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Research Article

Studies on the Synthesis of Some Novel Polyfunctionally Substituted Pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*][1,2,4]triazepine Derivatives

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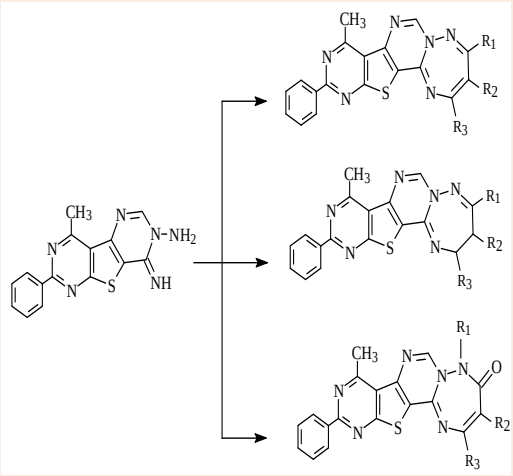
Abstract

A series of novel polyfunctionally substituted pyrimido-[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*][1,2,4]triazepines **7a-d, 9a-d**, **10**, **9g**, **18**, **20**, **22a**,**b**, **13** and **15** were synthesized by cyclocondensation of 7-amino-8-imino-pyrimido[3,2:4,5]-thieno[2,3-*d*]pyrimidine **5** with chalcones **6a-d**, (2*E*)-2-[(dimethylamino)methylene]-1,3-disubstituted-butane-1,3-diones **8a-c** and appropriate reactants **8d**, **8f**, **8g**, **16**, **19, 21a,b, 12** and **14** under acidic or pyridine condition, respectively. The structures of the newly synthesized compounds were confirmed by IR, ^{1}H NMR, mass spectra and elemental analysis.

Keywords: Thioxopyrimidine, Cyclocondensation chalcones, 7-amino-8-imino-pyrimido[3,2:4,5]thieno[2,3-*d*]-pyrimidine, , (2*E*)-2-[(dimethylamino)methylene]-1,3-disubstituted-butane-1,3-diones, polyfunctionally substituted pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*][1,2,4]-triazepines



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Introduction

Among the derivatives of thieno[2,3-*d*]pyrimidines, substances have been observed that have antiviral, fungicidal, insecticidal activity [1], antibacterial and antiplastic properties [2], antihypertensive [3], anticonvulsant activity [4] and antihistaminic action [5]. Likewise, fused triazepines with a bridgehead nitrogen atom in the molecule exhibit interesting biological properties[6]. On the other hand, the fusion of pyrimidine with triazepine moiety shows enhanced pharmacological effects as antiviral, antifungal [7], antidiabetic [8] and also act as inhibitors [9] in cancer chemotherapy. Accordingly, triazepines has thus attracted a great deal of attentions starting material in the synthesis of fused heterocyclic systems of potential pharmacological activities [10-13].

Various conventional methods for the synthesis of fused triazepines are exemplified in literature using cycloaddition and photochemical methods [14-16]. Saveleva, E. A. et al [17] reported on the preparation of mesoionic[1,2,3]triazolo[5,1-*d*][1,2,5]triazepines from 1-amino-3-(p-R-phenacyl)-4-(iso-propylidencarbox-amido)-1,2,3-triazolium-5-olate. In addition, the thiazolo[3,2-*b*][1,2,4]triazepines were also prepared by Rezzessy, B. et al [18] from the 3-amino-2-imini-4-R-thiazolines with chalcones. Although a number of papers concerning the synthesis of triazepine compounds have been published, those containing a new heterocyclic system of pyrimido-[3,2:4,5]thieno[2,3-*d*]pyrimidine moiety have not yet been reported. Therefore, based on our previous works [19-24], we report herein the synthesis of some novel polyfunctionally substituted pyrimido[3',2':4,5]-

thieno[3,2:4,5]pyrimido[1,6-*b*][1,2,4]triazepines by making use of the 7-amino-8-imino-pyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidine **5** as the starting material.

Experimental

General

IR spectra were recorded on a JASCO FTIR-3 spectrometer for KBr pellets. ^{1}H NMR spectra were obtained on a Bruker AM-300 WB FI-NMR spectrometer using TMS as an internal standard. Electron Impact mass spectra were obtained at 70 eV using a Finingan Mat TSQ-46C spectrometer. Elemental analysis was carried out on a Perkin-Elmer 240 elemental Analyzer. Melting point were determined on a Boetius hot stage apparatus and are not corrected. Commercially available reagents were purchased from Aldrich and used directly. Reactions were routinely monitored by thin later chromatography (TLC) on silica gel (precoated F245 Merck plates). Compounds **8a-c [25-27]**, **8d, 8e, 8g [28, 29]**, **14 [30]** and **21a, b [31, 32]** were prepared according to known procedures.

General procedure for the synthesis of 9-substituted-2,11-diphenyl-4-methyl-10,11-dihydropyrimido-[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*][1,2,4]triazepines (7a-d).
A mixture of compound **5** (0.308 g, 1 mmol) and appropriate chalcones **6a-d** (1 mmol) in glacial acetic acid (10 mL) was refluxed for 12 h. A crystalline solid obtained on cooling. It was recrystallized from DMF/ethanol.

General procedure for the synthesis of 10,11-disubstituted-4-methyl-2-phenyl-pyrimido[3',2':4,5]thieno-[3,2:4,5]pyrimido[1,6-*b*][1,2,4]triazepines (9a-c).
A mixture of compound **5** (1 mmol) and appropriate (2E)-2-[(dimethylamino)methylene]-1,3-disubstituted-butane-1,3-diones **8a-c** (1 mmol) in glacial acetic acid (10 mL) was refluxed for 10 h. It was recrystallized from DMF/ethanol.

Synthesis of 4-dimethyl-2-phenyl-pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*]indano[2,1-*f*][1,2,4]-triazepine (9d).
A mixture of compound **5** (0.308 g, 1 mmol) and 2-[(dimethylamino)methylene]-1H-indene-1,3-(2H)-dione **8d** (0.201 g, 1 mmol) in glacial acetic acid (10 mL) was refluxed for 7 h. A crystalline solid obtained on cooling. It was recrystallized from DMF/acetone to give as deep brown crystals.

Synthesis of 7-(5,5-dimethyl-cyclohexylidene-1,3-dione)amino-8-imino-4-methyl-2-phenyl-7,8-dihydro-pyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidine (9e).
A mixture of **5** (0.308 g, 1 mmol) and 2-[(dimethylamino)methylene]-5,5-dimethylcyclohexane-1,3-dione **8e** (0.20 g, 1 mmol) in glacial acetic acid (10 mL) was refluxed for 24 h. A crystalline solid obtained on cooling. It was recrystallized from DMF/ethanol to give as light yellow crystals.

Synthesis of 10-chloro-4-methyl-2-phenyl-12,12-dimethyl-pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*]-cyclohexene[3,2-*f*][1,2,4]triazepine (9f).
A solution of compound **9e** (0.458 g, 1 mmol) in $POCl_3$ (10 mL) was heated under reflux for 3 h. After cooling, the reaction mixture was poured into ice/water mixture (50 mL) and neutralized with ammonium hydroxide solution. The solid product form was filtered off and recrystallized from chloroform/ethanol to give as orange-yellow crystals.

Synthesis of 4,11-dimethyl-10-(4-methylcarbanilino)-2-phenyl-pyrimido[3',2':4,5]thieno[3,2: 4,5]pyrimido[1,6-*b*][1,2,4]triazepine (9g).
This compound was synthesized from compound **5** (0.308 g, 1 mmol) and 2(E)-2-[(dimethylamino)methylene]-N-(4-methylphenyl)-3-oxobutanamide **8g** (0.247 g, 1 mmol) in a similar to that described for the preparation of compound **9a-c**. It was recrystallized from DMF/ethanol to give as light yellow crystals.

Synthesis of 2,7-dimethyl-9-phenyl-pyrimido[3',2':4,5]thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]primidine (10).

Method A. This compound was synthesized from compound **5** (0.308 g, 1 mmol) and 4-acetoacetotoluidide **8f** (0.191 g, 1 mmol) in a similar to that described for the preparation of compound **9a-c**.
Method B**.** A mixture of compound **5** (0.308 g, 1mmol) and glacial acetic acid (10 mL) was refluxed for 2 h. After cooling, the precipitate was filtered and recrystallized from acetic acid/ethanol to furnish compound **10** as pale brown crystals.

Synthesis of butyl 4-methyl-9-oxo-2-phenyl-10,11-dihydropyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*]-[1,2,4]triazepine-8-ethylenecarboxylate (13).
A mixture of compound **5** (0.308 g, 1 mmol) and n-butylacrylate **12** (0.204 g, 1.6 mmol) in pyridine (10 mL) was refluxed for 11 h. The reaction mixture was cooled and poured into ice-water and neutralized with 10% hydrochloric acid. The precipitate was filtered and recrystallized from DMF/ethylacete to give as light orange crystals.

Synthesis of 10-benzamido-4-dimethyl-2,11-diphenyl-8H-9-oxo-pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido-[1,6-*b*][1,2,4]triazepine (15).
A mixture of compound **5** (0.308 g, 1mmol) and 4-benzylidene-2-phenyl-5-(4)-oxazolone **14** (0.25 g, 1 mmol) in pyridine (10 mL) was refluxed for 12 h. The reaction mixture was cooled and poured into ice-water and neutralized with glacial acetic acid. The precipitate was filtered and recrystallized from DMF/ethanol to give as orange-yellow crystals.

Synthesis of 7-(3-methylmethyleneamino-4,5-dihydro-2(3H)-furanone)-8-imino-4-methyl-2-phenyl-7,8-dihydro-pyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidine (17).
A mixture of compound **5** (0.308 g, 1 mmol) and α-acetyl-γ-butyrolactone **16** (0.130 g, 1 mmol) in glacial acetic acid (10 mL) was refluxed for 8 h. A crystalline solid obtained on cooling. It was recrystallized from DMF/acetone to give as pale yellowish brown crystals.

Synthesis of 4,9-dimethyl-2-phenyl-10,11-dihydro-pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*]furan[3,2-*f*][1,2,4]triazepine (18).
Method A. A solution of compound **17** (0.418 g, 1 mmol) in CH_3COOH/HCl (1:1) was heated under reflux for 11 h. A crystalline solid obtained on cooling. It was recrystallized from DMF/acetone to give as pale yellow crystals. Yield 0.14 g (35%).
Method B. A mixture of compound **5** (0.308 g, 1 mmol) and α-acetyl-γ-butyrolactone **16** (0.130 g, 1 mmol) in glacial acetic acid (10 mL) was refluxed for 24 h. The resulting precipitate was collected by filtration and recrystallized. Yield 0.22 g (55%).

Synthesis of 4-methyl-9-oxo-2-phenyl-8*H*-pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*]cyclohexane[3,2-*f*]-[1,2,4]triazepine (20).
A mixture of compound **5** (0.308 g, 1 mmol) and ethyl cyclohexanone-2-carboxylate **19** (0.17 g, 1 mmol) in glacial acetic acid (10 mL) was refluxed for 8 h. A crystalline solid obtained on cooling. It was recrystallized from DMF/acetone to give as brownish black crystals.

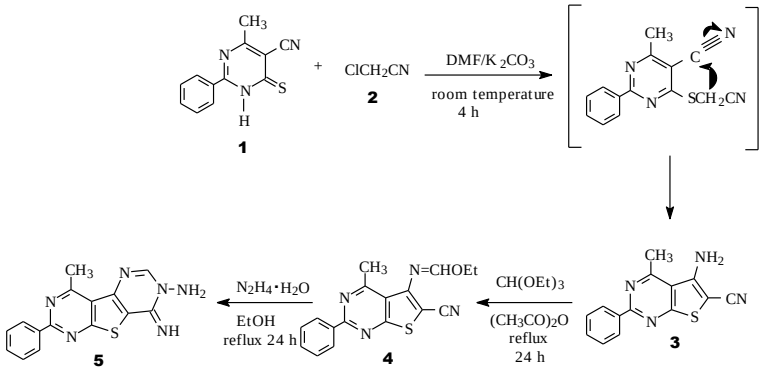
General procedure for the synthesis of 10,12-disubstituted-4-methyl-9-oxo-2-phenyl-8*H*-pyrimido-[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*]cyclohexene[3,2-*f*][1,2,4]triazepines (22a,b).
A mixture of compound **5** (0.308 g, 1 mmol) and ethyl 2-oxo-4,6-disubstituted-cyclohexe-3-en-1-carboxylates **21a,b** (1 mmol) in glacial acetic acid (10 mL) was refluxed for 24 h. A crystalline solid obtained on cooling. It was recrystallized from DMF/acetone.

Synthesis of 7-(2-methylmethyleneaminocyclopentanone)-8-imino-4-methyl-2-phenyl-pyrimido[3,2:4,5]thieno-[2,3-*d*]pyrimidine (24).

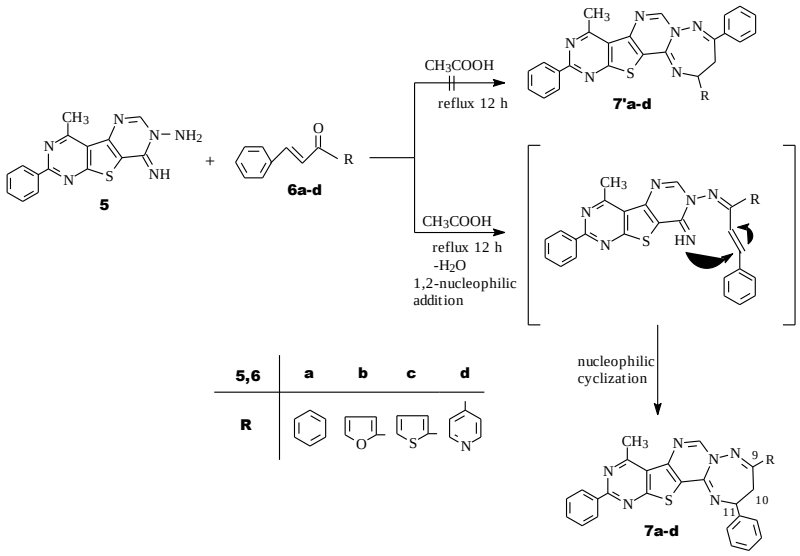
This compound was obtained from compound **5** (0.308 g, 1 mmol) and 2-acetylcyclopentanone **23** (0.130 g, 1 mmol) in a manner similar to that described for the preparation of compound **17**. It was recrystallized from DMF/acetone to give as brownish yellow crystals.

Results and Discussion

The required key intermediate 7-amino-8-imino-pyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidine **5** was prepared from our previous work [23] (Scheme 1).



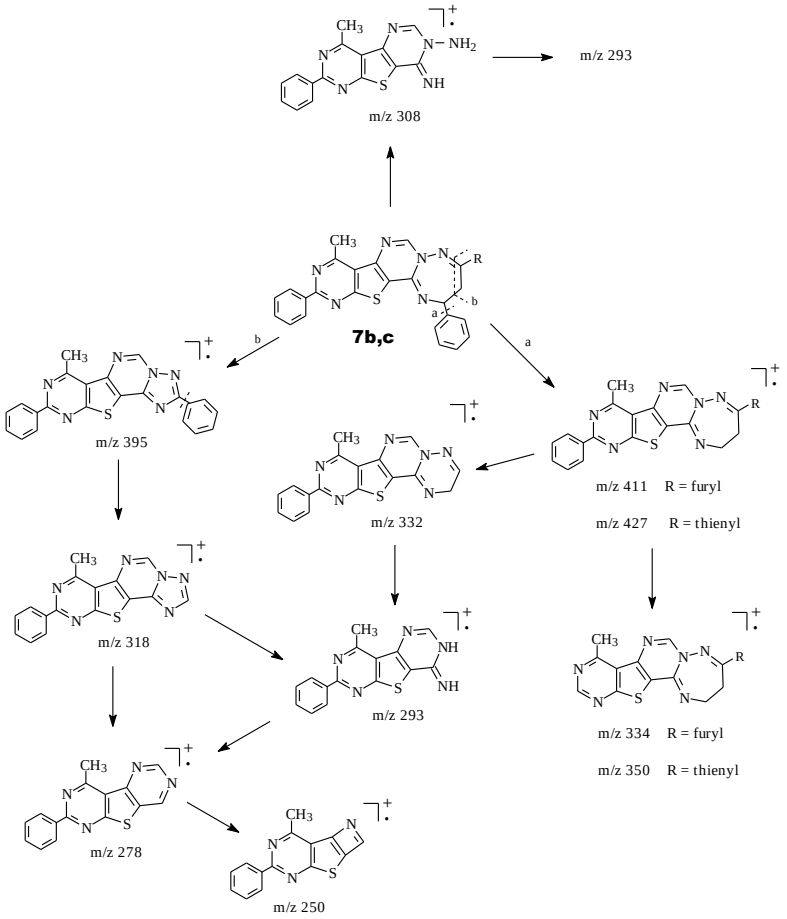
Scheme 1: Synthesis of 7-amino-8-imino-pyrimido[3,2:4,5]thieno[2,3-d]pyrimidine **5**



Scheme 2. Synthesis of 9-substituted-10,11-dihydrotriazepines **7a-d**

Treatment of compound **5** with appropriate chalcones **6a-d** in glacial acetic acid the corresponding 9-substituted-10,11-dihydrotriazepines **7a-d** were smoothly obtained, rather than the 11-substituted-2,9-diphenyl-triazepines **7'a-d** (Scheme 2). Similar cyclization reactions have been previously reported [23]. The mechanism involves 1,2-nucleophilic addition of 7-amino of compound **5** to the carbonyl group, followed by dehydration and subsequent nucleophilic cyclization with loss of water. The ^{1}H NMR spectra of compounds **7a-d** revealed a doublet at δ 2.36-3.15 (2H, d) ppm, which were readily assigned to the hydrogen attached at C_{10} of the triazepine ring and a sharp singlet at δ 9.19-9.83 (1H, s) ppm assigned to the hydrogen attached at C_6 of the thienopyrimidotriazepine ring. These structures get further support from mass spectroscopy. It has been observed that Electron Impact (EI) spectral has

many common features. For instance, compounds **7b, c** exhibited *m/z* 395, 332, 318, 308, 293, 278 and 250 piece peaks. The possible mass fragmentation pathway of compounds **7b** and **7c** is shown in **Scheme 3**.

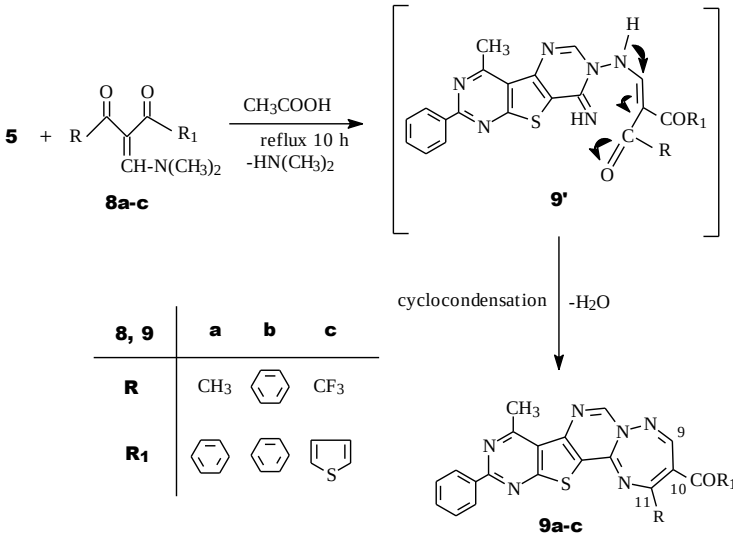


Scheme 3. The possible mass fragmention pathway of compounds **7b** and **7c**

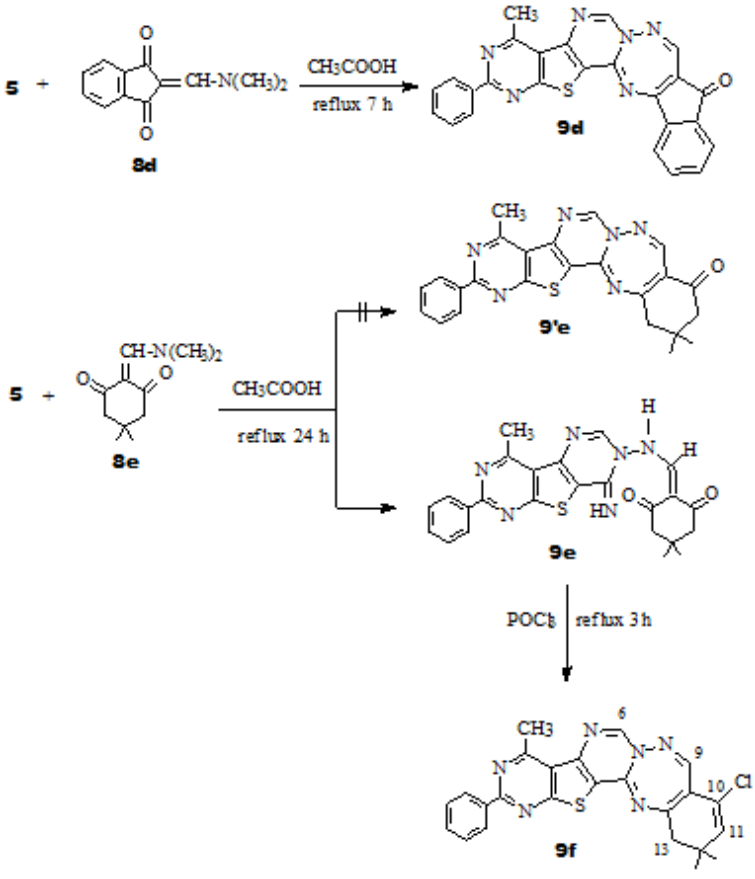
Furthermore, the study was extended to the behavior of compound **5** with (2*E*)-2-[(dimethylamino)methylene]-1,3-disubstituted-butane-1,3-diones **8a-c** were also investigated. Thus, the compound **5** was converted into the to the 10,11-disubstituted-triazepine derivatives **9a-c** by heating with compounds **8a-c** in refluxing glacial acetic acid (**Scheme 4**). The reaction probably involves the condensation of the 7-NH_2 of the compound **5** with the carbonyl group to form the intermediate **9'**, which then undergoes cyclization and aromatization via loss of both N,N-dimethylamine and water [24] affording the final product **9a-c**. The ^{1}H NMR spectra of compounds **9a-c**, which showed a sharp singlet at δ 7.83-8.45 (1H, s) ppm assigned to the hydrogen attached at C_9 of the triazepine ring and a sharp singlet at δ 9.05-9.15 (1H, s) ppm assigned to the hydrogen attached at C_6 of the thienopyrimidotriazepine ring. Under similar reaction conditions, treatment of compound **5** with 1,3-indanedione **8d** afforded indanotriazepine **9d**. Nevertheless, reaction of compound **5** with 1,3-cyclohexanedione **8e** did not afford the expected cyclohexanotriazepine **9'e** but resulted in the formation of open-chain product **9e**, which could be cyclized into chlorocyclohexenetriazepine **9f** in refluxing $POCl_3$ (**Scheme 5**).

The IR spectra of compound **9f** indicated the complete disappearance of the NH and C=O groups. The ^{1}H NMR spectra of compound **9f** revealed three additional singlet at δ 8.09 (1H, s), 5.52 (1H, s) and 3.32 (2H, s) ppm which were readily assigned to the hydrogen attached at C_9, C_{11} and C_{13} of the chlorocyclohexenetriazepine ring,

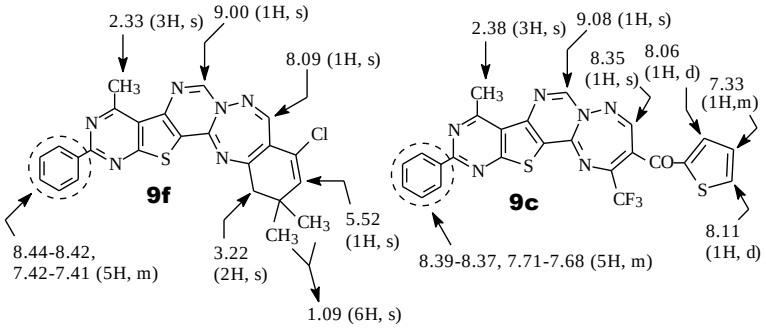
respectively and a sharp singlet at δ 1.09 (6H, s) ppm assigned to the two CH3 group attached at C12 of the chlorocyclohexenetriazepine ring.



Scheme 4. Synthesis of 10,11-disubstituted-triazepines **9a-c**



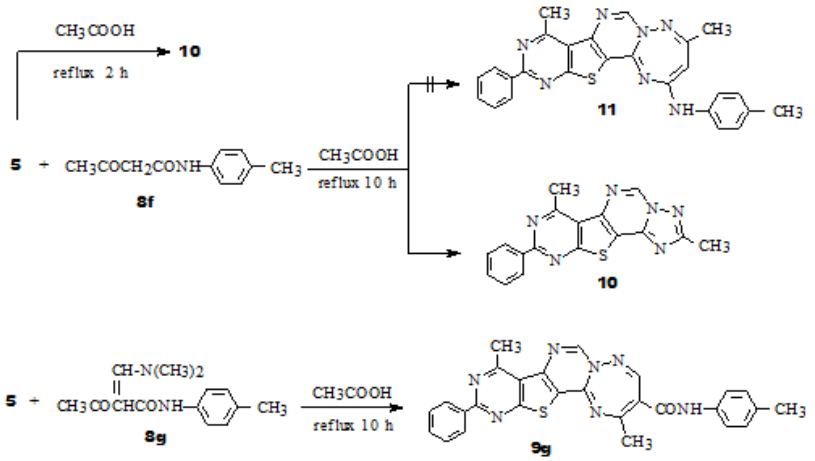
Scheme 5. Synthesis of indanotriazepine **9d** and chlorocyclohexenetriazepine **9f**



Scheme 6. Structural assignments of typical protons in compounds **9c** and **9f** by ^{1}H NMR

Typical assignments for compounds **9c** and **9f** by ^{1}H NMR are shown in **Scheme 6**. In comparison, treatment of compound **5** with 4-acetoacetotoluidide **8f** in refluxing glacial acetic acid, the reaction product was identified as the pyrimido[3',2':4,5]thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine **10** and not the expected triazepine **11**, whereas, when the same reaction was carried out by using 2(*E*)-2-[(dimethylamino)methylene]-N-(4-methylphenyl)-3-oxobutanamide **8g** the methylcarbanilino-triazepine **9g** was obtained. The structure of compound **10** is also supported by spectral data and by the independent synthesis of the same product from compound **5**, by heating under reflux glacial acetic acid for 2h (mp., mixed mp. and tlc) (**Scheme 7**).

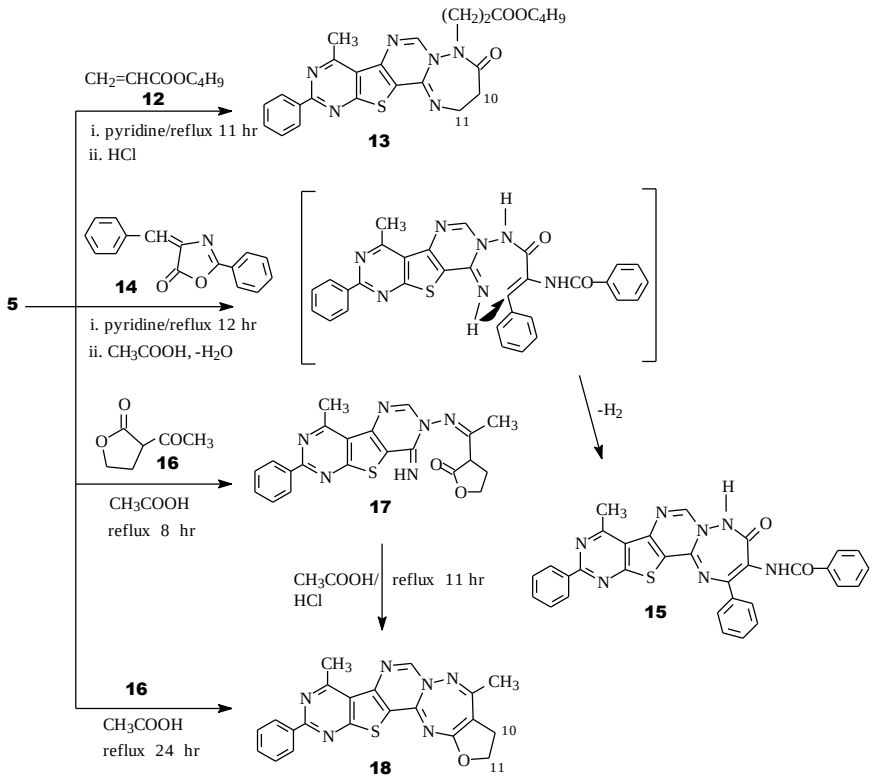
On the other hand, we also investigated the applicability and synthetic potency of compound **5** in a convenient route to different structure triazepines (Scheme 8). Thus, the reaction of compound **5** with excess n-butylacrylate **12** in refluxing pyridine afforded the ester-triazepine **13**, because of the molecular ion *m/z* 490 of compound **13** is unstable and could not be recorded in the Electron Impact mass spectra, but showed the presence of the ion peaks *m/z* 434[M—C_4H_9]$^+$, 362[M—$C_2H_4COOC_4H_9$]$^+$, 322, 318, 308, 293, 278 and 250. Also, the ^{1}H NMR spectrum revealed a butyl (at δ 0.98, 1.45, 1.74 and 2.90 ppm), an ethylene (at δ 3.50 and 3.60 ppm) groups and two additional triplets at δ 4.28 (2H, t) and 4.36 (2H, t) ppm which were readily assigned to the hydrogen attached at C_{10} and C_{11} of the triazepine ring, respectively.



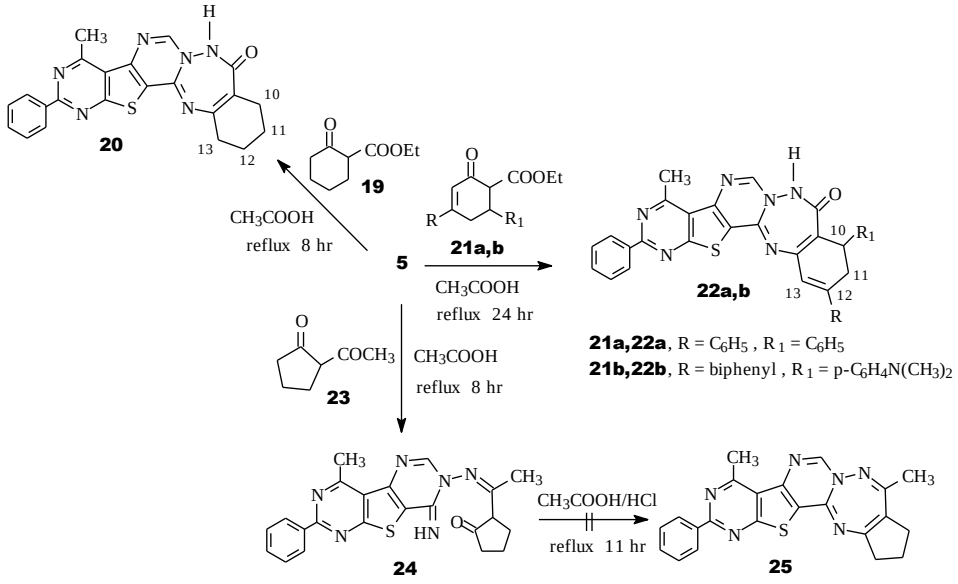
Scheme 7. Synthesis of [1,2,4]triazolo[1,5-c]pyrimidine **10** and methylcarbaniline-triazepine **9g**

Next, several pyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidines substituted at position 7 and 8 with different heterocyclic residues were obtained *via* treatment of compound **5** with different reagents (Scheme 8). Thus, treatment of compound **5** with 4-benzylidene-2-phenyl-5-(4)-oxazolone **14** under similar reaction conditions caused cyclization afforded the benzamido-triazepine **15**. It is noteworthy that when the reaction was carried out with compound **5** in α-

acety-γ-butyrolactone **16** at reflux glacial acetic acid for 8 h, the product was identified as the open-chain product **17**, which could be cyclized into the corresponding furantriazepine **18** by heating in refluxing CH_3COOH/HCl.



Scheme 8. Synthesis of ester-triazepine **13,** benzamido-triazepine **15** and furantriazepune **18**



Scheme 9. Synthesis of cyclohexanetriazepine **20**, 10,12-disubstituted-cyclohexenetriazepines **22 a,b** and cyclopentanone-pyrimido[3,2:4,5]thieno[2,3-d]pyrimidine **24**

The IR spectra of compound **18** indicated the complete disappearance of the NH and C=O groups. The ^{1}H NMR spectra of compound **18** revealed two additional triplets at δ 3.36 (2H, t) and 4.23 (2H, t) ppm which were readily assigned to the hydrogen attached at C_{10} and C_{11} of the furantriazepine ring, respectively. Moreover, spectra of compound **18** revealed two sharp singlet at δ 2.71 (3H, s) and 3.05 (3H, s) ppm assigned to the CH_3 group attached at C_6 and C_4 of the pyrimidothienopyrimidofurantriazepine ring, respectively. The structure of compound **18** is also supported by spectral data and by the independent synthesis of the same product from compound **5** with α-acety-γ-butyrolactone **16**, by heating under reflux glacial acetic acid for 24h (mp., mixed mp. and tlc) (Scheme 8).

Table 1 Physicochemical Characteristics of Compounds 7a-d, 9a-g, 10, 13, 15, 17, 18, 20, 22a,b and 24

Compound	Mp (°C)	Yield (%)	Molecular formula	Elemental Analysis (%) Found/Calcd		
				C	H	N
7a	262-265	26	$C_{30}H_{22}N_6S$	72.46	4.28	16.68
				72.29	4.42	16.87
7b	281-284	41	$C_{28}H_{20}N_6OS$	68.99	4.28	17.38
				68.85	4.10	17.21
7c	260-264	36	$C_{28}H_{20}N_6S_2$	66.79	4.18	16.48
				66.67	3.97	16.67
7d	282-285	40	$C_{29}H_{21}N_7S$	69.97	4.38	19.84
				69.74	4.21	19.64
9a	183-185	52	$C_{26}H_{18}N_6OS$	67.39	4.02	18.38
				67.53	3.90	18.18
9b	233-234	72	$C_{31}H_{20}N_6OS$	70.76	3.98	16.21
				70.99	3.82	16.03
9c	255-257	68	$C_{24}H_{13}F_3N_6OS_2$	55.47	2.63	16.25
				55.17	2.49	16.09
9d	243-244	56	$C_{25}H_{14}N_6OS$	67.12	3.32	18.99
				67.26	3.54	18.83
9e	295-297	72	$C_{24}H_{22}N_6O_2S$	62.97	5.01	18.59
				62.88	4.80	18.34
9f	215-217	68	$C_{24}H_{19}ClN_6S$	62.77	4.32	18.59
				62.81	4.14	18.32
9g	315-316	61	$C_{27}H_{21}N_7OS$	66.12	4.53	20.21
				65.99	4.28	19.96
10	271-273	93	$C_{17}H_{12}N_6S$	61.45	3.61	25.30
				61.69	3.42	25.55
13	225-228	40	$C_{25}H_{26}N_6O_3S$	61.39	5.45	17.26
				61.22	5.31	17.14
15	162-164	56	$C_{31}H_{21}N_7O_2S$	67.39	4.01	17.88
				67.03	3.78	17.66
17	225-227	65	$C_{21}H_{18}NOS$	60.44	4.48	20.36
				60.29	4.31	20.10
18	258-260	55	$C_{21}H_{16}N_6OS$	63.24	4.22	21.26
				63.00	4.00	21.00
20	195-197	58	$C_{22}H_{18}N_6OS$	63.98	4.52	20.48
				63.77	4.35	20.29
22a	196-199	61	$C_{34}H_{24}N_6OS$	72.58	4.32	15.08
				72.34	4.26	14.89
22b	176-177	65	$C_{42}H_{33}N_7OS$	73.98	4.92	14.59
				73.79	4.83	14.35
24	200-203	68	$C_{22}H_{20}N_6OS$	63.66	4.68	20.36
				63.46	4.81	20.19

Table 2 Spectral Characteristics of Compounds 7a-d, 9a-g, 10, 13, 15, 17, 18, 20, 22a,b and 24

Com-pound	MS (m/e M^+)	IR (KBr) ν (cm^{-1})	^{1}H-NMR[a] (CF_3COOD) δ (ppm)
7a	498(M^+,60), 463(10), 421(5), 395(100), 350(9), 332(12), 318(4), 293(5), 278(10), 255(7), 248(9), 229(3), 191(7), 118(5), 104(25), 77(19)	1615 (C=N)	2.58 (3H, s, CH_3); 3.15 (2H, d, *J* = 1.20 Hz, 10-H); 8.52-8.44, 7.44- 7.16 (16H, m, 11-H and Ar); 9.37 (1H, s, 6-H)[b]
7b	488(M^+,12), 411(5), 395(6), 350(69), 334(4), 332(10), 318(3), 308(100), 293(15), 278(22), 250(12), 229(3), 196(8), 176(12), 148(10), 104(23), 77(16)	1621 (C=N)	2.42 (2H, d, *J* = 1.00 Hz, 10-H); 2.66 (3H, s, CH_3); 8.59-8.57, 7.93-7.90 (12H, m, 4-H furyl, 11-H and Ar); 8.05 (2H, m, 3,5-H furyl); 9.24 (1H, s, 6-H)[b]
7c	504(M^+,8), 427(7), 395(6), 350(79), 332(12), 318(5), 308(100), 293(15), 278(20), 250(10), 212(8), 179(9), 176(9), 129(80), 104(13), 77(9)	1628 (C=N)	2.36 (2H, d, *J* = 1.0 Hz, 10-H); 2.60 (3H, s, CH_3); 8.53-8.51, 7.87-7.84 (12H, m, 4-H thienyl, 11-H and Ar); 8.00 (2H, m, 3,5-H thienyl); 9.19 (1H, s, 6-H)
7d	499(M^+,5), 421(4), 395(12), 379(7), 350(10), 332(100), 318(11), 308(30), 293(58), 278(23), 251(8), 229(22), 208(38), 190(21), 149(40), 104(51), 77(57)	1630 (C=N)	2.46 (3H, s, CH_3); 2.95 (2H, d, *J* = 1.00 Hz, 10-H); 8.53-8.51, 7.87-7.84 (13H, m, 3,5-H pyridyl, 11-H and Ar); 9.04 (2H, m, 2,6-H pyridyl); 9.83 (1H, s, 6-H)[c]
9a	462(M^+,14), 433(100), 419(10), 401(24), 366(42), 332(21), 318(31), 293(8), 229(5), 215(10), 165(4), 128(4), 104(9), 77(9)	1686 (C=O), 1626(C=N)	2.19 (3H, s, 11-CH_3); 2.85 (3H, s, 4-CH_3); 7.83 (H, s, 9-H); 8.05- 8.04, 7.54-7.09 (10H, m, Ar); 9.05 (1H, s, 6-H)
9b	524(M+,18), 447(2), 419(14), 315(2), 277(7), 247(10), 174(5), 171(7), 114(8), 103(81), 77(100)	1679 (C=O), 1613 (C=N)	2.20 (3H, s, CH_3); 8.45 (H, s, 9-H); 8.37-8.35, 7.81-7.28 (15H, m, Ar); 9.15 (1H, s, 6-H)
9c	522(M^+,11), 512(11), 493(2), 426(2), 386(6), 332(100), 318(8), 283(2), 229(24), 187(2), 166(8), 111(5), 77(8)	1689 (C=O), 1628 (C=N)	2.94 (3H, s, CH_3); 7.33 (1H, m, 4-H thienyl); 8.06 (1H, d, *J* = 1.00 Hz, 3-H thienyl); 8.11 (1H, d, *J* = 1.00 Hz, 5-H thienyl); 8.35 (1H, s, 9-H); 8.39-8.37, 7.71-7.68 (5H, m, Ar); 9.08 (1H, s, 6-H)
9d	446(M^+,7), 350(45), 332(80), 318(100), 308(80), 292(59), 278(68), 251(10), 229(18), 175(24), 146(27), 103(14), 77(7)	1683 (C=O), 1611 (C=N)	2.38 (3H, s, CH_3); 8.15 (1H, s, 9-H); 8.33-8.25, 7.92-7.62 (9H, m, Ar); 9.04 (1H, s, 6-H)
9e	458(M^+,12), 440(40), 425(100), 387(2), 356(6), 319(10), 293(74), 277(26), 251(6), 223(4), 190(17), 147(4), 104(16), 77(3)	3324 (NH), 1663 (C=O), 1614 (C=N)	1.96 (6H, s, 5,5-CH_3 cyclohexyl); 2.97 (3H, s, CH_3); 3.38 (2H, s, 6-CH_2 cyclohexyl); 3.47 (2H, s, 4-CH_2 cyclohexyl); 9.19-9.12, 8.61-8.45 (6H, m, -NCH= and Ar); 10.27 (1H, s, 6-H)
9f	458.5(M^+,5), 444(100), 429(11), 424(36), 379(4), 355(1), 278(68), 278(4), 221(1), 169(4), 77(7)	1612 (C=N)	1.09 (6H, s, 12,12-CH_3); 2.33 (3H, s, 4-CH_3); 3.32 (2H, s, 13-H); 5.52 (1H, s, 11-H); 8.09 (1H, s, 9-H); 8.44-8.42, 7.42-7.41 (5H, m, Ar); 9.00 (1H, s, 6-H)[b]
9g	491(M^+,8), 426(1), 388(1), 374(100), 333(10), 318(5), 293(24), 251(6), 238(2), 173(9), 131(10), 106(22), 77(16)	3312 (NH), 1673 (C=O), 1606 (C=N)	2.70 (3H, s, CH_3); 2.85 (3H, s, 11-CH_3); 2.99 (3H, s, 4-CH_3); 8.05-8.04, 7.54-7.09 (10H, m, 9-H and Ar); 9.31 (1H, s, 6-H); 9.68 (1H, br, NH)

Table 2 (continued)

Com-pound	MS (m/e M^+)	IR (KBr) ν (cm^{-1})	^{1}H-NMR[a] (CF_3COOD) δ (ppm)
10	332(M^+,20), 318(6), 293(100), 278(11), 267(1), 229(5), 190(24), 163(9), 103(4)	1615 (C=N)	2.06 (3H, s, CH_3), 3.17 (3H, s, CH_3), 8.51-8.49, 7.58-7.53 (5H, m, Ar), 8.72 (1H, s, 6-H)[b]
13	434(M^+,7), 362(3), 322(3), 319(21), 308(100), 293(17), 278(28), 250(6), 223(2), 174(4), 104(4)	1673 (C=O), 1606 (C=N)	0.98 (3H, t, *J* = 2.05 Hz, CH_3); 1.45 (2H, m, $COOCH_2CH_2\underline{CH_2}$); 1.74 (2H, m, $COOCH_2\underline{CH_2}CH_2$); 2.90 (2H, t, *J* = 1.26 Hz, $COO\underline{CH_2}CH_2CH_2$); 3.50 (2H, t, *J* = 1.26 Hz, $NCH_2\underline{CH_2}$); 3.60 (2H, t, *J* = 1.10 Hz, $N\underline{CH_2}CH_2$); 3.70 (3H, s, CH_3); 4.28 (2H, t, *J* = 1.35 Hz, 10-CH_2); 4.36 (2H, t, *J* = 1.36 Hz, 11-CH_2); 8.40-8.37, 7.89- 7.71 (5H, m, Ar); 9.08 (1H, s, 6-H)[c]
15	555(M^+,13), 540(9), 512(6), 435(3), 422(4), 407(31), 394(56), 273(3), 333(20), 318(38), 293(100), 279(14), 249(4), 190(2), 105(4), 77(7)	3310 (NH), 1677 (C=O), 1613 (C=N)	2.98 (3H, s, CH_3); 8.40-8.03, 7.55-7.30 (16H, m, 6-H and Ar); 8.48 (1H, br, NH)[b]
17	418(M^+,16), 400(10), 387(100), 320(2), 277(20), 223(2), 194(7), 174(3), 104(4), 77(3)	3319 (NH), 1659 (C=O), 1619 (C=N), 1146 (C-O)	2.14 (3H, s, CH_3), 3.06 (3H, s, CH_3); 2.43 (2H, m, 4-H furanonyl); 3.55 (1H, t, *J* = 1.41 Hz, 3-H furanonyl); 4.08 (2H, t, *J* = 1.39 Hz, 5-H furanonyl); 8.42-8.41, 7.44-7.39 (5H, m, Ar); 8.86 (1H, s, 6-H)[b]
18	400(M^+,12), 385(2), 346(100), 331(12), 243(10), 83(2).	1609 (C=N), 1150 (C-O)	2.71 (3H, s, 9-CH_3); 3.05 (3H, s, 4-CH_3); 3.26 (2H, t, *J* = 2.10 Hz, 10-H); 4.23 (2H, t, *J* = 1.10 Hz, 11-H); 8.59-8.53, 7.51-7.45 (5H, m, Ar); 8.92 (1H, s, 6-H)[d]
20	414(M^+,100), 386(45), 332(12), 293(29), 277(18), 215(1), 190(8), 163(5), 121(4), 104(10), 94(5), 58(7)	3312 (NH), 1668 (C=O), 1612 (C=N)	1.81-1.73 (4H, m, 11,12-H); 2.44 (2H, t, *J* = 1.00 Hz, 10-H); 2.66 (2H, t, *J* = 1.00 Hz, 13-H); 3.20 (3H, s, CH_3), 8.51 (1H, br, NH); 8.56-8.55, 7.48 (5H, m, Ar); 8.86 (1H, s, 6-H)[d]
22a	564(M^+,5), 487(1), 332(12), 308(8), 293(100), 278(10), 245(32), 228(8), 190(21), 163(10), 103(7), 77(3)	3314 (NH), 1664 (C=O), 1607 (C=N)	3.08 (3H, s, CH_3); 3.01 (1H, t, *J* = 1.00 Hz, 10-H); 3.13 (2H, d, *J* = 1.00 Hz, 11-H); 6.74 (1H, s, 13-H); 8.47-8.40, 7.44-7.19 (15H, m, Ar); 9.44 (1H, s, 6-H)[b]
22b	683(M^+,28), 654(24), 635(16), 564(19), 510(5), 494(9), 484(62), 473(86), 470(88), 444(12), 427(10), 364(100), 318(40), 308(10), 294(31), 190(3), 152(4), 77(4)	3316 (NH), 1651 (C=O), 1605 (C=N)	2.12 (6H, s, $N(CH_3)_2$); 3.06 (3H, s, CH_3); 2.98 (1H, t, *J* = 1.00 Hz, 10-H); 3.18 (2H, d, *J* = 1.10 Hz, 11-H); 6.82 (2H, d, *J* = 1.00 Hz, Ar); 7.27 (1H, s, 13-H); 7.39 (2H, d, *J* = 1.0 Hz, Ar); 7.76 (2H, d, *J* = 1.00 Hz, Ar); 8.00 (2H, d, *J* = 1.00 Hz, Ar); 8.63-8.61, 7.51-7.48 (10H, m, Ar); 8.70 (1H, s, 6-H)[d]
24	416(M^+,9), 398(100), 388(18), 356(25), 333(8), 303(16), 293(21), 277(12), 251(4), 222(2), 199(7), 174(4), 104(10), 77(3)	3321 (NH), 1652 (C=O), 1615 (C=N)	3.09 (3H, s, CH_3), 3.70 (4H, m, 3,4-H cyclopentanonyl), 3.42 (3H, s, CH_3), 4.29 (1H, t, *J* = 1.11 Hz, 2-H cyclopentanonyl), 4.58 (2H, t, *J* = 1.09 Hz, 5-H cyclopentanonyl), 8.75-8.72, 8.61-8.58 (5H, m, Ar); 9.21 (1H, s, 6-H); 10.28 (1H, s, NH)

a : Abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet;
b: Measured in DMSO-d_6 ; c: Measured in CF_3COOD +$CDCl_3$; d: Measured in $CDCl_3$

Furthermore, the cyclohexanetriazepine **20** and cyclohexenetriazepines **22a,b** were also obtained by treatment of compound **5** with β-ketoesters **19** and **21a,b** under acidic condition, respectively (Scheme 9). The ^{1}H-NMR spectra of compound **20** revealed two additional triplets at δ 2.44 (2H, t) and 2.62 (2H, t) ppm assigned to the hydrogen attached at C_{10} and C_{13} of cyclohexanetriazepine ring and a multiple at δ 1.73-1.81 (4H, m) ppm assigned to the hydrogen attached at C_{11} and C_{12} of cyclohexanetriazepine ring, was also confirmed by the mass spectrum *m/z* 414. Also, in

particular, the ^{1}H NMR spectra of compounds **22a, b** revealed a triplets at δ 2.98-3.01 (1H, t), a doublet at δ 3.13-3.18 (2H, d) and a sharp singlet at δ 6.74-7.27 (1H, s) ppm which were readily assigned to the hydrogen attached at C_{10}, C_{11} and C_{13} of the cyclohexenetriazepine ring, respectively. These structures get further support from mass spectroscopy. Finally, the reaction of compound **5** with 2-acetyl-cyclopentanone **23** at reflux glacial acetic acid for 8 h afforded the open-chain product 2-methylmethylene- aminocyclopentane-pyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidine **24**. Attempted cyclization of compound **24** by heating in refluxing CH_3COOH/HCl to the triazepine **25** was unsuccessful and the starting material was recovered (Scheme 9). The physical and spectral data for compounds **7a-d**, **9a-g**, **10**, **13**, **15**, **17**, **18**, **20**, **22a,b** and **24** are given in Tables 1 and 2.

Conclusions

In conclusion, the 7-amino-8-imino-pyrimido[3,2:4,5]thieno[2,3-*d*]pyrimidine **5** proved to be a versatile compound by virtue of its vicinal amino and imino functions that were used to synthesis some novel polyfunctionally substituted pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-*b*][1,2,4]triazepinepine derivatives. The structures of the newly synthesized compounds were confirmed by IR, ^{1}H NMR, mass spectra and elemental analysis.

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