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Synthesis and antimicrobial evaluation of some new thienopyrimidine derivatives

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Reaction of heteroaromatic *o*-aminonitrile with ethyl *N*-[*bis*(methylthio)methylene]amino acetate resulted in annelation of a thieno[3,2-e]imidazo[1,2-c]pyrimidine moiety in a one step process. [1,2,4]Triazolo[4,3-c]thieno- [3,2-e]pyrimidine derivatives were prepared by initial treatment of *o*-aminonitrile with carbon disulfide, followed by methylation with methyl iodide and subsequent reaction with benzhydrazide and thiosemicarbazide, respectively. Hydrazinothieno[2,3-d]pyrimidine was prepared by cyclization of heteroaromatic *o*-aminoester with formamide, followed by chlorination and subsequent displacement with hydrazine. Treatment of the hydrazino derivative with acetylacetone, benzaldehyde and acetic anhydride afforded pyrazolylpyrimidine, benzylidenehydrazonopyrimidine and triazolopyrimidine derivatives, respectively. Some of these derivatives exhibited pronounced antimicrobial activity.

Keywords: imidazopyrimidine, triazolopyrimidine, antimicrobial activity

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Fused pyrimidines are found in a variety of natural products (*e.g.*, purines, pyrrolopyrimidines, pyridopyrimidines, pteridines), agrochemicals and veterinary products (1–3). Pyrimidine derivatives and heterocyclic annelated pyrimidines continue to attract great interest due to the wide variety of interesting biological activities observed for these compounds, such as anticancer (4), antiviral (5), antitumor (6), anti-inflammatory (7), antimicrobial (8), antifungal (9), antihistaminic (10) and analgesic (11) activities. Aromatic and heteroaromatic compounds bearing an *o*-aminonitrile or *o*-aminoester group are useful substrates for the preparation of various condensed pyrimidine heterocyclic systems (12). In view of these reports and as continuation of our earlier studies (13–16), the synthesis of a new series of thieno-pyrimidine derivatives is now reported. Several compounds were screened for their antimicrobial activity.

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EXPERIMENTAL

Melting points were determined on an electrothermal apparatus in an open capillary tube and are uncorrected. The ^1H and ^{13}C NMR spectra were measured on a Bruker AC 200 spectrophotometer (Germany) using DMSO-d_6 or $CDCl_3$ as the solvent and chemical shifts were expressed as δ values in ppm against TMS as an internal standard. TLC using silica gel G_{60} (Merck, Germany) routinely checked the purity of the compounds and the spots were exposed in iodine vapour for visualization.

Syntheses

The starting materials, 2-amino-4,5,6,7-tetrahydrobenzothiophen-3-carbonitrile (**1**) and ethyl 2-amino-4,5,6,7-tetrahydrobenzothiophen-3-carboxylate (**8**), were prepared by condensation of cyclohexanone, elemental sulfur and malononitrile or ethyl cyanoacetate as described (17). The annelating reagent, ethyl *N*-[*bis*(methylthio)methylene]amino acetate (**2**) was prepared according to the literature procedure (18).

5-Methylthio-8,9,10,11-tetrahydrobenzothieno[3,2-e]imidazo[1,2-c]pyrimidin-2(3H)-one (**3**). – A solution of *o*-aminonitrile **1** (0.01 mol) and annelating reagent **2** (0.01 mol) in dry acetic acid (10 mL) was refluxed for 8 h. The solution was then poured onto ice-water under constant stirring and the product was extracted with chloroform. After solvent evaporation, the obtained solid was recrystallized from ethanol to give **3** as colourless crystals.

2,4-Dimethylthio-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (**5**). – To a solution of *o*--aminonitrile **1** (0.01 mol) in pyridine (4 mL), carbon disulfide (0.05 mol) was added and the mixture was heated on a water-bath for 8 h. After cooling, ethanol was added to the mixture and the separated solid was collected by filtration, washed with ether to give tetrahydrobenzothieno[2,3-d]pyrimidine-2,4(*1H,3H*)-dithione (**4**). Methyl iodide (0.02 mol) was added dropwise to the crude product **4** in aqueous NaOH (10 mL) and stirred at room temperature for 12 h. The obtained yellowish solid was collected and recrystallized from ethanol to give **5** as yellow crystals.

5-Methylthio-3-phenyl-8,9,10,11-tetrahydro[1,2,4]triazolo[4,3-c]benzothieno[3,2-e]pyrimidine (**6**). – A mixture of **5** (0.01 mol) and benzhydrazide (0.01 mol) in pyridine (10 mL) was refluxed for 14 h. The mixture was concentrated in vacuum and was then allowed to set in the refrigerator for 6 h. The separated solid was recrystallized from ethanol to give **6** as yellow crystals.

3-Amino-5-methylthio-8,9,10,11-tetrahydro[1,2,4] triazolo[4,3-c]benzothieno[3,2-e]pyrimidine (**7**). – A mixture of **5** (0.01 mol) and thiosemicarbazide (0.01 mol) in pyridine (10 mL) was refluxed for 14 h. The separated solid was collected and recrystallized from ethanol to give **7** as yellow crystals.

5,6,7,8-Tetrahydrobenzothieno[2,3-d]pyrimidin-4(3H)-one (**9**). – A solution of *o*-amino ester **8** (0.01 mol) and formamide (10 mL) was refluxed for 4 h. The precipitated product was collected and recrystallized from ethanol to give **9** as yellow crystals.

4-Chloro-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (**10**). – A mixture of pyrimidone **9** (0.05 mol) and thionyl chloride (20 mL) was refluxed for 4 h. After cooling, the mixture was poured onto ice-water and stirred for another 30 min. The separated solid was recrystallized from dioxane to give **10** as yellow crystals.

4-Hydrazino-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (**11**). – A mixture of chloro compound **10** (0.05 mol) and hydrazine hydrate (3 mL) in dioxane (30 mL) was refluxed for 2 h. The separated solid was filtered off and recrystallized from dioxane to give **11** as yellow crystals.

4-Benzylidenehydrazono-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (**12**). – A mixture of hydrazino compound **11** (0.01 mol) and benzaldehyde (0.01 mol) in acetic acid (5 mL) was refluxed for 1 h. The separated solid was filtered off and recrystallized from ethanol to give **12** as white crystals.

4-(3,5-Dimethylpyrazolyl)-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (**13**). – A mixture of hydrazino compound **11** (0.01 mol) and acetylacetone (1 mL) in ethanol (20 mL) was refluxed for 8 h. The separated solid was recrystallized from ethanol to give **13** as pale brown crystals.

Table I. Elemental analyses of the synthesized compounds

Compd. No.	Yield (%)	M.p. (°C)	Mol. formula (M_r)	Found/calcd. (%)		
				C	H	N
3	75	170–171	$C_{13}H_{13}N_3OS_2$ (291.40)	53.48 53.59	4.53 4.50	14.37 14.42
5	81	127–128	$C_{12}H_{14}N_2S_3$ (282.40)	51.00 51.03	5.05 5.00	9.87 9.92
6	65	150–152	$C_{18}H_{16}N_4S_2$ (352.48)	61.23 61.34	4.52 4.45	15.78 15.89
7	68	252–254	$C_{12}H_{13}N_5S_2$ (291.40)	49.32 49.46	4.55 4.50	24.10 24.03
9	70	235–236	$C_{10}H_{10}N_2OS$ (206.27)	58.17 58.23	4.94 4.89	13.52 13.58
10	78	178–180	$C_{10}H_9ClN_2S$ (224.71)	53.40 53.45	4.07 4.04	12.44 12.47
11	70	202–203	$C_{10}H_{12}N_4S$ (220.30)	54.47 54.52	5.53 5.49	25.40 25.43
12	70	232–234	$C_{17}H_{16}N_4S$ (308.41)	66.16 66.21	5.23 5.28	18.13 18.17
13	72	> 250	$C_{15}H_{16}N_4S$ (284.39)	63.29 63.35	5.71 5.67	19.63 19.70
14	75	> 250	$C_{12}H_{12}N_4S$ (244.32)	58.92 58.99	4.99 4.95	22.98 22.93
15	68	209–211	$C_{11}H_{12}N_2O_3S_2$ (284.36)	46.40 46.46	4.28 4.25	9.88 9.85
16	72	127–129	$C_{16}H_{14}N_2O_3S_2$ (346.43)	55.42 55.47	4.10 4.07	8.13 8.09

3-Methyl-8,9,10,11-tetrahydrobenzothieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (**14**). – A mixture of hydrazino compound **11** (0.01 mol) and acetic anhydride (2 mL) was refluxed for 6 h. After cooling the mixture was poured onto ice-water and extracted with ether and the solvent was evaporated. The obtained solid was recrystallized from ethanol to give **14** as yellow crystals.

4-Oxo-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine-3-methyl sulfonate ester (**15**) or *4--oxo-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine-3-phenyl sulfonate ester* (**16**). – A mixture

Table II. Spectral data of the prepared compounds

Compd. No.	^{1}H NMR (δ, ppm) (DMSO-d_6/$CDCl_3$)	^{13}C NMR (δ, ppm) (DMSO-d_6/$CDCl_3$)
3	4.22 (s, 2H, CH_2), 2.89 (m, 4H, 2×CH_2), 2.71 (s, 3H, SCH_3), 1.86 (m, 4H, 2×CH_2)	183.4, 165.6, 164.7, 152.9, 134.5, 130.5, 115.1, 49.5, 29.7, 25.2, 22.8, 22.0, 14.1
5	2.65 (s, 3H, SCH_3), 2.61 (s, 3H, SCH_3), 2.49 (m, 8H, 4×CH_2)	165.2, 163.1, 133.7, 130.8, 126.8, 124.1, 39.9, 25.9, 24.8, 21.7, 13.6, 12.0
6	7.92 (m, 2H, Ar-H), 7.54 (m, 3H, Ar-H), 3.48 (m, 8H, 4×CH_2), 2.49 (s, 3H, SCH_3)	167.3, 147.5, 140.7, 135.5, 134.0, 128.8, 128.6, 127.5, 126.7, 123.0, 34.9, 33.5, 26.2, 24.7, 18.6
7	2.48 (m, 8H, 4×CH_2), 2.43 (s, 3H, SCH_3), 1.78 (bs, 2H, NH_2).	165.2, 165.0, 163.2, 133.8, 126.9, 124.1, 106.8, 26.0, 24.9, 21.9, 13.7, 12.2
9	12.1 (bs, 1H, NH), 7.94 (s, 1H, 2-H), 3.0 (t, 2H, 8-H), 2.77 (t, 2H, 5-H), 1.87 (m, 4H, 6- and 7-H)	168.2, 161.0, 143.5, 142.8, 133.9, 130.8, 34.6, 30.9, 24.7, 18.4
10	7.61 (s, 1H, 2-H), 3.0 (t, 2H, 8-H), 2.74 (t, 2H, 5-H), 1.85 (m, 4H, 6- and 7-H)	158.4, 140.8, 133.6, 128.2, 123.0, 34.9, 26.1, 23.5
11	7.84 (s, 1H, 2-H), 5.35 (s, 1H, NH), 4.23 (t, 2H, 5-H), 3.71 (t, 2H, 8-H), 3.03 (br, 2H, NH_2), 2.10 (m, 4H, 6- and 7-H)	166.9, 154.3, 140.7, 133.8, 128.2, 123.1, 35.0, 25.9, 24.0
12	8.67 (s, 1H, =CH), 7.86 (s, 1H, 2-H), 7.76 (m, 5H, Ph), 5.35 (s, 1H, NH), 4.20 (t, 2H, 5-H), 3.78 (t, 2H, 8-H), 1.80 (m, 4H, 6- and 7-H)	165.7, 162.1, 146.4, 133.3, 131.3, 130.4, 128.8, 128.6, 127.2, 82.2, 30.5, 29.6, 27.6, 26.9
13	8.19 (s, 1H, 2-H), 5.28 (s, 1H, 4′-H), 3.98 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.70 (t, 2H, 5-H), 3.48 (t, 2H, 8-H), 1.86 (m, 4H, 6- and 7-H)	166.5, 160.3, 145.4, 138.9, 132.2, 130.3, 127.2, 121.4, 30.1, 29.7, 21.6, 16.5, 11.9
14	8.10 (s, 1H, 6-H), 3.95 (m, 4H, 9- and 10-H), 3.66 (m, 4H, 8- and 11-H), 1.20 (s, 3H, CH_3)	172.2, 171.0, 170.1, 168.0, 166.8, 131.3, 129.6, 30.0, 28.5, 24.8, 20.8, 20.5
15	8.34 (s, 1H, 2-H), 2.80 (t, 2H, 5-H), 2.60 (t, 2H, 8-H), 1.80 (m, 4H, 6- and 7-H), 1.20 (s, 3H, CH_3)	169.5, 162.8, 143.8, 142.7, 134.6, 131.6, 36.9, 34.6, 33.2, 25.8, 19.1
16	8.42 (s, 1H, 2-H), 7.54 (m, 5H, Ph), 2.83 (t, 2H, 8-H), 2.62 (t, 2H, 5-H), 1.82 (m, 4H, 6- and 7-H)	169.3, 162.5, 143.6, 142.4, 138.5, 134.8, 131.6, 130.9, 128.4, 125.0, 35.1, 34.3, 25.1, 19.3

of **9** (0.01 mol) and methanesulfonyl chloride (0.015 mol) or benzenesulfonyl chloride (0.015 mol) in pyridine (5 mL) was stirred at room temperature for 6 h. The mixture was poured onto ice-water, neutralized with 10% HCl and extracted with chloroform. The solvent was removed under reduced pressure and the separated solid was recrystallized from ethanol to give **15** or **16**.

Structures **3**, **5**–**7**, **9**–**16** were established by elemental analysis, ^{1}H NMR and ^{13}C NMR spectral data (Tables I and II).

Antimicrobial activity

Some of the synthesized compounds (**3**, **6**, **7**, **9**–**14**) were screened for antibacterial activity against pathogenic organisms; *Bacillus cereus* (BTCC 19), *Shigella dysenteriae* (AE 14396) and *Salmonella typhi* (AE 14612) (Table III) and for antifungal activity against *Macrophomina phaseolina* (Tassi) Goid, *Fusarium equiseti* (Corda) Sacc, *Alternaria alternata* (Fr.) Kedissler and *Collectotrichum corchori* Ikata (Yoshida) (Table IV). The disc diffusion method (19) and poisoned-food techniques (20) were used for antibacterial and antifungal activities, respectively.

The tested compounds were dissolved in *N*,*N*-dimethylformamide (DMF) to get a solution of 1 mg mL^{-1}. The inhibition zones were measured in millimeters at the end of an incubation period of 48 h at 28 °C. DMF alone showed no inhibition zone. Nutrient agar (NA) and potato dextrose agar (PDA) were used as basal media to test the bacteria and fungi, respectively. Commercial antibacterial ampicillin and antifungal nystatin were also tested under similar conditions for comparison.

RESULTS AND DISCUSSION

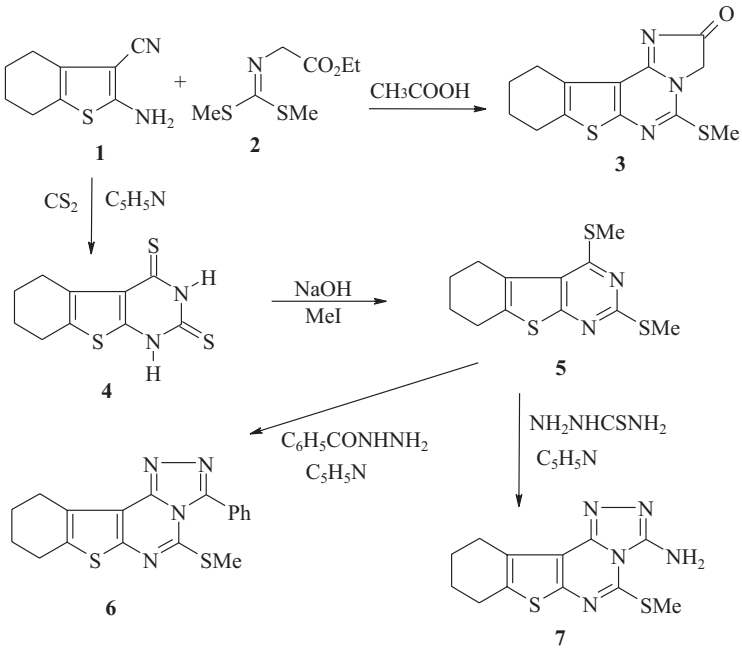
Reaction of *o*-aminonitrile **1** with ethyl *N*-[*bis*(methylthio)methylene]amino acetate (**2**) gave double annelated product, 5-methylthio-8,9,10,11-tetrahydrobenzothieno[3,2-e]--imidazo[1,2-c]pyrimidin-2(3*H*)-one (**3**), in one-pot reaction (Scheme 1). The structure of **3** was established by its elemental analysis and compatible spectroscopic data. The ^{1}H NMR spectrum of **3** exhibited a two-proton singlet for CH_2 at δ 4.22 ppm, a three-proton singlet for SCH_3 at δ 2.71 ppm. The ^{13}C NMR spectrum displayed signals at δ 183.4 ppm for C=O carbon and at δ 49.5 ppm for methylene carbon at position C-3 of the molecule. The rest of the spectrum was in good agreement with the structure **3**. Compound **1** was readily cyclized to the corresponding tetrahydrobenzothieno[2,3-d]pyrimidine-2,4(*1H*,*3H*)--dithione (**4**) upon treatment with CS_2 in refluxing pyridine. Methylation of the dithione **4** with MeI in aqueous NaOH afforded compound 2,4-dimethylthio-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (**5**). The ^{1}H and ^{13}C NMR spectra of product **5** were compatible with the proposed structure.

The reaction of **5** with benzhydrazide in boiling pyridine gave the cyclized product 5-methylthio-3-phenyl-8,9,10,11-tetrahydro[1,2,4]triazolo[4,3-c]benzothieno[3,2-e]pyrimidine (**6**). Also, treatment of **5** with thiosemicarbazide led to the formation of 3-amino--5-methylthio-8,9,10,11-tetrahydro[1,2,4]triazolo[4,3-c]benzothieno[3,2-e]pyrimidine (**7**). The structures of **6** and **7** were established by their compatible spectral data.

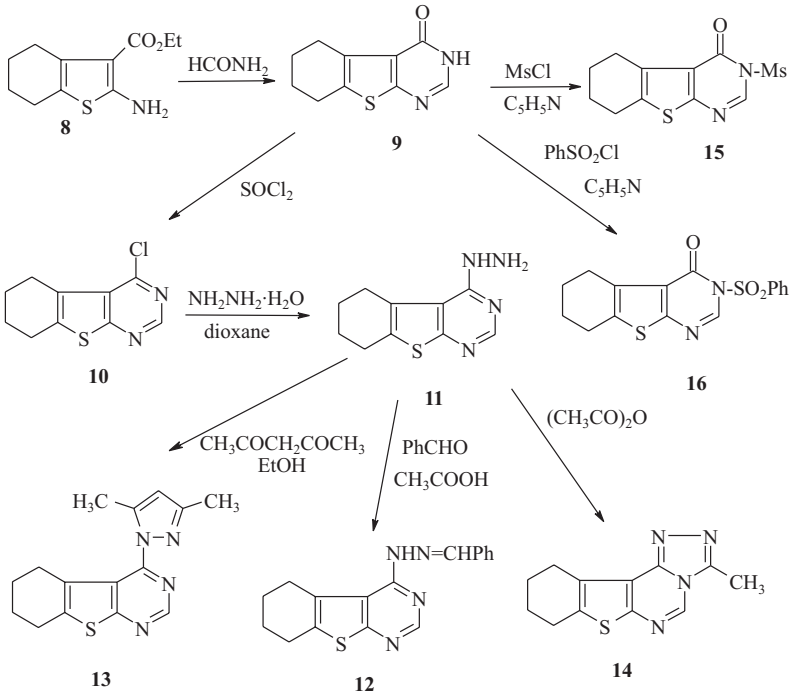
Refluxing of *o*-aminoester **8** with formamide afforded 5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidin-4(3*H*)-one (**9**) (Scheme 2). Chlorination of **9** with thionyl chloride gave 4-chloro-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (**10**), while, acylation of **9** with methanesulfonyl chloride or benzenesulfonyl chloride furnished the corresponding 4-oxo-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine-3-methyl sulfonate ester (**15**) or 4--oxo-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine-3-phenyl sulfonate ester (**16**). The structures of **9**, **10**, **15** and **16** were established from their respective elemental and spectral data.

The chlorine group of **10** underwent nucleophilic displacement by reflux with hydrazine hydrate in dioxane to produce 4-hydrazino-5,6,7,8-tetrahydrobenzothieno--[2,3-d]pyrimidine (**11**), which was condensed with benzaldehyde to give 4-benzylidenehydrazono-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine (**12**). Similarly, heating **11** with acetylacetone produced the corresponding 4-(3,5-dimethylpyrazolyl)pyrimidine derivative (**13**). Furthermore, upon boiling compound **11** in acetic anhydride, the cyclized product 3-methyl-8,9,10,11-tetrahydrobenzothieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (**14**) was formed. Assignments of the structures of **12**–**14** to the proposed reaction products are based on elemental and spectral data.

Amongst the compounds **3**, **6**, **7**, **9**–**14** screened for antimicrobial activity, compound **13** showed the highest activity against all bacteria. It exhibited stronger activity than ampicillin also towards *B. cereus* and *S. typhi*. It was followed by compound **3**, which showed the highest activity against *B. cereus* and *S. typhi*. As far as antifungal activity is concerned, all compounds



Scheme 1



Scheme 2

Table III. Antibacterial activity of some synthesized compounds

	Zone of inhibition (mm)[a]		
Compd.	*B. cereus*	*S. dysenteriae*	*S. typhi*
3	20	13	26
6	8	–	8
7	10	6	–
9	10	–	12
10	11	14	11
11	9	12	15
12	19	18	17
13	31	28	29
14	15	7	15
Ampicillin	21	30	24

– no inhibition.
[a] 1 mg mL^{-1} per disc
DMF – negative control

Table IV. Antifungal activity of some synthesized compounds

	Inhibition of mycelial growth (%)[a]			
Compd.	*M. phaseolina*	*F. equiseti*	*A. alternata*	*C. corchori*
3	34.5	37.5	54.0	50.0
6	62.0	14.8	27.8	29.0
7	95.0	47.6	42.8	29.0
9	46.0	40.0	39.5	33.6
10	49.3	36.3	35.7	34.6
11	47.5	29.3	38.8	30.3
12	70.0	28.0	34.6	36.4
13	48.3	65.6	65.4	54.5
14	58.6	43.8	27.0	41.0
Nystatin	71.8	44.7	51.6	40.5

[a] 1 mg mL^{-1} per disc

showed good to excellent activity against all the fungi. Compounds **3** and **13** exhibited even stronger activity than nystatin against *A. alternata* and *C. corchori*, compounds **7** and **12** against *M. phaseolina*, compounds **7**, **13** and **14** against *F. equiseti*. Compounds **6**, **7**, **9**–**12** and **14** were either inactive or moderately to fairly active against the tested bacteria whereas compounds **6**, **9**–**11** exhibited good to excellent results against all the fungi. Introduction of imidazo (**3**) or pyrazolo (**13**) moiety to the pyrimidine derivatives might be responsible for antimicrobial activity enhancement of these compounds.

CONCLUSIONS

The structure activity relationship suggested that fused pyrimidines containing imidazo (**3**) and pyrazolo (**13**) rings showed higher antibacterial and antifungal activities than the corresponding other moieties (like triazolo, halo, sulfonyl groups). These findings encourage us to explore other molecules by introducing these potent moieties into other fused heterocycles such as furano- and pyridopyrimidines. Our prediction is that these compounds with new ring systems may show even better antimicrobial activities.

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S A Ž E T A K

Sinteza i antimikrobno djelovanje novih derivata tienopirimidina

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Reakcijom heteroaromatskih *o*-aminonitrila s etil *N*-[bis(metiltio)metilen]amino acetatom u jednom sintetskom koraku došlo je do anelacije u tieno[3,2-e]imidazo[1,2-c]pirimidin. Derivati [1,2,4]triazolo[4,3-c]tieno[3,2-e]pirimidina pripravljeni su reakcijom *o*-aminonitrila s ugljikovim disulfidom, te metilacijom s metil-jodidom i naknadnom reakcijom s benzhidrazidom, odnosno tiosemikarbazidom. Hidrazinotieno[2,3-d]pirimidin je pripravljen ciklizacijom heteroaromatskog *o*-aminoestera s formamidom, te kloriranjem i supstitucijom s hidrazinom. Reakcijom hidrazinskog derivata s acetilacetonom, benzaldehidom ili anhidridom octane kiseline nastali su derivati pirazolilpirimidina, benzilidenehidrazonopirimidina, odnosno trizolopirimidina. Neki od tih derivata djeluju antimikrobno.

Ključne riječi: imidazopirimidin, triazolopirimidin, antimikrobno djelovanje

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