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Mendeleev Commun., 2021, **31**, 370–372

Mendeleev Communications

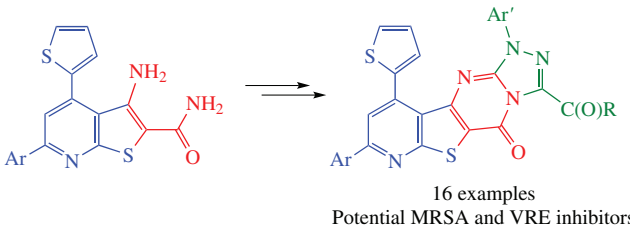
New thieno[2,3-*b*]pyridine-fused [1,2,4]triazolo[4,3-*a*]pyrimidinone hybrids as potential MRSA and VRE inhibitors

Sherif M. H. Sanad,* Ahmed E. M. Mekky, Ahmed Y. Said and Mohamed A. A. Elneairy

Chemistry Department, Faculty of Science, Cairo University, Giza 12613, Egypt.
E-mail: sherif_hamed1980@yahoo.com

DOI: 10.1016/j.mencom.2021.05.029

New thieno[2,3-*b*]pyridine-fused [1,2,4]triazolo[4,3-*a*]pyrimidinones were obtained by the [5+1] heterocyclization of the appropriate thieno[2,3-*b*]pyridines followed by the Smiles-type reaction protocol. In general, the triazoles tested exhibited better antibacterial activity against Gram-positive than against Gram-negative bacterial strains. Compounds containing 3-acetyl-1-(4-methoxyphenyl)[1,2,4]triazole unit demonstrated more potent inhibitory activities than the reference Linezolid.



Keywords: [1,2,4]triazolo[4,3-*a*]pyrimidinones, pyrimidinones, thieno[2,3-*b*]pyridines, Smiles-type reaction, hybrid molecules, heterocyclization, antibacterial activity, MRSA inhibitors, VRE inhibitors.

Bacterial infection is a major cause of morbidity and mortality in the world, which is cured using the appropriate antibiotics.[1,2] Antibiotic resistance happens as the use of these drugs makes changes in response to bacteria.[3] It is crucial to develop new scaffolds with high antibacterial activity to solve this problem.[4] In development of modern antibacterial drugs, heterocycle part as [1,2,4]triazole units is very effective.[5] [1,2,4]Triazole moiety can affect the hybrid lipophilicity, polarity and hydrogen bonding ability, enhancing its pharmacokinetic and physicochemical properties.[6] [1,2,4]Triazole-based scaffolds[7,8] exhibit diverse pharmacological properties including anticancer,[9,10] antiviral,[11,12] antitubercular,[13] antifungal,[14] and antibacterial activities.[15,16]

Studies[17,18] describe the preparation of thieno[2,3-*b*]pyridine-fused pyrimidines linked to various arene and/or thiophene units at C^7 and C^9. Pyrimidines are primarily obtained from cell metabolites, and the *de novo* biosynthetic pathway of pyrimidine is found intact in most organisms.[19] Therefore, [1,2,4]triazole-pyrimidine hybrids are reasonable candidates of new antibacterial agents.[20,21]

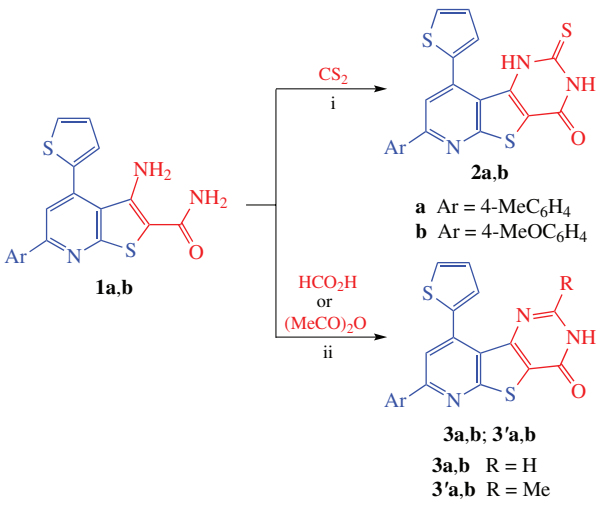
Several reports have documented the synthesis of [1,2,4]triazolo[4,3-*a*]pyrimidines[22–24] and those with related fused thieno[2,3-*b*]pyridine skeletons[25–27] linked to different arene and/or thiophene units using the Smiles-type reaction.[28] Some of these hybrids showed more powerful bacterial efficacy against Gram-positive bacteria.[29] The goal of this study was to prepare new thieno[2,3-*b*]pyridine-fused [1,2,4]triazolo[4,3-*a*]-pyrimidinone hybrids linked to arene and thiophene units at C^8 and C^{10}, respectively. The new hybrids were tested as potential MRSA and VRE inhibitors.

In our experiments, thieno[2,3-*b*]pyridines **1a**,**b**[30] were reacted with carbon disulfide in pyridine at reflux for 12 h to give the corresponding 2-thioxopyrimidinones **2a**,**b** (Scheme 1).[31,32] Alternatively, 2-carboxamides **1a**,**b** were reacted with formic acid or acetic anhydride to give the corresponding pyrimidinones **3a**,**b** and **3′a**,**b** (see Scheme 1 and Online Supplementary Materials).[17,33]

Next, 2-thioxopyrimidinones **2a**,**b** were used as key intermediates to build up a fused [1,2,4]triazole ring utilizing the Smiles-type reaction.[26,27] For this purpose, they were refluxed with acetylated hydrazonyl chlorides **4a–d** in dioxane in the presence of triethylamine to produce the corresponding [1,2,4]triazolo[4,3-*a*]pyrimidinones **6a–h** in good yields (Scheme 2). In the same way, the use of ethoxycarbonyl-containing hydrazonyl chlorides **5a–d** afforded derivatives **7a–h**.

The *in vitro* antibacterial efficacies of new hybrids were assessed against *Staphylococcus aureus* (ATCC:6538), *Enterococcus faecalis* (ATCC:29212), *Klebsiella pneumoniae* (ATCC:10031) and *Escherichia coli* (ATCC:9637) strains using Ciprofloxacin as a standard drug with MIC/MBC values of 2.7/5.4 μM against all the tested strains (Table 1).[34–36]

Pyrimidinones **3a**,**b** showed moderate efficacies with MIC and MBC values ranging between 9.9 and 20.7 μM against the tested strains. Other pyrimidinones **2a**,**b** and **3′a**,**b** revealed



Scheme 1 *Reagents and conditions*: i, pyridine, reflux, 12 h; ii, reflux, 4 h.

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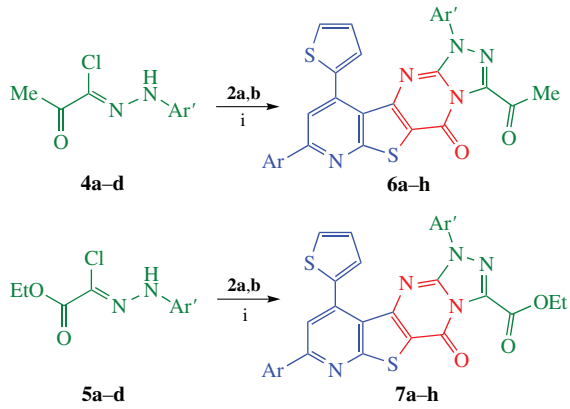

4a, **5a** Ar′ = Ph
4b, **5b** Ar′ = 4-ClC_6H_4
4c, **5c** Ar′ = 4-MeC_6H_4
4d, **5d** Ar′ = 4-$MeOC_6H_4$

6a, **7a** Ar = 4-MeC_6H_4, Ar′ = Ph
6b, **7b** Ar = 4-MeC_6H_4, Ar′ = 4-ClC_6H_4
6c, **7c** Ar = Ar′ = 4-MeC_6H_4
6d, **7d** Ar = 4-MeC_6H_4, Ar′ = 4-$MeOC_6H_4$
6e, **7e** Ar = 4-$MeOC_6H_4$, Ar′ = Ph
6f, **7f** Ar = 4-$MeOC_6H_4$, Ar′ = 4-ClC_6H_4
6g, **7g** Ar = 4-$MeOC_6H_4$, Ar′ = 4-MeC_6H_4
6h, **7h** Ar = Ar′ = 4-$MeOC_6H_4$

Scheme 2 *Reagents and conditions*: i, Et_3N, dioxane, reflux, 8 h.

Table 1 MIC and MBC values (in μM) of the new pyrimidinones **2**, **3** and **3′** and [1,2,4]triazolo[4,3-*a*]pyrimidinones **6** and **7**.[a]

Compound	Gram-positive bacteria				Gram-negative bacteria			
	S. aureus ATCC:6538		*E. faecalis* ATCC:29212		*K. pneumoniae* ATCC:10031		*E. coli* ATCC:9637	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
2a	38.2	76.4	38.2	76.4	38.2	38.2	38.2	76.4
2b	36.8	73.6	36.8	73.6	36.8	36.8	36.8	73.6
3a	10.3	20.7	10.3	20.7	10.3	20.7	20.7	20.7
3b	9.9	19.9	9.9	19.9	9.9	19.9	19.9	19.9
3′a	20.0	20.0	20.0	40.0	40.0	80.0	40.0	80.0
3′b	19.2	19.2	19.2	38.4	38.4	76.8	38.4	76.8
6a	29.2	58.4	29.2	58.4	58.4	ND	58.4	ND
6b	54.9	ND	54.9	ND	110.0	ND	110.0	ND
6c	3.4	7.1	7.1	14.2	28.4	56.9	14.2	28.4
6d	1.6	3.3	3.3	6.9	27.6	55.2	13.8	13.8
6e	28.3	56.7	28.3	56.7	56.7	ND	56.7	ND
6f	53.4	ND	53.4	ND	107.0	ND	107.0	ND
6g	3.3	6.9	6.9	13.8	27.6	55.2	13.8	27.6
6h	1.5	3.2	3.2	6.7	26.9	53.8	13.4	13.4
7a	>250	ND	>250	ND	>250	ND	>250	ND
7b	>250	ND	>250	ND	>250	ND	>250	ND
7c	216.4	ND	216.4	ND	>250	ND	>250	ND
7d	26.2	26.2	26.2	52.5	105.2	ND	52.5	ND
7e	>250	ND	>250	ND	>250	ND	>250	ND
7f	>250	ND	>250	ND	>250	ND	>250	ND
7g	210.5	ND	210.5	ND	>250	ND	>250	ND
7h	25.5	25.5	25.5	51.1	102.5	ND	51.1	ND
Ciprofloxacin	2.7	5.4	2.7	5.4	2.7	5.4	2.7	5.4

[a] ND: not determined.

decreased activities against the tested strains with MIC and MBC values in the range of 19.2 and 80.0 μM.

Among all tested acetyl-containing triazoles **6**, hybrids **6d**,**h** bearing 4-methoxyphenyl units at C^1, demonstrated the best antibacterial activity against *S. aureus* strain (MIC/MBC values of 1.6/3.3 and 1.5/3.2 μM, respectively) which is exceeding that of Ciprofloxacin. Additionally, compounds **6c**,**g** with *p*-tolyl units, were the second-best antibacterial hybrids with MIC/MBC values of 3.4/7.1 and 3.3/6.9 μM, respectively, against the prior strain. Hybrids **6c**,**d**,**g**,**h** showed good efficacies against *E. faecalis* strain with MIC and MBC values in the ranges of 3.2–7.1 and 6.9–14.2 μM, respectively. The rest of hybrids of series **6** displayed decreased efficacies against the above strains with MIC values in the range of 28.3–54.9 μM.

Table 2 MIC and MBC values (in μM) of some new triazole hybrids against MRSA and VRE strains.

Compound	*S. aureus* (MRSA)				*E. faecalis* (VRE)			
	ATCC:33591		ATCC:43300		ATCC:51299		ATCC:51575	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
6c	7.1	14.2	3.4	7.1	7.1	14.2	7.1	14.2
6d	3.3	6.9	1.6	3.3	3.3	6.9	1.6	3.3
6g	6.9	13.8	3.3	6.9	6.9	13.8	6.9	13.8
6h	3.2	6.7	1.5	3.2	3.2	6.7	1.5	3.2
Linezolid	5.2	31.1	2.6	31.1	5.2	92.4	2.6	46.2

As for ethoxycarbonyl-containing triazoles **7**, these hybrids showed decreased antibacterial efficacies when compared with acetyltriazoles **6**. Hybrids **7d**,**h** exhibited MIC and MBC values in the range of 28.3–54.9 μM against *S. aureus* and *E. faecalis* strains. Other hybrids **7** displayed poor efficacies with MIC values in the range of 210.5 to more than 250 μM.

In general, triazole hybrids **6** and **7** showed less potency against *E. coli* and *K. pneumoniae* strains. Hybrids **6d**,**h** revealed the best activities with MIC and MBC values ranging between 13.4 and 55.2 μM. Other triazoles exhibited poor efficacies with MIC values in the range of 51.1 to more than 250 μM.

Inspired by the findings of antibacterial assessment against *Staphylococcus aureus* and *Enterococcus faecalis* strains, some of new hybrids were examined as potential inhibitors of MRSA and VRE strains. In this regard, the inhibitory activity of triazole hybrids **6c**,**d**,**g**,**h** were examined against two different MRSA (ATCC:33591 and ATCC:43300) and VRE (ATCC:51299 and ATCC:51575) strains using Linezolid as a reference (Table 2). Hybrids **6d**,**h** displayed more potent efficacies than the reference Linezolid. They displayed MIC/MBC values of 3.3/6.9 and 3.2/6.7 μM against ATCC:33591 MRSA or ATCC:51299 VRE strains, respectively, while they gave MIC/MBC values of 1.6/3.3 and 1.5/3.2 μM against ATCC:43300 MRSA or ATCC:51575 VRE strains, respectively. Hybrids **6c**,**g** showed decreased efficacies against the prior strains with MIC and MBC values in the ranges of 3.3–7.1 and 6.9–14.2 μM.

To sum up, a facile procedure for the synthesis of sixteen new [1,2,4]triazolo[4,3-*a*]pyrimidinone hybrids fused with thieno[2,3-*b*]pyridine moiety has been developed. In general, the tested acetyltriazole-containing compounds displayed more potent antibacterial efficacies against Gram-positive strains as compared to ethoxycarbonyltriazoles. Hybrids containing 4-methoxyphenyl unit demonstrated more potent inhibitory activity against MRSA and VRE strains in comparison with Linezolid.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.05.029.

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Received: 8th February 2021; Com. 21/6445