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Synthesis, reactions and antimicrobial activity of new cyclopenta[*e*]thieno-[2,3-*b*]pyridines and related heterocyclic systems

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Reaction of the arylidene cyanothioacetamides **1a**, **b** with cyclopentanone was proved to give a mixture of 4-aryl-3-cyanocyclopenta[*b*]pyridine-2(1*H*)-thiones **2a**, **b** and the corresponding 7-arylidene derivatives **3a**, **b**. Compounds **2a**, **b** were reacted with ethyl chloroacetate or chloroacetamide to give the promising S-substituted thiopyridines **6a**–**d**. On treatment of the latter compounds with sodium ethoxide in boiling ethanol, they underwent intramolecular *Thorpe-Ziegler* cyclization to yield the corresponding 3-amino-4-aryl-2-functionalized-cyclopenta[*e*]thieno[2,3-*b*]pyridines (**7a**–**d**). Most of these thienopyridines were reacted with a variety of reagents to produce other new cyclopentathienopyridines as well as numerous of their condensed heterocyclic derivatives. Some of the compounds synthesized were tested *in vitro* for their antibacterial and antifungal activity.

1. Introduction

Numerous thieno[2,3-*b*]pyridines are known to possess a broad spectrum of biological activities. Some of them are useful as prolactin production inhbitors [1], as antiatherosclerotics [2] and as gonadotropin releasing hormone antagonists [3]. Others are reported to exhibit a good antibacterial [4–7], antianaphylactic [8] and antihypertensive [9, 10] activity. Also, many pyridothienopyrimidine derivatives have been found applications as analgesics [11], antipyretics [12, 13] and antiinflammatories [14, 15]. Moreover, some pyridothienotriazines have been associated with antianaphylactic [16] and antiallergic [17] activities. In view of these benefits and as a continuation of our previous work on annelated thienopyridines [18–22], the present investigation was planned to synthesize new cyclopenta[*e*]thieno[2,3-*b*] pyridines and to study their reactions with a variety of reagents in the hope of obtaining compounds with enhanced biological and medicinal properties. Some of the compounds synthesized were screened *in vitro* for their antibacterial and antifungal activities.

2. Investigations, results and discussion

2.1. Chemistry

The synthesis of the target compounds started from the reaction of arylidene cyanothioacetamides **1a**, **b** with cyclopentanone, by refluxing in ethanol containing a catalytic amount of piperidine, which gave a mixture of pyridinethiones **2a**, **b** and the corresponding 7-arylidene derivatives **3a**, **b**, not only the expected pyridinethiones **2a**, **b** as reported by Elgemeie et al. [23] (Scheme 1). This result is in agreement with those reported by Saito *et. al.* [24] who proved the behaviour of cyclopentanone towards arylidene ethyl cyanoacetate to be different from that of other cycloalkanones.

The separation of the mixtures obtained into their components **2a**, **b** and **3a**, **b** was carried out by fractional crystallization using ethanol as a solvent.

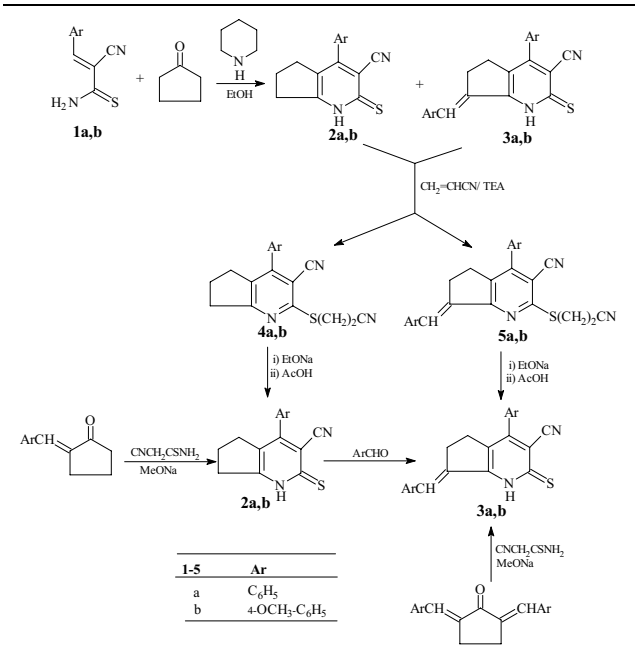
Another interesting method for separation of these mixtures into **2a**, **b** and **3a**, **b** was found to be refluxing with acrylonitrile in ethanol containing triethylamine upon which two completely separateable cyanoethylthiopyridines **4a**, **b** and **5a**, **b** were obtained. On treatment of the latter compounds with sodium ethoxide followed by acidification with acetic acid, the desired compounds **2a**, **b** and **3a**, **b** were isolated (Scheme 1).

The proposed pathway of the reaction under investigation is depicted in Scheme 2. Thus, this reaction involves the formation of Michael addition product **A** which was converted into the products **2a**, **b** and **3a**, **b** *via* two routes (a and b). In route a, the intermediate **A** underwent dehydration followed by spontaneous oxidation to yield **2a**, **b**. Route b involves the elimination of the cyanothioacetamide molecule to produce the chalcone **B** which may be reacted with **1a**, **b** or reacted with cyanothioacetamide again to yield **3a**, **b** or **2a**, **b** respectively.

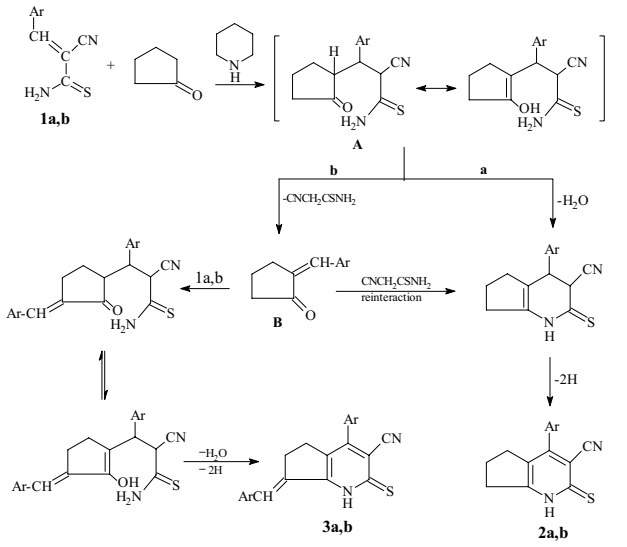
The structure of compounds **2a**, **b** and **3a**, **b** was further confirmed by independent syntheses. Thus, compounds **2a**, **b** were prepared by reaction of 2-arylidene-cyclopentanones with cyanothioacetamide, while compounds **3a**, **b** were obtained *via* the interaction of 2,5-diarylidenecyclopentanones with cyanothioacetamide [25] or direct condensation of **2a**, **b** with the respective aromatic aldehydes (Scheme 1).

The 4-Aryl-3-cyanocyclopenta[*b*]pyridine-2(1 *H*)-thiones (**2a**, **b**) were used as starting materials for the target compounds. Thus, the reaction of **2a**, **b** with ethyl chloroacetate or chloroacetamide by refluxing in ethanol containing sodium acetate gave the corresponding *S*-substituted thiopyridines **6a**–**d**. On heating of these compounds in ethanol in

Scheme 1



Scheme 2



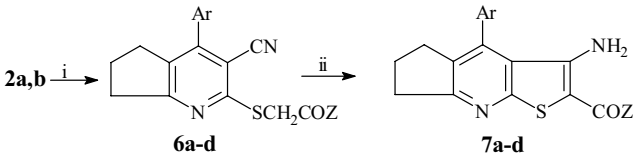
the presence of catalytic amounts of sodium ethoxide, they underwent intramolecular *Thorpe-Ziegler* cyclization to yield the corresponding 4-aryl-3-amino-2-functionalized-cyclopenta[*e*]thieno[2,3-*b*]pyridines **7a**–**d** (Scheme 3).

The reaction of ester **6a**, **b** with hydrazine hydrate by refluxing in ethanol yielded the (4-aryl-3-cyanocyclopenta[*b*]pyridin-2-ylthio)acethydrazides **8a**, **b**. When the latter reaction was performed in neat, the products were identified as 3-amino-4-aryl-cyclopenta[*e*]thieno[2,3-*b*]pyridine-2-carbohydrazides **9a**, **b**. On treatment of **8b** with excess ethyl potassium xanthate in the presence of pyridine, the 1,3,4-oxadiazole-5(4 *H*)-thione derivative **10** was isolated. The reaction of **10** with chloro-*N*-phenylacetamide, in refluxing ethanol containing sodium acetate, yielded the thioether **11** (Scheme 4).

The 3-Amino-4-aryl-2-functionalized-cyclopenta[*e*]thieno-[2,3-*b*]pyridines **7b**–**d** and **9b** underwent different sequence reactions to provide other new cyclopentathienopyridines as well as a large number of their fused heterocyclic derivatives.

Saponification of the ester **7b** with an ethanolic sodium hydroxide solution followed by acidification with acetic acid resulted in the formation of the *o*-aminocarboxylic acid **12**. On refluxing **12** with acetic anhydride, the oxazinone derivative **13** was obtained. The compound **13** was recyclized into the pyrimidinones **14**, **15** and **16** upon treatment with ammonium acetate/acetic acid, aniline or hydrazine hydrate, respectively. The reactivity of the ami-

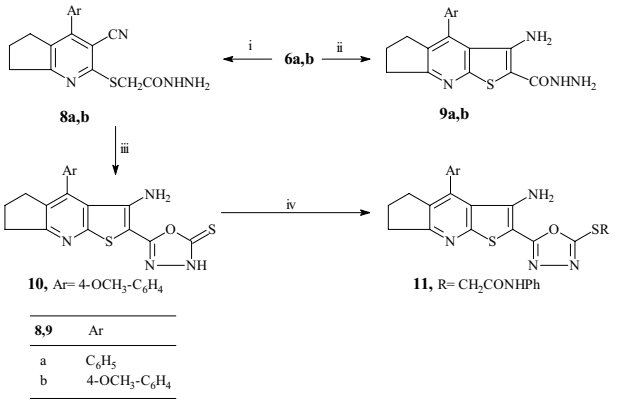
Scheme 3



6,7	Ar	Z
a	C_6H_5	OEt
b	4-OCH_3-C_6H_5	OEt
c	C_6H_5	NH_2
d	4-OCH_3-C_6H_5	NH_2

i: $ClCH_2COZ$/AcONa; ii: EtONa

Scheme 4



8,9	Ar
a	C_6H_5
b	4-OCH_3-C_6H_4

i: $N_2H_4.H_2O$/EtOH; ii: $N_2H_4.H_2O$; iii:EtO-CSS$^-K^+$; iv: $ClCH_2CONHPh$

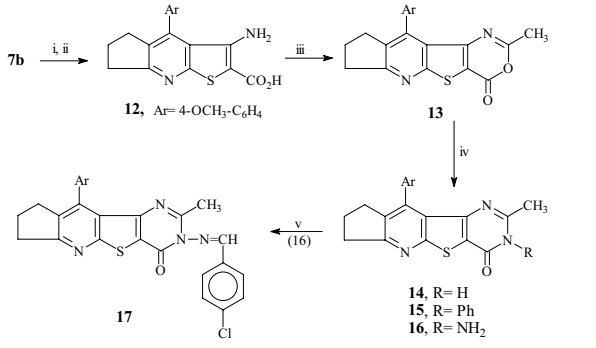
no group of compound **16** was tested by its condensation with *p*-chlorobenzaldehyde where the Schiff's base **17** was produced (Scheme 5).

The reaction of *o*-aminoamides **7c**, **d** with *p*-chlorobenzaldehyde by refluxing in acetic acid gave the tetrahydropyrimidinone derivatives **18a**, **b**. Cyclocondensation of **7c**, **d** with triethyl orthoformate resulted in the formation of pyrimidine-4(3H)-ones **19a**, **b**. Compound **7d** was also reacted with carbon disulfide and/or phenyl isothiocyanate to yield the corresponding thioxopyrimidinones **20** and **21**. Reaction of **21** with ethyl iodide gave 2-ethylthiopyrimidinone **22**. When compounds **7c**, **d** were allowed to react with nitrous acid, they underwent diazotization followed by self coupling to give the 1,2,3-triazinone derivatives **23a,b**. Compound **23a** was reacted with phenacyl bromide, ethyl chloroacetate or chloroacetamide to yield the *N*-alkylated products **24a**–**c** (Scheme 6).

On refluxing **19b** with phosphorus oxychloride, the chloropyrimidine **25** was obtained. Reaction of **25** with thiourea or with hydrazine hydrate gave pyrimidinethione **26** and/or hydrazinopyrimidine **28** respectively. Compound **26** was ethylated with ethyl iodide to give the 4-ethylthiopyrimidine derivative **27**. The cyclocondensation of **28** with acetylacetone yielded the dimethylpyrazolyl derivative **29**. The fused pentacyclic compounds **30** and **31** were obtained by treating **28** with formic or nitrous acid respectively (Scheme 7).

3-Amino-4-(*p*-methoxyphenyl)-cyclopenta[*e*]thieno[2,3-*b*]-pyridine-2-carbohydrazide (**9b**) was reacted with acetylacetone by refluxing in 2-propanol to furnish the 3,5-dimethylpyrazolyl derivative **32**. Heating of **9b** in formic acid or acetic anhydride yielded *N*-formylaminopyrimidi-

Scheme 5



i: NaOH/EtOH; ii: AcOH; iii: Ac_2O; iv: $CH_3CO_2NH_4$/AcOH, $PhNH_2$/AcOH or $N_2H_4.H_2O$/EtOH; v: p-Chlorobenzaldehyde/piperidine/EtOH

Table 1: Characterization data of the synthesized compounds

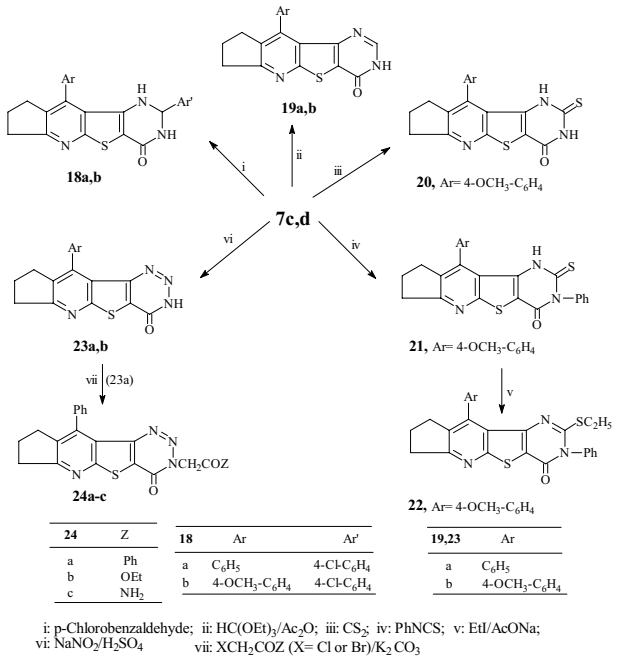
Compd.	M.P.(°C) (yield: %)	Formula[a] (M.W.)	Spectral data
2a	265 (42)[b]	$C_{15}H_{12}N_2S$ (252.3)	IR: 3180 (NH); 2210 (C≡N). ^{1}H NMR (DMSO): 14.39 (s, 1 H, NH); 7.46–7.53 (m, 5 H, Ar-H); 2.96 (t, 2 H, CH_2 at C-7); 2.54 (t, 2 H, CH_2 at C-5); 2.05 (p, 2 H, CH_2 at C-6). MS: 252 (M^+, 51%)
2b	280 (45)[b]	$C_{16}H_{14}N_2OS$ (282.4)	IR: 3190 (NH); 2210 (C≡N). ^{1}H NMR (DMSO): 14.30 (s, 1 H, NH); 7.06–7.46 (dd, 4 H, Ar-H); 3.82 (s, 3 H, OCH_3); 2.94 (t, 2 H, CH_2 at C-7); 2.58 (t, 2 H, CH_2 at C-5); 2.02 (p, 2 H, CH_2 at C-6). MS: 282 (M^+, 22%)
3a	258[c] (11)[b]	$C_{22}H_{16}N_2S$ (340.4)	IR: 3170 (NH); 2210 (C≡N). ^{1}H NMR (DMSO): 7.86 (s, 1 H, CH=C); 7.33–7.53 (m, 10 H, Ar-H); 3.03 (t, 2 H, CH_2); 2.68 (t, 2 H, CH_2). MS: 340 (M^+, 35%)
3b	270 (15)[b]	$C_{24}H_{20}N_2O_2S$ (400.5)	IR: 3180 (NH); 2210 (C≡N). ^{1}H NMR (DMSO): 7.74 (s, 1 H, CH=C); 6.97–7.45 (m, 8 H, Ar-H); 3.82, 3.78 (2s, 6 H, 2XOCH_3); 2.93 (t, 2 H, CH_2); 2.67 (t, 2 H, CH_2). MS: 400.8 (M^+, 73%)
4a[d]	122	$C_{18}H_{15}N_3S$ (305.4)	IR: 2220 (C≡N); 2200 (C≡N). ^{1}H NMR ($CDCl_3$): 7.25–7.65 (m, 5 H, Ar-H); 3.60 (t, 2 H, SCH_2); 3.10 (t, 2 H, CH_2 at C-7); 2.70–3.00 (m, 4 H, CH_2CN and CH_2 at C-5); 2.15 (p, 2 H, CH_2 at C-6). MS: 305 (M^+, 13%)
4b[d]	126	$C_{19}H_{17}N_3OS$ (335.4)	IR: 2220 (C≡N); 2200 (C≡N). ^{1}H NMR ($CDCl_3$): 6.98–7.40 (dd, 4 H, Ar-H); 3.87 (s, 3 H, OCH_3); 3.52 (t, 2 H, SCH_2); 3.07 (t, 2 H, CH_2 at C-7); 2.82–2.93 (m, 4 H, CH_2CN and CH_2 at C-5); 2.13 (p, 2 H, CH_2 at C-6). MS: 335 (M^+, 100%)
5a[d]	200	$C_{25}H_{19}N_3S$ (393.5)	IR: 2210 (2C≡N). ^{1}H NMR ($CDCl_3$): 7.14–7.63 (m, 11 H, Ar-H and CH=C); 3.66 (t, 2 H, SCH_2); 3.15 (t, 2 H, CH_2); 2.87–2.98 (m, 4 H, CH_2CN and CH_2). MS: 393 (M^+, 28%)
5b[d]	200	$C_{27}H_{23}N_3O_2S$ (453.6)	IR: 2210 (2C≡N). ^{1}H NMR ($CDCl_3$): 7.57 (s, 1 H, CH=C); 6.95–7.54 (two dd, 8 H, Ar-H); 3.87, 3.85 (2s, 6 H, 2 × OCH_3); 3.62 (t, 2 H, SCH_2); 3.10 (t, 2 H, CH_2); 2.95–3.01 (m, 4 H, CH_2CN and CH_2). MS: 453 (M^+, 97%)
6a	132 (91)	$C_{19}H_{18}N_2O_2S$ (338.4)	IR: 2200 (C≡N); 1730 (C=O)
6b	142 (80)	$C_{20}H_{20}N_2O_3S$ (368.4)	IR: 2200 (C≡N); 1730 (C=O). ^{1}H NMR ($CDCl_3$): 6.80–7.45 (dd, 4 H, Ar-H), 4.22 (q, 2 H, OCH_2); 3.95 (s, 2 H, SCH_2); 3.80 (s, 3 H, OCH_3); 2.70–3.15 (m, 4 H, 2xCH_2 at C-5,7); 2.05 (p, 2 H, CH_2 at C-6); 1.37 (t, 3 H, CH_3). MS: 368 (M^+, 19%)
6c	160 (88)	$C_{17}H_{15}N_3OS$ (309.4)	IR: 3420–3150 (NH_2); 2210 (C≡N); 1660 (C=O)
6d	190 (81)	$C_{18}H_{17}N_3O_2S$ (339.4)	IR: 3420–3150 (NH_2); 2210 (C≡N); 1660 (C=O). ^{1}H NMR ($CDCl_3$): 6.90–7.30 (dd, 4 H, Ar-H); 5.80 (s, 2 H, NH_2); 3.85 (s, 2 H, SCH_2); 3.80 (s, 3 H, OCH_3); 3.00 (t, 2 H, CH_2 at C-7); 2.75 (t, 2 H, CH_2 at C-5); 2.02 (p, 2 H, CH_2 at C-6)
7a	178 (90)	$C_{19}H_{18}N_2O_2S$ (338.4)	IR: 3490, 3340 (NH_2); 1660 (C=O)
7b	162 (93)	$C_{20}H_{20}N_2O_3S$ (368.4)	IR: 3490, 3340 (NH_2); 1660 (C=O). ^{1}H NMR ($CDCl_3$): 6.90–7.40 (dd, 4 H, Ar-H); 5.60 (s, 2 H, NH_2); 4.32 (q, 2 H, OCH_2); 3.85 (s, 3 H, OCH_3); 3.17 (t, 2 H, CH_2 at C-7); 2.72 (t, 2 H, CH_2 at C-5); 2.15 (p, 2 H, CH_2 at C-6); 1.37 (t, 3 H, CH_3)
7c	275 (94)	$C_{17}H_{15}N_3OS$ (309.4)	IR: 3450, 3330, 3150 (2NH_2); 1640 (C=O)
7d	188 (93)	$C_{18}H_{17}N_3O_2S$ (339.4)	IR: 3450, 3330, 3150 (2 NH_2); 1650 (C=O). ^{1}H NMR (DMSO): 6.90–7.60 (m, 6H, Ar-H and $CONH_2$); 5.75 (s, 2 H, NH_2); 3.80 (s, 3 H, OCH_3); 3.07 (t, 2 H, CH_2 at C-7); 2.67 (t, 2 H, CH_2 at C-5); 2.12 (p, 2 H, CH_2 at C-6)
8a	172 (95)	$C_{17}H_{16}N_4OS$ (324.4)	IR: 3350–3100 ($NHNH_2$); 2200 (C≡N); 1660 (C=O)
8b	200 (86)	$C_{18}H_{18}N_4O_2S$ (354.4)	IR: 3350–3100 ($NHNH_2$); 2200 (C≡N); 1650 (C=O). ^{1}H NMR (DMSO): 9.35 (s, 1 H, NH); 7.05–7.60 (dd, 4 H, Ar-H); 4.30 (s, 2 H, NH_2); 4.00 (s, 2 H, SCH_2); 3.85 (s, 3 H, OCH_3); 3.02 (t, 2 H, CH_2 at C-7); 2.77 (t, 2 H, CH_2 at C-5); 2.07 (p, 2 H, CH_2 at C-6)
9a	280 (78)	$C_{17}H_{16}N_4OS$ (324.4)	IR: 3490–3260 (2NH_2, NH); 1620 (C=O)
9b	230 (75)	$C_{18}H_{18}N_4O_2S$ (354.4)	IR: 3490–3260 (2NH_2, NH); 1620 (C=O). ^{1}H NMR (DMSO): 7.55 (s, 1 H, NH); 6.85 to 7.40 (dd, 4 H, Ar-H); 5.70 (s, 2 H, NH_2); 4.00 (s, 2 H, NNH_2); 3.85 (s, 3 H, OCH_3); 3.10 (t, 2 H, CH_2 at C-7); 2.70 (t, 2 H, CH_2 at C-5); 2.05 (p, 2 H, CH_2 at C-6)
10	225 (50)	$C_{19}H_{16}N_4O_2S_2$ (396.5)	IR: 3420, 3320 (NH_2); 3100 (NH). ^{1}H NMR (DMSO): 7.00–7.40 (dd, 4 H, Ar-H); 5.25 (s, 2 H, NH_2); 3.80 (s, 3 H, OCH_3); 3.00 (t, 2 H, CH_2 at C-7); 2.62 (t, 2 H, CH_2 at C-5); 2.05 (p, 2 H, CH_2 at C-6)
11	230 (70)	$C_{27}H_{23}N_5O_3S_2$ (529.6)	IR: 3490, 3310 (NH_2); 3210 (NH); 1650 (C=O). ^{1}H NMR ($CDCl_3$): 9.20 (s, 1 H, NH); 6.99–7.46 (m, 9H, Ar-H); 5.42 (s, 2 H, NH_2); 3.92 (s, 2 H, SCH_2); 3.84 (s, 3 H, OCH_3); 3.09 (t, 2 H, CH_2 at C-7); 2.69 (t, 2 H, CH_2 at C-5); 2.09 (p, 2 H, CH_2 at C-6). MS: 529 (M^+, 100%).
12	180 (85)	$C_{18}H_{16}N_2O_3S$ (340.4)	IR: 3480, 3320 (NH_2); 1640 (C=O)
13	190 (82)	$C_{20}H_{16}N_2O_3S$ (364.4)	IR: 1740 (C=O). ^{1}H NMR ($CDCl_3$): 6.85–7.40 (dd, 4 H, Ar-H); 3.85 (s, 3 H, OCH_3); 3.15 (t, 2 H, CH_2 at C-7); 2.87 (t, 2 H, CH_2 at C-9); 1.95–2.35 (m, 5 H, CH_3 and CH_2 at C-8). MS: 364 (M^+, 100%)
14	340–42 (82)	$C_{20}H_{17}N_3O_2S$ (363.4)	IR: 3200–2400 (NH); 1650 (C=O). ^{1}H NMR (DMSO): 6.80–7.40 (dd, 4 H, Ar-H); 3.80 (s, 3 H, OCH_3); 3.07 (t, 2 H, CH_2 at C-7); 2.77 (t, 2 H, CH_2 at C-9); 1.80–2.30 (m, 5 H, CH_3 and CH_2 at C-8).
15	254 (73)	$C_{26}H_{21}N_3O_2S$ (439.5)	IR: 1660 (C=O)
16	225 (92)	$C_{20}H_{18}N_4O_2S$ (378.5)	IR: 3300, 3200 (NH_2); 1660 (C=O). ^{1}H NMR ($CDCl_3$): 6.90–7.40 (dd, 4 H, Ar-H); 5.00 (s, 2 H, NH_2); 3.85 (s, 3 H, OCH_3); 3.17 (t, 2 H, CH_2 at C-7); 2.87 (t, 2 H, CH_2 at C-9); 2.45 (s, 3 H, CH_3); 2.15 (p, 2 H, CH_2 at C-8). MS: 378 (M^+, 36%)

Table 1: (contd.)

Compd.	M.P.(°C) (yield: %)	Formula (M.W.)	Spectral data
17	240 (83)	$C_{27}H_{21}ClN_4O_2S$ (501.0)	IR: 1660 (C=O). ^{1}H NMR ($CDCl_3$): 9.10 (s, 1 H, N=CH); 6.90–7.80 (m, 8H, Ar-H); 3.85 (s, 3 H, OCH_3); 3.22 (t, 2 H, CH_2 at C-7); 2.92 (t, 2 H, CH_2 at C-9); 2.40 (s, 3 H, CH_3); 2.17 (p, 2 H, CH_2 at C-8)
18a	>360 (81)	$C_{24}H_{18}ClN_3OS$ (431.9)	IR: 3390, 3180 (2NH); 1640 (C=O)
18b	318 (83)	$C_{25}H_{20}ClN_3O_2S$ (462.0)	IR: 3390, 3180 (2NH); 1630 (C=O). ^{1}H NMR ($CDCl_3$): 8.00 (s, 1 H, CONH); 6.90–7.60 (m, 8H, Ar-H); 5.70 (s, 1 H, NH), 5.20 (s, 1 H, CH), 3.80 (s, 3 H, OCH_3); 3.10 (t, 2 H, CH_2 at C-7); 2.80 (t, 2 H, CH_2 at C-9); 2.20 (p, 2 H, CH_2 at C-8). MS: 462 (M^+, 33%)
19a	310–12 (90)	$C_{18}H_{13}N_3OS$ (319.4)	IR: 3200–2400 (NH); 1660 (C=O)
19b	309–310 (95)	$C_{19}H_{15}N_3O_2S$ (349.4)	IR: 3200–2400 (NH); 1660 (C=O). ^{1}H NMR (TFA): 8.80 (s, 1 H, CH pyrimidine); 6.85 to 7.35 (m, 4 H, Ar-H); 3.80 (s, 3 H, OCH_3); 3.12 (t, 2 H, CH_2 at C-7); 2.82 (t, 2 H, CH_2 at C-9); 2.15 (p, 2 H, CH_2 at C-8)
20	310 (79)	$C_{19}H_{15}N_3O_2S_2$ (381.5)	IR: 3350–3100 (2NH); 1680 (C=O); 1130 (C=S). ^{1}H NMR (TFA): 7.10–7.50 (dd, 4 H, Ar-H); 3.90 (s, 3 H, OCH_3); 3.15 (t, 2 H, CH_2 at C-7); 2.82 (t, 2 H, CH_2 at C-9); 2.17 (p, 2 H, CH_2 at C-8)
21	285 (71)	$C_{25}H_{19}N_3O_2S_2$ (457.6)	IR: 3300 (NH); 1680 (C=O); 1150 (C=S). ^{1}H NMR (DMSO): 12.50 (s, 1 H, NH); 7.00 to 7.70 (m, 9H, Ar-H); 3.90 (s, 3 H, OCH_3); 2.70–3.30 (m, 4 H, 2 × CH_2 at C-7,9); 2.30 (p, 2 H, CH_2 at C-8). MS: 457 (M^+, 6%)
22	189 (75)	$C_{27}H_{23}N_3O_2S_2$ (485.6)	IR: 1660 (C=O)
23a	310 (88)	$C_{17}H_{12}N_4OS$ (320.4)	IR: 3200–2400 (NH); 1660 (C=O)
23b	305–306 (87)	$C_{18}H_{14}N_4O_2S$ (350.4)	IR: 3200–2400 (NH); 1680 (C=O)
24a	250 (76)	$C_{25}H_{18}N_4O_2S$ (438.5)	IR: 1670 (2 C=O)
24b	202 (70)	$C_{21}H_{18}N_4O_3S$ (406.5)	IR: 1750 (C=O, ester); 1680 (C=O, triazinone). ^{1}H NMR ($CDCl_3$): 7.10–7.60 (m, 5 H, Ar-H); 5.10 (s, 2 H, NCH_2); 4.17 (q, 2 H, OCH_2); 3.17 (t, 2 H, CH_2 at C-7); 2.87 (t, 2 H, CH_2 at C-9); 2.12 (p, 2 H, CH_2 at C-8); 1.22 (t, 3 H, CH_3)
24c	300–302 (75)	$C_{19}H_{15}N_5O_2S$ (377.4)	IR: 3350, 3150 (NH_2); 1680 (2C=O)
25	210–211 (88)	$C_{19}H_{14}ClN_3OS$ (467.9)	IR: 1600 (C=N)
26	275 (82)	$C_{19}H_{15}N_3OS_2$ (365.5)	IR: 3330–3120 (NH)
27	160 (74)	$C_{21}H_{19}N_3OS_2$ (393.5)	IR: 1600 (C=N). ^{1}H NMR ($CDCl_3$): 8.73 (s, 1 H, CH pyrimidine); 6.99–7.36 (dd, 4 H, Ar-H); 3.89 (s, 3 H, OCH_3); 3.38 (q, 2 H, SCH_2); 3.20 (t, 2 H, CH_2 at C-7); 2.90 (t, 2 H, CH_2 at C-9); 2.16 (p, 2 H, CH_2 at C-8); 1.43 (t, 3 H, CH_3)
28	271 (90)	$C_{19}H_{17}N_5OS$ (363.4)	IR: 3460, 3320, 3180 ($NHNH_2$); 1640 (C=N); ^{1}H NMR (DMSO): 8.80 (s, 1 H, CH pyrimidine); 8.00 (s, 1 H, NH); 6.80–7.35 (dd, 4 H, Ar-H); 4.30 (s, 2 H, NH_2); 3.70 (s, 3 H, OCH_3); 2.97 (t, 2 H, CH_2 at C-7); 2.62 (t, 2 H, CH_2 at C-9); 1.95 (p, 2 H, CH_2 at C-8).
29	220 (83)	$C_{24}H_{21}N_5OS$ (427.5)	IR: 1600 (C=N). ^{1}H NMR ($CDCl_3$): 8.71 (s, 1 H, CH pyrimidine); 7.01–7.38 (dd, 4 H, Ar-H); 6.06 (s, 1 H, CH pyrazole); 3.90 (s, 3 H, OCH_3); 3.21 (t, 2 H, CH_2 at C-7); 2.90 (t, 2 H, CH_2 at C-9); 2.75, 2.36 (2s, 6H, 2 × CH_3, attached to pyrazole ring); 2.16 (p, 2 H, CH_2 at C-8)
30	260 (82)	$C_{20}H_{15}N_5OS$ (373.4)	IR: 1600 (C=N); ^{1}H NMR ($CDCl_3$): 9.07 (s, 1 H, CH pyrimidine); 8.40 (s, 1 H, CH triazole); 7.00–7.35 (dd, 4 H, Ar-H); 3.90 (s, 3 H, OCH_3); 3.21 (t, 2 H, CH_2 at C-10); 2.91 (t, 2 H, CH_2 at C-8); 2.18 (p, 2 H, CH_2 at C-9). MS: 375 (M^++2, 19%); 374 (M^++1, 90%); 371 (M^+−2, 100%)
31	213 (80)	$C_{19}H_{14}N_6OS$ (374.4)	IR: 1600 (C=N). ^{1}H NMR (DMSO): 9.10 (s, 1 H, CH pyrimidine); 6.90–7.50 (dd, 4 H, Ar-H); 3.90 (s, 3 H, OCH_3); 3.12 (t, 2 H, CH_2 at C-10); 2.87 (t, 2 H, CH_2 at C-8); 2.20 (p, 2 H, CH_2 at C-9)
32	210 (79)	$C_{23}H_{22}N_4O_2S$ (418.5)	IR: 3470, 3300 (NH_2); 1630 (C=O). ^{1}H NMR ($CDCl_3$): 6.95–7.40 (dd, 4 H, Ar-H); 6.60 (s, 2 H, NH_2); 5.95 (s, 1 H, CH pyrazole); 3.80 (s, 3 H, OCH_3); 3.12 (t, 2 H, CH_2 at C-7); 2.45–2.80 (m, 5 H, CH_3 attached to pyrazole ring and CH_2 at C-5); 2.35 (s, 3 H, CH_3 attached to pyrazole ring); 2.10 (t, 2 H, CH_2 at C-6). MS: 418 (M^+, 100%)
33	142 (59)	$C_{20}H_{16}N_4O_3S$ (392.4)	IR: 3250 (NH); 1720 (C=O, formyl group); 1670 (C=O, pyrimidinone). ^{1}H NMR (DMSO): 8.40 (s, 1 H, CH pyrimidine); 8.20 (s, 1 H, NH); 7.90 (s, 1 H, CHO); 6.90–7.55 (dd, 4 H, Ar-H); 4.00 (s, 3 H, OCH_3); 3.35 (t, 2 H, CH_2 at C-7); 2.95 (t, 2 H, CH_2 at C-9); 2.30 (p, 2 H, CH_2 at C-8). MS: 391 (M^+−1, 47%); 393 (M^++1, 11%)
34	205 (54)[b]	$C_{24}H_{22}N_4O_4S$ (462.5)	IR: 1730 (C=O, acetyl); 1680 (C=O, pyrimidinone). ^{1}H NMR ($CDCl_3$): 7.00–7.50 (m, 4 H, Ar-H); 3.90 (s, 3 H, OCH_3); 3.27 (t, 2 H, CH_2 at C-7); 2.97 (t, 2 H, CH_2 at C-9); 2.45 (s, 6H, 2x$COCH_3$); 2.22 (m, 5 H, CH_3 at C-2 and CH_2 at C-8). MS: 462 (M^+, 34%)
35	100 (dec.) (82)	$C_{18}H_{15}N_5O_2S$ (365.4)	IR: 3480, 3320 (NH_2); 2120 (N_3); 1680 (C=O)
37	290 (89)	$C_{18}H_{15}N_3O_2S$ (337.4)	IR: 3500–2500 (NH); 1680 (C=O). ^{1}H NMR (DMSO): 11.02, 9.48 (2s, 2 H, 2NH imidazolone); 7.04–7.32 (dd, 4 H, Ar-H); 3.82 (s, 3 H, OCH_3); 2.98 (t, 2 H, CH_2 at C-6); 2.81 (t, 2 H, CH_2 at C-8); 2.04 (p, 2 H, CH_2 at C-7). MS: 337 (M^+, 100%)

[a] Satisfactory analyses were obtained for all compounds
[b] Yield of method A)
[c] Lit. m.p. [25]: 254–255 °C
[d] Yield can not be calculated

Scheme 6



24	Z
a	Ph
b	OEt
c	NH_2

18	Ar	Ar'
a	C_6H_5	4-Cl-C_6H_4
b	4-OCH_3-C_6H_4	4-Cl-C_6H_4

19,23	Ar
a	C_6H_5
b	4-OCH_3-C_6H_4

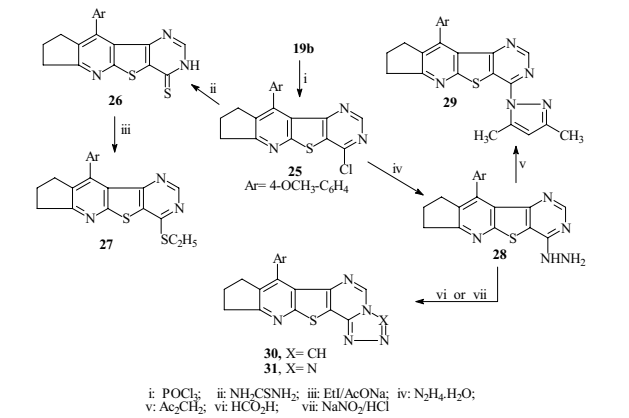
none **33** and *N*-diacetylaminopyrimidinone **34**, respectively. Compound **34** was also prepared by treating **16** with acetic anhydride. Diazotisation of **9b** in glacial acetic acid with an equimolar quantity of sodium nitrite produced the *o*-aminocarboazide **35**. On refluxing **35** in dry toluene, it underwent *Curtius* rearrangement into 4-(*p*-methoxyphenyl)-1 *H*-cyclopenta[*e*]imidazolo[4′,5′:4,5]thieno[2,3-*b*]pyridine-2(3 *H*)-one (**37**) *via* the isocyanate derivative **36** as an intermediate (Scheme 8).

The structures of all the compounds synthesized were elucidated and confirmed by elemental analyses, IR, ^{1}H NMR and mass spectral data (Table 1).

2.2. Antimicrobial activity

Some of the compounds synthesized were screened *in vitro* for their antimicrobial activities against four strains of bacteria (*Staphylococcus aureus, Sarcina spp., Bacillus cereus* and *Escherichia coli*) and two species of fungi (*Aspergillus niger* and *Aspergillus fumigatus*) using the filter paper disc method [26]. The screening results given in Table 2 indicated that: all the compounds tested exhibit considerable activities against most bacterial species ex-

Scheme 7



Scheme 8

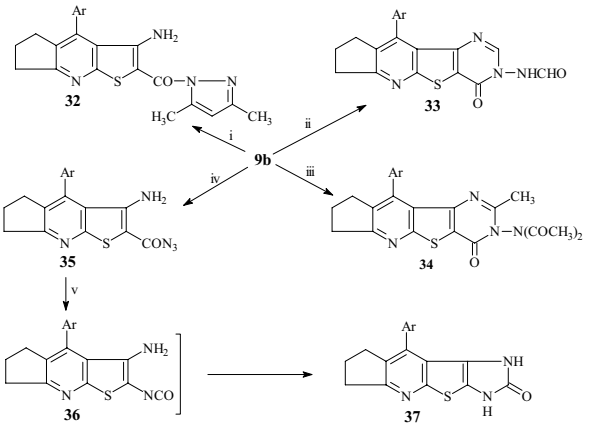


Table 2: The antibacterial and antifungal activities of some compounds synthesized

Compd.	*Staph. aureus*	*Sarcina spp.*	*Bacillus cereus*	*Escher. coli*	*Asp. niger*	*Asp. fumigatus*
2a	−	−	−	−	−	−
3b	+	+	−	−	−	−
4b	−	−	−	−	−	−
7d	−	−	++	−	−	−
9b	+++	−	++	+	−	−
13	++	+	−	−	−	−
16	−	+++	+++	−	−	−
20	++	+	−	−	−	−
21	−	++	++	++	+	−
24c	+	−	−	−	−	−
28	+	−	−	−	−	−
34	−	−	−	−	−	−
37	−	+++	++	+	−	−
Tioconazole (Tyrosyd®)	+	+++	+++	+	++	+++

−: No activity; +: moderate activity (inhibition zone 5–10 mm); ++: strong activity (inhibition zone 11–15 mm); +++: very strong activity (inhibition zone 16–20 mm)

cept for compounds **2a**, **4b** and **34** which possess no activity against any of the microorganisms under investigation. As far as the antifungal activity is concerned, only **21** showed a moderate activity against *Asp. niger.* The other compounds tested showed no activity against the two fungal species used.

3. Experimental

All m.p.'s are uncorrected and measured on a Gallenkamp apparatus. IR spectra were recorded on a Shimadzu 470 IR-Spectrophotometer (KBr; υ_{max} in cm^{-1}); ^{1}H-NMR spectra on a Varian EM-390, 90 MHz specrometer with TMS as internal standard or on a Jeol LA 400 MHz FT-NMR spectrometer (δ in ppm); MS on a Jeol JMS-600 mass spectrometer and elemental analyses on a Perkin-Elmer 240C elemental analyser.

3.1. Arylidenecyanothioacetamides **1a, b**

These compounds were prepared according to a known method [27].

3.2. Cyclopenta[b]pyridinethione derivatives **2a**, **b** *and* **3a**, **b**

3.2.1. Method A

To a mixture of **1a**, **b** (0.01 mol) and cyclopentanone (0.9 ml, 0.01 mol) in C_2H_5OH (30 ml), a few drops of piperidine were added. The resulting mixture was refluxed for 3 h and left to cool. The precipitated solid was collected and identified as a mixture of 4-aryl-3-cyanocyclopenta[*b*]pyridine-2(1H)-thione (**2a**, **b**) and the corresponding 4-aryl-7-arylidene-3-cyanocyclopenta[*b*]pyridine-2(1 *H*)-thione (**3a**, **b**).

The mixture was dissolved in boiling C_2H_5OH; the insoluble portion was identified as **3a**, **b** but the soluble fraction which crystallized on cooling as **2a**, **b**.
The components could also be seperated by the following procedure: To the mixture obtained from the former experiment in C_2H_5OH (30 ml), acrylonitrile (4 ml) and triethylamine (2 ml) were added. The reaction mixture was heated under reflux for 2 h. During the reaction time a yellow solid precipitated. It was filtered off and recrystallized from acetic acid to give 4-aryl-7-arylidene-3-cyano-2-(2′-cyanoethylthio)-cyclopenta[*b*]pyridine (**5a**, **b**). The mother liquor from the above crude product was diluted with H_2O (30 ml) to give a pale yellow precipitate which was collected and recrystallized from aqueous C_2H_5OH to give 4-aryl-3-cyano-2-(2′-cyanoethylthio)-cyclopenta[*b*]pyridine (**4a**, **b**).
The cyanoethylthiopyridine derivative **4a**, **b** or **5a**, **b** so obtained (0.01 mol) in C_2H_5ONa solution (250 mg Na in 30 ml abs. C_2H_5OH) was heated under reflux for 1 h. The reaction mixture was cooled and acidified with acetic acid to give the corresponding pyridinethione **2a**, **b** or **3a**, **b** which was crystallized from C_2H_5OH or CH_3CO_2H, respectively.

3.2.2. Method B

A mixture of 2-arylidenecyclopentanone or 2,5-diarylidenecyclopentanone [25] (0.01 mol) and cyanothioacetamide (1.0 g, 0.01 mol) in CH_3ONa solution (0.05 g Na in 30 ml CH_3OH) was warmed at 50 °C on a water bath for 48 h. The crystalline solid that formed on cooling was collected and recrystallized from C_2H_5OH or CH_3CO_2H to give the corresponding cyclopenta[*b*]pyridinethiones **2a**, **b** (60–65%) and **3a**, **b** (43–60%) respectively.
The latter compounds (**3a**, **b**) were also prepared by refluxing equimolar quantities (0.01 mol) of **2a**, **b** and the respective aldehyde in dioxane (30 ml) containing a few drops of piperidine for 3 h. The products upon recrystallization from acetic acid were characterised as **3a**, **b**.

3.3. Reaction of 2a, b *with ethyl chloroacetate or chloroacetamide; synthesis of S-substituted thiopyridines* 6a–d

A mixture of **2a**, **b** (0.1 mol), ethyl chloroacetate or chloroacetamide (0.1 mol) and $CH_3CO_2Na \cdot 3H_2O$ (13.6 g, 0.1 mol) in C_2H_5OH (400 ml) was heated under reflux for 2 h. The precipitate thus formed on cooling or dilution with H_2O was filtered off, washed with H_2O, dried in air and recrystallized from C_2H_5OH.

3.4. 3-Amino-4-aryl-2-functionalized-cyclopenta[e]thieno[2,3-b]pyridines 7a–d

Compound **6a**–**d** (0.01 mol) was suspended in C_2H_5ONa solution (50 mg Na in 30 ml abs. C_2H_5OH) and heated under reflux for 5 min. The solid that formed after cooling was collected and recrystallized from C_2H_5OH to give yellow crystals of **7a**–**d**.

3.5. (4-Aryl-3-cyanocyclopenta[b]pyridin-2-ylthio)acethydrazides 8a, b

A mixture of ester **6a**, **b** (0.01 mol) and hydrazine hydrate 99% (1.0 ml, 0.02 mol) in C_2H_5OH (30 ml) was heated under reflux for 4 h. The precipitated product thus formed on cooling was filtered off and recrystallized from C_2H_5OH as white crystals of **8a**, **b**.

3.6. 3-Amino-4-arylcyclopenta[e]thieno[2,3-p]pyridine-2-carbohydrazides 9a, b

Compounds **6a**, **b** (0.003 mol) in hydrazine hydrate 99% (1.5 ml, 0.03 mol) was heated under reflux for 2 h. The reaction mixture was triturated with C_2H_5OH (30 ml) and allowed to cool. The precipitate thus formed was collected and recrystallized from C_2H_5OH as yellow crystals of **9a**, **b**.

3.7. 2-(3-Amino-4-(p-methoxyphenyl)-cyclopenta[e]thieno[2,3-e]pyrdin-2-yl)-1,3,4-oxadiazole-5(4H)-thione (10)

To a suspension of acethydrazide **8b** (1.42 g, 0.004 mol) and ethyl potassium xanthate (1.3 g, 0.008 mol) in abs. C_2H_5OH (30 ml), 0.4 ml of pyridine was added. The resulting mixture was refluxed for 6 h, concentrated and left to cool. The yellow product thus separated on acidification with CH_3CO_2H was collected and recrystallized from C_2H_5OH as yellow needles of **10.**

3.8. 2-(3-Amino-4-(p-methoxyphenyl)-cyclopenta[e]thieno[2,3-b]pyridin-2-yl)-5-(N-phenyl)carbamoylmethylthio-1,3,4-oxadiazole (11)

A mixture of **10** (0.4 g, 0.001 mol), chloro-*N*-phenylacetamide (0.17 g, 0.001 mol) and $CH_3CO_2Na \cdot 3H_2O$ (0.27 g, 0.002 mol) in C_2H_5OH (10 ml) was heated under reflux for about 2 h. The precipitate thus formed was collected by filtration, washed with H_2O and recrystallized from C_2H_5OH as pale yellow crystals of **11**.

3.9. 3-Amino-4-(p-methoxyphenyl)-cyclopenta[e]thieno[2,3-b]pyridine-2-carboxylic acid (12)

The ester **7b** (3.68 g, 0.01 mol) in an ethanolic NaOH solution (100 ml, 5%) was refluxed for 2 h. The reaction mixture was cooled, diluted with H_2O (40 ml) and acidified with dilute CH_3CO_2H upon which a yellow precipitate was formed. It was collected by filtration, dried in air and recrystallized from CH_3OH as yellow crystals of **12**.

3.10. 2-Methyl-10-(p-methoxyphenyl)-cyclopenta[5′,6′]pyrido[3′,2′:4,5]-thieno[3,2-d] oxazine-4-one (13)

The amino acid **12** (2.04 g, 0.006 mol) was heated under reflux for 4 h with redistilled $(CH_3CO)_2O$ (40 ml). The reaction mixture was then concentrated by normal distillation and allowed to cool. The solid precipitate was collected by filtration and dried in air.

3.11. Reaction of oxazinone 13 *with ammonium acetate or aniline; formation of pyrimidinones* 14 *and* 15

A mixture of **13** (0.36 g, 0.001 mol) and $CH_3CO_2NH_4$ or aniline (0.006 mol) in glacial CH_3CO_2H (10 ml) was heated under reflux for 4 h. The cooled reaction mixture was diluted with H_2O (10 ml) upon which a yellow compound precipitated. It was collected by filtration, dried and crystallized from a $C_2H_5OH/CHCl_3$ mixture to give compounds **14** and **15**, respectively

3.12. 3-Amino-10-(p-methoxyphenyl)-2-methylcyclopenta[5′,6′]pyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3H)-one (16)

A mixture of **13** (0.36 g, 0.001 mol) and hydrazine hydrate 99% (0.5 ml, 0.01 mol) in C_2H_5OH (20 ml) was heated under reflux for 2 h. The product thus obtained was recrystallized from C_2H_5OH as white needles of **16**.

3.13 3-(p-Chlorobenzylideneamino)-10-(p-methoxyphenyl)-2-methylcyclopenta[5′,6′] pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3H)-one (17)

To a suspension of **16** (0.75 g, 0.002 mol) and *p*-chlorobenzaldehyde (0.28 g, 0.002 mol) in C_2H_5OH (20 ml), three drops of piperidine were added. The resulting mixture was refluxed for 3 h; and the solid which formed while hot was collected and recrystallized from dioxane as yellow needles of **17**.

3.14. 10-Aryl-2-(p-chlorophenyl)-4-oxo-1,2,3,4-tetrahydrocyclopenta[5′,6′]-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidines 18a, b

A mixture of **7c**, **d** (0.001 mol) and *p*-chlorobenzaldehyde (0.14 g, 0.001 mol) in glacial CH_3CO_2H (15 ml) was refluxed for 3 h. The product was collected and recrystallized from dioxane as fine yellow needles of **18a**, **b**.

3.15. 10-Arylcyclopenta[5′,6′]pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3H)-ones 19a, b

A mixture of **7c**, **d** (0.01 mol) and $HC(OC_2H_5)_3$ (4 ml) in redistilled $(CH_3CO)_2O$ (20 ml) was heated under reflux at 120 °C for 3 h. The solid that formed on cooling was collected and recrystallized from C_2H_5OH as colourless plates of **19a**, **b**.

3.16. 10-(p-Methoxyphenyl)-4-oxo–2-thioxo-1,2,3,4-tetrahydrocyclopenta[5′,6′]pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine (20)

A mixture of **7d** (0.34 g, 0.001 mol) and CS_2 (4 ml) in dry pyridine (30 ml) was heated on a water bath for 48 h. The solvent was removed by distillation under reduced pressure and the residue was crystallized from CH_3CO_2H as yellow crystals of **20**.

3.17. 10-(p-Methoxyphenyl)-4-oxo-3-phenyl-2-thioxo-1,2,3,4-tetrahydrocyclopenta[5′,6′]pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine (21)

A mixture of **7d** (0.67 g, 0.002 mol) and PhNCS (0.24 ml, 0.002 mol) in glacial CH_3CO_2H (15 ml) was refluxed for 8 h. The product that separated after cooling was collected and recrystallized from C_2H_5OH as yellow needles of **21**.

3.18. 10-Aryl-cyclopenta[5′,6′]pyrido[3′,2′:4,5]thieno[3,2-d][1,2,3]triazine-4(3H)-ones 23a, b

Sodium nitrite solution (8 ml, 10%; 0.01 mol) was added to a solution of **7c**, **d** (0.009 mol) in concentrated H_2SO_4 (5 ml) and glacial CH_3CO_2H (5 ml) at 0 °C over 5 min with stirring. The solid thus precipitated was collected and recrystallized from C_2H_5OH as white crystals of **23a**, **b**.

3.19. Alkylation of triazinone 23a; *formation of* 24a–c: *General procedure*

A solution of **23a** (0.32 g, 0.001 mol) in DMF (7 ml) was stirred for a while with K_2CO_3 (0.3 g), and then alkylating agent (0.001 mol) in DMF (7 ml) was added. The reaction mixture was stirred for 2 h at room temperature and then diluted with H_2O. The precipitate thus formed was filtered off, dried and crystallized from a $C_2H_5OH/CHCl_3$ mixture to give **24a**–**c**.

3.20. 4-Chloro-10-(p-methoxyphenyl)-cyclopenta[5′,6′]pyrido[3′,2′:4,5]-thieno [3,2-d]pyrimidine (**25**)

A suspension of **19b** (1.4 g, 0.004 mol) in an excess amount of $POCl_3$ (15 ml) was heated under reflux for 3 h. The cooled reaction mixture was poured with vigorous stirring into ice H_2O (50 ml). The solid that separated was collected and crystallized from C_2H_5OH as white needles of **25**.

3.21. 10-(p-Methoxyphenyl)-cyclopenta[5′,6′]pyrido[3′,2′:4,5]thieno[3,2-d] pyrimidine-4(3 H)-thione (**26**)

A mixture of **25** (0.73 g, 0.002 mol) and $(NH_2)_2C{=}S$ (0.3 g, 0.004 mol) in $(CH_3)_2CHOH$ (20 ml) was refluxed for 3 h. On cooling the precipitated solid was collected, dissolved in warm 10% NaOH solution and filtered. The filtrate was acidified with CH_3CO_2H upon which a yellow precipitate separated. It was collected and crystallized from C_2H_5OH as yellow needles of **26.**

3.22. Reaction of compound **21** *or* **26** *with ethyl iodide; formation of* **22** *and* **27**

To a suspension of **21** or **26** (0.001 mol) and $CH_3CO_2Na \cdot 3H_2O$ (0.40 g, 0.003 mol) in C_2H_5OH (20 ml), C_2H_5I (1 ml) was added. The resulting mixture was refluxed for 1 h. The precipitated product was filtered and recrystallized from C_2H_5OH as yellow plates of **22** or **27**, respectively.

3.23. 4-Hydrazino-10-(p-methoxyphenyl)-cyclopenta[5′,6′]pyrido[3′,2′:4,5]-thieno[3′,2′:4,5]thieno[3,2-d]pyrimidine (**28**)

A mixture of **25** (4.68 g, 0.01 mole) and hydrazine hydrate (4 ml) in abs. C_2H_5OH (100 ml) was refluxed for 1 h. The product which precipitated after cooled was collected and recrystallized from dioxane as white crystals of **28**.

3.24. 4-(3,5-Dimethyl-1H-pyrazol-1-yl)-10-(p-methoxyphenyl)-cyclopenta[5′,6′]pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine (**29**)

Compound **28** (0.36g, 0.001 mol) in acetylacetone (5 ml), was heated under reflux for 4 h. The reaction mixture was triturated with C_2H_5OH (5 ml) and left to cool. The precipitated solid was collected by filtration and recrystallization from ethanol as pale yellow needles of **29**.

3.25. 7-(p-Methoxyphenyl)-s-triazolo[4″,3″-c]cyclopenta[5′,6′]pyrido[3′,2′: 4,5] thieno[3,2-d]pyrimidine (**30**)

Compound **28** (0.36 g, 0.001 mol) in HCO_2H (15 ml) was heated under reflux for 5 h. The reaction mixture was diluted with H_2O (15 ml) upon which a white compound was precipitated. It was collected by filtration and crystallized from C_2H_5OH.

3.26. 7-(p-Methoxyphenyl)-tetrazolo[1″,5″-c]cyclopenta[5′,6′]pyrido[3′,2′: 4,5] thieno [2,3-e]pyrimidine (**31**)

To a solution of **28** (0.36 g, 0.001 mol) in concentrated HCl (5 ml) at 0 °C, a cold solution of $NaNO_2$ 10% (7 ml, 0.01 mol) was added with stirring over 10 min. The precipitate that separated was collected and crystallized from C_2H_5OH as white crystals of **31.**

3.27. 1-(3-Amino-4-(p-methoxyphenyl)-cyclopenta[e]thieno[2,3-b]pyridin-2-yl) carbonyl-3,5-dimethyl-1 H-pyrazole (**32**)

A mixture of **9b** (0.35 g, 0.001 mol) and acetylacetone (1 ml, 0.01 mol) in $(CH_3)_2CHOH$ (30 ml) was refluxed for 4 h. The solid that obtained after cooling was recrystallized from C_2H_5OH as yellow needles of **32.**

3.28. 3-Formylamino-10-(p-methoxyphenyl)-cyclopenta[5′,6′]pyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3 H)-one (**33**)

Compound **9b** (0.35 g, 0.001 mol) was refluxed for 4 h with HCO_2H (15 ml). The reaction mixture was then diluted with H_2O (15 ml) upon which a white solid precipitated. It was collected and recrystallized from benzene to give **33.**

3.29. 3-Diacetylamino-2-methyl-10-(p-methoxyphenyl)-cyclopenta[5′,6′]-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3H)-one (**34**)

3.29.1. Method A

Compound **9b** (0.35 g, 0.001 mol) in $(CH_3CO)_2O$ (10 ml) was refluxed for 3 h. The reaction mixture was cooled, diluted with H_2O (20 ml) and allowed to stand at room temperature for 2 h. The precipitated solid was collected and recrystallized from C_2H_5OH.

3.29.2. Method B

Compound **16** (1.89 g, 0.005 mol) in $(CH_3CO)_2O$ (30 ml) was refluxed for 3 h. The reaction mixture was diluted with H_2O (20 ml) and left overnight at room temperature. The precipitate thus formed was filtered and crystallized from C_2H_5OH to give **34** in 79% yield.

3.30. 3-Amino-4-(p-methoxyphenyl)-cyclopenta[e]thieno[2,3-b]pyridine-2-carbonylazide (**35**)

Sodium nitrite solution 10% (7 ml, 0.01 mol) was added to a solution of compound **9b** (3.54 g, 0.01 mol) in glacial CH_3CO_2H (10 ml) at room temperature over 5 min with stirring. The precipitated solid was filtered, dried in air and used in the next reaction without purification.

3.31. 4-(p-Methoxyphenyl)-1H-cyclopenta[e]-imidazo[4′,5′:4,5]thieno[2,3-b]-pyridine-2(3 H)-one (**37**)

The acid azide **35** (1.8 g, 0.005 mol) was refluxed for 3 h in dry toluene (30 ml). The reaction mixture was cooled upon which a solid preciptate formed. It was collected and recrystallized from toluene as pale yellow crystals of **37**.

3.32. Biological Screening

The filter paper disc method was performed in Nutrient agar for bacteria and Dox agar for fungi. These agar media were inoculated with 0.5 ml of the 24 h liquid cultures. Filter paper discs (5 mm diameter) saturated with each compound solution (10 mg/1ml of DMSO) were placed on the indicated agar media. The incubation time was 48 h (at 37 °C for bacteria and at 28 °C for fungi). Discs saturated with DMSO were used as control. Tioconazole (Tyrosyd) was used as a reference substance. The diameters of inhibition zones (mm) were measured and recorded.

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