and the *N*-hydrogen, each of them has a resonance form.



Scheme 5. Plausible structures for the minor product tautomers (3k-m).

3. Conclusions

A simple and efficient method for the synthesis of the tricyclic pyrimidine-fused 1,5-benzodiazepine (PFBZD) derivatives **3a-q** with the 1,5-benzodiazepine-2,4-dione (BZD) core has been developed. An enaminone-based approach has been found to be a useful route for the construction of some fused heterocyclic systems including tricyclic pyrimidine-fused heterocycles (PFHs). The scope and generality of this methodology have been successfully demonstrated by synthesizing a variety of fused pyrimidine derivatives. The prominent advantages of the described report are the novelty of synthesized compounds, operational simplicity in terms of step count, mild conditions, absence of catalysts, isolable intermediate, and good to excellent yields. Furthermore, this method proved to be versatile since the pyrimidine system can be replaced by other *N*-heterocycles such as pyrazoles, isoxazoles, pyridazines, pyridines, and triazole to obtain various ring-fused systems. This strategy provides an efficient method to access a library of polycyclic PFHs from privileged C-H acidic carbonyl compounds that are of great interest in drug discovery.

4. Experimental

4.1. General

Chemical Reagents and solvents were purchased from commercial suppliers (Merck, Aldrich, and Fluka) and were used as received without further purification. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on a Bruker Advance spectrometer in deuterated dimethylsulfoxide (DMSO-d_6) solutions and chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are reported in Hertz (Hz). A Perkin-Elmer 843 spectrophotometer Fourier-transform infrared (FT-IR) spectrometer was employed for characterization of the products in KBr disc form and is reported in wavenumbers (cm^{-1}). The melting points were determined in open capillary tubes using an

Electrothermal 9100 apparatus and are uncorrected. Reaction monitoring was accomplished by thin-layer chromatography (TLC) using aluminium sheets with silica gel 60 F_{254} (Merck) and the spots were visualized with UV light. Elemental analysis was determined with a Perkin-Elmer CHN analyzer (2400 series II).

4.2.General procedure for the synthesis of the BZDs (1a-e)

The starting material, 1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione (BZD) (**1a**) was synthesized on the basis of earlier published methods by condensing 1,3-propanedioic acid with benzene 1,2-diamine in hydrochloric acid, with minor modifications as mentioned below.[48-53] One equivalent (eq) 1,3-propanedioic acid (2.08 g, 20 mmol) was first stirred with 2 eq HCl (4 N) and then treated with 1 eq benzene-1,2-diamine (2.17 g, 20 mmol). The reaction was heated to 80 °C for 3 h. The progress of the reaction was monitored by TLC. After the completion of the reaction and cooling of the mixture, the obtained suspension was filtered and washed with cold ethanol and water. The other BZD derivatives (**1b-e**) were prepared by the same method in good yields (62-72%).

1*H*-1,5-Benzodiazepine-2,4(3*H*,5*H*)-dione (1a). White solid (Yield: 2.25 g, 64%); m.p. 350 °C (d) [lit[54,48] m.p. >350 °C (d)]. IR (KBr, cm^{-1}): 3193, 3054, 2955, 2891, 1704, 1670, 1597, 1503, 1428, 1400, 1350, 822. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.16 (2H, s, CH_2), 7.09-7.16 (4H, m, Ar), 10.39 (2H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 45.1, 122.2, 124.9, 129.7, 165.8. Anal. Calcd for $C_9H_8N_2O_2$ (176.17): C, 61.36; H, 4.58; N, 15.90. Found: C, 61.38; H, 4.38; N, 16.10.

7-Methyl-1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione (1b). Pale brown solid (Yield: 2.66 g, 70%); m.p. 337-339 °C (d) [lit[48] m.p. >350 °C (d)]. IR (KBr, cm^{-1}): 3188, 3082, 2950, 2869, 1696, 1670, 1596, 1499, 1427, 1344, 812. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.25 (3H, s, CH_3), 3.13 (2H, s, CH_2), 6.90 (1H, s, Ar), 6.97 (1H, d, J = 8.3 Hz, Ar), 6.98 (1H, d, J = 8.3 Hz, Ar), 10.27 (1H, s, NH), 10.31 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.3, 45.0, 122.1, 122.2, 125.6, 127.3, 129.4, 134.2, 165.6, 165.7. Anal. Calcd for $C_{10}H_{10}N_2O_2$ (190.20): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.00; H, 5.31; N, 14.62.

7,8-Dimethyl-1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione (1c). Yellow solid (Yield: 2.60 g, 63%); m.p. >350 °C (d) [lit[48] m.p. >350 °C (d)]. IR (KBr, cm^{-1}): 3193, 3076, 2971, 2858, 1695, 1655, 1595, 1514, 1430, 1348, 821. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.15 (6H, s, 2 CH_3), 3.10 (2H, s, CH_2), 6.86 (2H, s, Ar), 10.21 (2H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.7, 45.0, 122.7, 127.3, 133.0, 165.6. Anal. Calcd for $C_{11}H_{12}N_2O_2$ (204.23): C, 64.69; H, 5.92; N, 13.72. Found: C, 64.88; H, 5.93; N, 13.51.

7-Chloro-1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione (1d). Dark brown solid (Yield: 3.05 g, 72%); m.p. 336-339 °C (d) [lit[48] m.p. >250 °C (d)]. IR (KBr, cm^{-1}): 3194, 3056, 2948, 2854,

1708, 1668, 1600, 1593, 1494, 1422, 1396, 814. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.20 (2H, s, CH_2), 7.12 (1H, d, J = 8.6 Hz, Ar), 7.14 (1H, d, J = 2.1 Hz, Ar), 7.22 (1H, dd, J = 8.6, 2.1 Hz, Ar), 10.47 (2H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 45.1, 121.5, 123.9, 124.7, 128.4, 128.7, 130.9, 165.6, 165.8. Anal. Calcd for $C_9H_7ClN_2O_2$ (210.62): C, 51.32; H, 3.35; N, 13.30. Found: C, 51.23; H, 3.17; N, 13.20.

7-Bromo-1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione (1e). Brown solid (Yield: 3.16 g, 62%); m.p. 336-338 °C (d). IR (KBr, cm^{-1}): 3192, 3053, 2947, 2851, 1706, 1669, 1594, 1490, 1424, 1395, 813. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.20 (2H, s, CH_2), 7.06 (1H, d, J = 8.5 Hz, Ar), 7.28 (1H, d, J = 2.0 Hz, Ar), 7.33 (1H, dd, J = 8.5, 2.0 Hz, Ar), 10.45 (2H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 45.1, 116.2, 124.0, 124.3, 127.4, 129.1, 131.1, 165.5, 165.6. Anal. Calcd for $C_9H_7BrN_2O_2$ (255.07): C, 42.38; H, 2.77; N, 10.98. Found: C, 42.39; H, 2.71; N, 10.97.

4.3. General procedure for the synthesis of β-enaminonamide intermediates (2a-e)

1*H*-1,5-Benzodiazepine-2,4(3*H*,5*H*)-dione (BZDs) derivatives (**1a-e**) (2 mmol) and an excess of *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA, 2.5 mL) were heated under reflux (110 °C) either solvent free (for **2a**, **2b**,**2c**) or in 5-8 mL toluene or *p*-xylene as a medium (for **2d**, **2e**) with less DMF-DMA (1 mL) for 4-6 h. Progress and completion of the reaction was monitored by TLC then the reaction was left to cool to room temperature. The crude product that formed upon cooling was filtered and washed with cold diethyl ether to give the corresponding β-enaminoamide derivatives (**2a-e**). The benzodiazepinic β-enaminoamides were obtained in good isolated yields (55-68%).

3-((Dimethylamino)methylene)-1*H*-benzo[*b*][1,4]diazepine-2,4(3*H*,5*H*)-dione (2a). White powder (Yield: 0.30 g, 63%); m.p. 219-222 (d) °C. IR (KBr, cm^{-1}): 3159, 3031, 2900, 1653, 1616, 1576, 1503, 1381, 1127, 1094, 970, 783, 736, 661, 625, 534, 452. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.92 (6H, broad, s, 2 CH_3), 6.98 (4H, s, Ar), 7.48 (1H, s, =CH), 9.23 (1H, s, NH), 9.45 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 47.2 (2 CH_3), 95.5 (*C*=CH), 120.9, 121.9, 123.7, 123.9, 130.2, 131.5 (Ar), 155.9 (C=*C*H), 166.5 (CONH), 171.4 (CONH). Anal. Calcd for $C_{12}H_{12}BrN_3O_2$ (231.25): C, 62.33; H, 5.67; N, 18.17. Found: C, 62.32; H, 5.48; N, 18.24.

3-((Dimethylamino)methylene)-7-methyl-1*H*-benzo[*b*][1,4]diazepine-2,4(3*H*,5*H*)-dione (2b). Brown powder (Yield: 0.32 g, 65%); m.p. 236-239 (d) °C. IR (KBr, cm^{-1}): 3184, 3028, 2924, 1653, 1611, 1577, 1521, 1384, 1128, 1100, 966, 808, 770, 677, 627, 553, 435. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.18 (3H, s, CH_3), 2.90 (6H, s, broad, 2 CH_3), 6.77-6.80 (2H, m, Ar), 6.86 (1H, d, J = 8.4 Hz, Ar), 7.45 (1H, s, =CH), 9.13 (1H, s, NH), 9.36 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.3 (CH_3), 46.1 (2 CH_3), 95.7 (*C*=CH), 121.0, 124.5, 127.7, 129.0, 131.3, 133.0 (Ar), 155.6 (C=*C*H), 166.5 (CONH), 171.3 (CONH). Anal. Calcd for $C_{13}H_{15}N_3O_2$ (245.28): C, 63.66; H, 6.16; N, 17.13. Found: C, 63.83; H, 6.32; N, 17.12.

3-((Dimethylamino)methylene)-7,8-dimethyl-1*H*-benzo[*b*][1,4]diazepine-2,4(3*H*,5*H*)-dione (2c). Cream powder (Yield: 0.32 g, 62%); m.p. 286-288 (d) °C. IR (KBr, cm^{-1}): 3139, 3027, 2932, 1668, 1612, 1597, 1512, 1388, 1348, 1116, 875, 790, 678, 643, 534, 456. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.09 (6H, s, 2 CH_3), 2.89 (6H, broad, s, 2 N-CH_3), 6.73 (2H, s, Ar), 7.42 (1H, s, =CH), 9.06 (1H, s, NH), 9.30 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.7 (2 CH_3), 54.4 (2 NCH_3), 95.9 *(C*=CH), 121.7, 121.8, 127.7, 129.0, 131.4, 131.7 (Ar), 155.3 (C=*C*H), 166.6 (CONH), 171.4 (CONH). Anal. Calcd for $C_{14}H_{17}N_3O_2$ (259.3): C, 64.85; H, 6.61; N, 16.20. Found: C, 64.61; H, 6.67; N, 15.94.

7-Chloro-3-((dimethylamino)methylene)-1*H*-benzo[*b*][1,4]diazepine-2,4(3*H*,5*H*)-dione (2d). Creamy-yellow powder (Yield: 0.36 g, 68%); m.p. 226-229 (d) °C. IR (KBr, cm^{-1}): 3170, 3023, 2940, 1658, 1619, 1576, 1501, 1430, 1378, 1125, 1096, 774, 673, 626, 500. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.79 (3H, broad, s, CH_3), 3.08 (3H, s, CH_3), 6.97-7.06 (3H, m, Ar), 7.54 (1H, s, =CH), 9.35 (1H, s, NH), 9.48 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.4 (2 CH_3), 94.9 *(C*=CH), 120.2, 122.4, 123.4, 127.2 (Ar), 156.6 (C=*C*H), 166.1 (CONH). Anal. Calcd for $C_{12}H_{12}ClN_3O_2$ (265.7): C, 54.25; H, 4.55; N, 15.82. Found: C, 54.13; H, 4.54; N, 15.64.

7-Bromo-3-((dimethylamino)methylene)-1*H*-benzo[*b*][1,4]diazepine-2,4(3*H*,5*H*)-dione (2e). Purple powder (Yield: 0.34 g, 55%); m.p. 246-248 (d) °C. IR (KBr, cm^{-1}): 3177, 3044, 2936, 1660, 1619, 1578, 1496, 1384, 1340, 1124, 810, 769, 736, 669, 624, 482. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.77 (3H, s, CH_3), 3.06 (3H, s, CH_3), 6.93 (1H, d, J = 8.9 Hz, Ar), 7.14-7.17 (2H, m, Ar), 7.54 (1H, s, =CH), 9.35 (1H, s, NH), 9.47 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 53.3 (2 CH_3), 94.8 *(C*=CH), 115.1, 122.6, 123.0, 126.3, 139.1, 139.4 (Ar), 156.6 (C=*C*H), 166.6 (CONH). Anal. Calcd for $C_{12}H_{12}BrN_3O_2$ (310.15): C, 46.47; H, 3.90; N, 13.55. Found: C, 46.50; H, 3.82; N, 13.39.

4.4. General procedure for the synthesis of compound 3a-q

The compound **2a-e** (1 mmol) was added to a mixture of guanidine nitrate, aminoguanidine bicarbonate, cyanoguanidine, nitroguanidine, or thiourea (1.1 mmol) in a solution of sodium ethoxide (1.1 mmol) and absolute ethanol (10 mL), and then mixture was stirred under reflux for 3-4 h. After completion of the reaction, the solvent was removed by distillation and the residue was treated with glacial acetic acid (2 mL), just enough to dissolve the pyrimidine sodium salt and then heated at reflux for 15 min. The resulting solid products were collected by filtration, washed with ethanol and cold diethyl ether and dried to give the corresponding derivatives (**3a-q**). The tricyclic pyrimidine-fused 1,5-benzodiazepine (PFBZD) derivatives were obtained in good to excellent yields. Among these products, six PFBZD compounds with non-substituted and symmetrically substituted benzene rings (**3a, 3c, 3f, 3h, 3n, 3p**) were synthesized as a single isomer in 70-94% pure yield, and eight PFBZD products containing non-symmetrically substituted benzene rings (**3b, 3d, 3e, 3g, 3i, 3j, 3o, 3q**) were obtained as a mixture of two isomers in 72-94% yield.

2-Amino-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-5-one (3a). Green powder (Yield: 0.20 g, 88%); m.p. 325-327 (d) °C. IR (KBr, cm^{-1}): 3461, 3322, 3197, 3121, 3052, 1677, 1625, 1601, 1541, 1472, 1441, 1420, 1333, 1269, 796, 744, 597. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.86-6.95 (4H, m, Ar), 6.91-6.98 (2H, m, NH_2), 8.45 (1H, s, =CH), 8.90 (1H, s, NH), 9.48 (1H, s, NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ 101.6 (*C*=CH), 121.0, 121.4, 124.7, 124.9, 128.4, 132.3 (Ar), 163.3 (C=*C*H), 164.0 (C=N), 164.3 (*C*-NH_2), 166.0 (CONH). Anal. Calcd for $C_{11}H_9N_5O$ (227.22): C, 58.14; H, 3.99; N, 30.82. Found: C, 57.91; H, 4.03; N, 30.53.

2-Amino-8-methyl-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-5-one (3b). Yellow powder (Crude yield: 0.23 g, 94%); m.p. 313-315 (d) °C. IR (KBr, cm^{-1}): 3487, 3386, 3354, 3210, 1639, 1599, 1542, 1427, 1418, 1377, 1334, 1270, 800, 611. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.13 (3H, s, CH_3), 6.77-6.95 (2H, broad s, NH_2), 6.80 (1H, d, *J* = 8.0 Hz, Ar), 6.86 (1H, s, Ar), 6.94 (1H, d, *J* = 8.0 Hz, Ar), 8.43 (1H, s, =CH), 8.79 (1H, s, NH,, 9.39 (1H, s, NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 101.0 (*C*=CH), 124.4, 125.8, 128.0, 129.4, 131.8, 132.9 (Ar), 162.6 (C=*C*H), 163.5 (C=N), 164.1 (*C*-NH_2), 165.4 (CONH). Anal. Calcd for $C_{12}H_{11}N_5O$ (241.25): C, 59.74; H, 4.60; N, 29.03. Found: C, 59.51; H, 4.35; N, 28.80.

2-Amino-8,9-dimethyl-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-5-one (3c). Yellow powder (Yield: 0.24 g, 94%); m.p. 268-271 (d) °C. IR (KBr, cm^{-1}): 3392, 3322, 3193, 1629, 1594, 1546, 1467, 1409, 795. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.04 (6H, s, 2 CH_3), 6.68 (1H, s, Ar), 6.82 (1H, s, Ar), 6.83 (2H, broad s, NH_2), 8.43 (1H, s, =CH), 8.71 (1H, s, NH), 9.31 (1H, s, NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.5, 18.6 (2 CH_3), 100.9 (*C*=CH), 121.4, 121.6, 125.7, 129.3, 131.4, 131.5 (Ar), 162.6 (C=*C*H), 163.5 (C=N), 164.1 (*C*-NH_2), 165.3 (CONH). Anal. Calcd for $C_{13}H_{13}N_5O$ (255.28): C, 61.17; H, 5.13; N, 27.43. Found: C, 60.82; H, 4.86; N, 27.13.

2-Amino-8-chloro-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-5-one (3d). Cream powder (Crude yield: 0.24 g, 92%); m.p. 350-352 (d) °C. IR (KBr, cm^{-1}): 3491, 3384, 3328, 3208, 1636, 1599, 1546, 1476, 1419, 1370, 1328, 1264, 795, 598. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.94-7.16 (2H, br, NH_2, overlap with aromatic protons), 6.97 (1H, dd, *J* = 10.2, 2.5 Hz, Ar), 7.08 (1H, d, *J* = 8.5 Hz, Ar), 7.16 (1H, s, Ar), 8.46 (1H, s, =CH), 9.03 (1H, s, NH), 9.57 (1H, s, NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ 100.8 (*C*=CH), 119.8, 122.0, 123.3, 127.3, 129.6, 130.9 (Ar), 162.0 (C=*C*H), 163.7 (C=N), 164.2 (*C*-NH_2), 164.9 (CONH). Anal. Calcd for $C_{11}H_8ClN_5O$ (261.67): C, 50.49; H, 3.08; N, 26.76. Found: C, 50.24; H, 2.82; N, 26.57.

2-Amino-8-bromo-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-5-one (3e). Brown powder (Crude yield: 0.29 g, 93%); m.p. 331-335 (d) °C. IR (KBr, cm^{-1}): 3399, 3340, 3214, 1638, 1597, 1545, 1476, 1419, 1368, 1328, 1259, 797, 601. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.87 (1H, d, *J* = 8.4 Hz, Ar), 7.00-7.12 (2H, br, NH_2), 7.12 (1H, s, Ar), 7.29 (1H, s, Ar), 8.46 (1H, s, =CH), 9.02 (1H, s, NH), 9.57 (1H, s, NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ 100.81 (*C*=CH), 115.2, 122.3, 122.5, 126.2, 129.8, 133.5 (Ar), 162.0 (C=*C*H), 163.6 (C=N),

164.1 (*C*-NH_2), 164.9 (CONH). Anal. Calcd for $C_{11}H_8BrN_5O$ (306.12): C, 43.16; H, 2.63; N, 22.88. Found: C, 42.97; H, 2.46; N, 22.65.

***N*-(5-oxo-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-2-yl)cyanamide (3f).** Yellow powder (Yield: 0.19 g, 70%); m.p. >350 °C. IR (KBr, cm^{-1}): 3271, 3207, 3122, 3059, 2157, 1676, 1602, 1549, 1465, 1404, 1306, 1269, 792, 737, 602. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.82-7.13 (4H, m, Ar), 8.35 (1H, s, =CH), 8.64 (1H, s, NH), 9.26 (1H, s, NHCO), 10.39 (1H, s, NHCN). ^{13}C NMR (75 MHz, DMSO-d_6): δ 99.5 (*C*=CH), 120.3 (C≡N), 120.5, 122.0, 123.6, 125.0, 128.4, 132.7 (Ar), 162.5 (C=*C*H), 162.7 (C=N), 165.8 (*C*-NHCN), 171.3 (CONH). Anal. Calcd for $C_{12}H_8N_6O$ (252.23): C, 57.14; H, 3.20; N, 33.32. Found: C, 56.92; H, 2.97; N, 32.94.

***N*-(8-methyl-5-oxo-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-2-yl)cyanamide (3g).** Yellow powder (Crude yield: 0.20 g, 75%); m.p. 335-337 (d) °C. IR (KBr, cm^{-1}): 3287, 3221, 3122, 2154, 1657, 1610, 1554, 1456, 1378, 1301, 1272, 789, 615. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.12 (3H, s, CH_3), 6.63-6.93 (3H, m, Ar), 8.35 (1H, s, =CH), 8.57 (1H, s, NH), 9.19 (1H, s, NHCO), 10.38 (1H, s, NHCN). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3) 99.5 (*C*=CH), 120.2 (C≡N), 120.5, 122.0, 123.7, 124.2, 132.1, 132.6 (Ar), 162.5 (C=*C*H), 162.7 (C=N), 165.8 (*C*-NHCN), 170.6 (CONH). Anal. Calcd for $C_{13}H_{10}N_6O$ (266.26): C, 58.64; H, 3.79; N, 31.56. Found: C, 58.32; H, 4.07; N, 31.74.

***N*-(8,9-dimethyl-5-oxo-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-2-yl)cyanamide (3h).** White powder (Yield: 0.20 g, 72%); m.p. 344-346 (d) °C. IR (KBr, cm^{-1}): 3281, 3211, 3125, 2155, 1654, 1608, 1542, 1457, 1340, 1358, 1299, 1279, 789, 631. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.04 (6H, s, $2CH_3$), 6.66 (1H, s, Ar), 6.79(1H, s, Ar), 8.33 (1H, s, =CH), 8.46 (1H, s, NH), 9.11 (1H, s, NHCO), NHCN signal was not observed. ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.5, 18.6 (CH_3), 99.5 (*C*=CH), 121.2 (C≡N), 121.4, 122.0, 125.8, 130.0, 130.6, 131.2 (Ar), 162.6 (C=*C*H), 165.7 (C=N), 165.8 (*C*-NHCN), 170.6 (CONH). Anal. Calcd for $C_{14}H_{12}N_6O$ (280.28): C, 59.99; H, 4.32; N, 29.98. Found: C, 60.17; H, 4.13; N, 29.63.

***N*-(8-chloro-5-oxo-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-2-yl)cyanamide (3i).** Milky powder (Crude yield: 0.24 g, 84%); m.p. 349-353 (d) °C. IR (KBr, cm^{-1}): 3635, 3304, 3200, 2151, 1682, 1596, 1544, 1457, 1410, 1372, 1261, 1102, 792, 629. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.85-7.12 (3H, m, Ar), 8.37 (1H, s, =CH), 8.84 (1H, s, NH), 9.39 (1H, s, NHCO), NHCN signal was not observed. ^{13}C NMR (75 MHz, DMSO-d_6): δ 99.3 (*C*=CH), 119.6 (C≡N), 121.8, 123.1, 127.1, 129.7, 131.5, 134.0 (Ar), 161.9 (C=*C*H), 162.8 (C=N), 165.2 (*C*-NHCN), 170.7 (CONH). Anal. Calcd for $C_{12}H_7ClN_6O$ (286.68): C, 50.28; H, 2.46; N, 29.32. Found: C, 49.92; H, 2.37; N, 29.12.

***N*-(8-bromo-5-oxo-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-2-yl)cyanamide (3j).** Brown powder (Crude yield: 0.25 g, 73%); m.p. 336-340 (d) °C. IR (KBr, cm^{-1}): 3284, 3208, 3100, 2151, 1658, 1594, 1546, 1454, 1406, 1368, 1260, 792. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.82-7.25 (3H, m, Ar), 8.36 (1H, s, =CH), 8.84 (1H, s, NH), 9.35 (1H, s,

NHCO), NHCN signal was not observed. ^{13}C NMR (75 MHz, DMSO-d_6): δ 99.0 (*C*=CH), 114.1 (C≡N), 122.3, 125.9, 127.8, 130.0, 132.0, 134.3 (Ar), 161.8 (C=*C*H), 162.7 (C=N), 165.3 (*C*-NHCN), 170.7 (CONH). Anal. Calcd for $C_{12}H_7BrN_6O$ (331.13): C, 43.53; H, 2.13; N, 25.38. Found: C, 43.22; H, 2.46; N, 25.61.

***N*-(5-oxo-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-2-yl)nitramide (3k).** Yellow powder (Crude yield: 0.23 g, 85%); m.p. 290-292 (d) °C. IR (KBr, cm^{-1}): 3497, 3210, 3069, 1663, 1596, 1529, 1473, 1321, 1266, 1054, 980, 779, 596. Major isomer: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.86-6.94 (3H, m, Ar), 7.05-7.08 (1H, m, Ar), 8.55 (1H, s, =CH), 9.07 (1H, s, NH), 9.53 (1H, s, NHCO), $NHNO_2$ signal was not observed. ^{13}C NMR (75 MHz, DMSO-d_6): δ 101.0 *(C*=CH), 120.4, 120.8, 123.6, 124.0, 128.1, 132.5 (Ar), 162.4 (C=*C*H), 163.5 (C=N), 165.3 (*C*-$NHNO_2$), 167.7 (CONH). Minor isomer: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.86-6.94 (3H, m, Ar), 7.05-7.08 (1H, m, Ar), 8.45 (1H, s, =CH), 8.89 (1H, s, NH), 9.46 (1H, s, NHCO), $NHNO_2$. ^{13}C NMR (75 MHz, DMSO-d_6): δ 103.1 *(C*=CH), 120.4, 120.8, 123.6, 124.0, 128.1, 132.5 (Ar), 162.6 (C=*C*H), 164.1 (C=N), 165.2 (*C*-$NHNO_2$), 167.7 (CONH). Anal. Calcd for $C_{11}H_8N_6O_3$ (272.22): C, 48.53; H, 2.96; N, 30.87. Found: C, 48.82; H, 2.77; N, 30.64.

***N*-(8-methyl-5-oxo-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-2-yl)nitramide (3l).** Yellow powder (Crude yield: 0.23 g, 81%); m.p. 293-296 (d) °C. IR (KBr, cm^{-1}): 3492, 3390, 3214, 1666, 1598, 1528, 1471, 1321, 1360, 1051, 981, 796, 609. Major isomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.13 (3H, s, CH_3), 6.70 (1H, m, Ar), 6.84 (1H, m, Ar), 6.95 (1H, d, J = 7.9 Hz, Ar), 8.54 (1H, s, =CH), 9.01 (1H, s, NH), 9.47 (1H, s, NHCO), $NHNO_2$ signal was not observed. ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 103.2 (*C*=CH), 120.8, 124.1, 124.5, 125.7, 132.6, 133.1 (Ar), 162.4 (C=*C*H), 163.4 (C=N), 165.2 (*C*-$NHNO_2$), 167.7 (CONH). Minor isomer: δ 2.13 (3H, s, CH_3), 6.70 (1H, m, Ar), 6.84 (1H, m, Ar), 6.95 (1H, d, J = 7.9 Hz, Ar), 8.44 (1H, s, =CH), 8.79 (1H, s, NH), 9.40 (1H, s, NHCO), $NHNO_2$ signal was not observed. ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 109.5 (*C*=CH), 120.4, 120.7, 124.3, 130.1, 132.4, 132.9 (Ar), 162.7 (C=*C*H), 164.1 (C=N), 165.1 (*C*-$NHNO_2$), 167.7 (CONH). Anal. Calcd for $C_{12}H_{10}N_6O_3$ (286.25): C, 50.35; H, 3.52; N, 29.36. Found: C, 50.78; H, 3.77; N, 29.04.

***N*-(8,9-dimethyl-5-oxo-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-2-yl)nitramide (3m).** Yellow-orange powder (Crude yield: 0.23 g, 75%); m.p. 326-327 (d) °C. IR (KBr, cm^{-1}): 3400, 3322, 3213, 1665, 1636, 1599, 1551, 1374, 1357, 1051, 867, 799, 778, 635. Major isomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.04 (6H, s, $2CH_3$), 6.68 (1H, s, Ar), 6.82 (1H, s, Ar), 8.52 (1H, s, =CH), 8.92 (1H, s, NH), 9.38 (1H, s, NHCO), $NHNO_2$ signal was not observed. ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.5 (CH_3), 18.6 (CH_3), 103.2 *(C*=CH), 121.3, 121.7, 125.6, 129.9, 131.2, 131.6 (Ar), 162.4 (C=*C*H), 163.4 (C=N), 165.3 (*C*-$NHNO_2$), 167.6 (CONH). Minor isomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.04 (6H, s, $2CH_3$), 6.68 (1H, s, Ar), 6.82 (1H, s, Ar), 8.42 (1H, s, =CH), 8.70 (1H, s, NH), 9.32 (1H, s, NHCO), $NHNO_2$ signal was not observed. ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.5 (CH_3), 18.6 (CH_3), 109.5 *(C*=CH), 121.4, 121.5, 125.6, 129.3, 131.4, 131.5 (Ar), 162.5 (C=*C*H), 162.7 (C=N), 165.3 (*C*-$NHNO_2$), 167.6

(CONH). Anal. Calcd for $C_{13}H_{12}N_6O_3$ (300.27): C, 52.00; H, 4.03; N, 27.99. Found: C, 52.17; H, 4.29; N, 28.12.

2-Mercapto-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-5-one (3n). Yellow powder (Yield: 0.23 g, 94%); m.p. 285-287 (d) °C. IR (KBr, cm^{-1}): 3343, 3202, 3105, 1652, 1614, 1591, 1529, 1380, 1335, 1185, 1095, 979, 782, 748, 604. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.79-6.91 (3H, m, Ar), 7.01 (1H, dd, J = 7.0, 2.2 Hz, Ar), 7.12 (1H, broad s, SH), 8.17 (1H, s, =CH), 8.76 (1H, s, NH), 9.30 (1H, s, NHCO). ^{13}C NMR (75 MHz, DMSO-d_6): δ 101.3 (*C*=CH), 120.1, 120.5, 123.0, 123.6, 128.3, 132.9 (Ar), 158.0 (C=*C*H), 159.2(C=N), 166.0 (*C*-SH), 183.8 (CONH). Anal. Calcd for $C_{11}H_8N_4OS$ (244.27): C, 54.09; H, 3.30; N, 22.94. Found: C, 53.82; H, 2.98; N, 22.66.

2-Mercapto-8-methyl-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-5-one (3o). Yellow powder (Crude yield: 0.20 g, 77%); m.p. 336-339 (d) °C. IR (KBr, cm^{-1}): 3297, 3192, 3087, 1647, 1585, 1527, 1370, 1175, 1090, 786, 614. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.12 (3H, s, CH_3), 6.61-6.89 (3H, m, Ar), 8.16 (1H, s, =CH), 8.56 (1H, s, NH), 9.18 (1H, s, NHCO), SH signal was not observed. ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_3), 101.3 (*C*=CH), 120.5, 124.2, 125.9, 128.1, 131.9, 132.7 (Ar), 158.4 (C=*C*H), 159.3 (C=N), 166.4 (*C*-SH), 190.2 (CONH). Anal. Calcd for $C_{12}H_{10}N_4OS$ (258.30): C, 55.80; H, 3.90; N, 21.69. Found: C, 55.62; H, 3.62; N, 21.84.

2-Mercapto-8,9-dimethyl-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-5-one (3p). Yellow powder (Yield: 0.22 g, 82%); m.p. 350 (d) °C. IR (KBr, cm^{-1}): 3291, 3195, 3102, 1642, 1578, 1518, 1370, 1318, 1175, 1126, 871, 780. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.03 (6H, s, $2CH_3$), 6.65 (1H, s, Ar), 6.74 (1H, s, Ar), 8.15 (1H, s, =CH), 8.43 (1H, s, NH), 9.09 (1H, s, NHCO), SH signal was not observed. ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.5 (CH_3), 18.6 (CH_3), 101.3 (*C*=CH), 121.0, 121.4, 125.8, 130.4, 131.2, 133.9 (Ar), 158.5 (C=*C*H), 159.4 (C=N), 166.3 (*C*-SH), 190.2 (CONH). Anal. Calcd for $C_{13}H_{12}N_4OS$ (272.33): C, 57.34; H, 4.44; N, 20.57. Found: C, 57.24; H, 4.36; N, 20.35.

8-Chloro-2-mercapto-6,11-dihydro-5*H*-benzo[*b*]pyrimido[4,5-*e*][1,4]diazepin-5-one (3q). Yellow powder (Crude yield: 0.22 g, 72%); m.p. >350 °C. IR (KBr, cm^{-1}): 3283, 3189, 3100, 1650, 1604, 1581, 1522, 1366, 1226, 1176, 1090, 988, 785, 604. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.83-7.02 (3H, m, Ar), 8.18 (1H, s, =CH), 8.86 (1H, s, NH), 9.38 (1H, s, NHCO), SH signal was not observed. ^{13}C NMR (75 MHz, DMSO-d_6): δ 101.1 (*C*=CH), 119.6, 121.8, 122.3, 123.1, 126.1, 127.4 (Ar), 158.5 (C=*C*H), 165.8 (C=N), 165.9 (*C*-SH), 192.6 (CONH). Anal. Calcd for $C_{12}H_{10}N_4OS$ (278.72): C, 47.40; H, 2.53; N, 20.10. Found: C, 47.84; H, 2.37; N, 19.87.

Supplementary data

Supplementary data related to this article can be found in the online version, at doi: … . These data include FT-IR, ^{1}H-NMR and ^{13}C-NMR spectra for all the synthesized compounds.

Acknowledgements

We would like to thank the partial financial support of the Deputy of Research and Technology of Kharazmi University.

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