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Research Article

A qualitative structure activity relationship (SAR) study of selected pyroglutamates

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ABSTRACT

A library of pyroglutamate derivatives (Fig. 1-4: **8a-8f**, **9a-9d**, **10a-10e**, **11a-11f**, **12a-12c**, **13** and **14**) have been analyzed qualitatively to investigate their Structure Activity Relationships (SAR). Antibacterial screening data used for this work was against the selected multidrug-resistant pathogens, including Gram-positive and Gram-negative bacteria. Among the synthesized compounds, pyroglutamates **8e** and **11d** are more potent as antibacterial agents..

Introduction

Pyrroglutamate is an intermediate of glutathione metabolism. It marks glutathione insufficiency. Glutathione, a potent anti-oxidant in the human body, is essential in throwing away toxins. Moreover, pyroglutamates play a vital role in drug discovery (Mollica et al., 2014; Stefanucci et al., 2015). We recently reported the preparation of highly functionalized pyroglutamates, pyrrolinones, and pyrrolidinones (Scheme 1) (Bagum et al., 2019a, 2019b, 2020). Antibacterial screening of the selected compounds was done (Table 1), which was further studied to find Structure-Activity Relationships, and we report the result of this work here.

Test method for bioassay

Oxford Antibiotic Group, Austria, screened the novel compounds against selected multidrug-resistant pathogens. The compounds were examined in a primary 96-well plate screening assay, according to SOP 0906. The compounds were diluted in "MHB" (Mueller-Hinton broth) for a bacteria culture test to a standard solution of 1000 µg/mL, serially diluted, and overlaid with a microbe solution in a 104 CFU/mL concentration. At 35°C, the plates were incubated for 24 hours. MIC values were assessed by visual inspection of optical density, and complete bacterial growth inhibition was achieved by a clear saturation of the solution following SOP.

Antibacterial screening

Representative compounds among the synthesized compounds were tested (Bagum et al., 2019a, 2019b, 2020) for antibacterial activity in the case of the following Gram-negative and Gram-positive bacteria (Table 1):

1. *E. coli* (EC 34)
2. *K. pneumoniae* (KL 18)
3. *P. aerogenosa* (PS 23)
4. Methicillin resistant *S. aureus* (MRSA 1)
5. Methicillin resistant *S. aureus* (MRSA 2)

It is to be mentioned that the antibacterial activity of selected compounds was not found against the tested Gram-negative bacteria (EC 34, KL 18, and PS 23).

Results and Discussion

Compounds **8d** and **11d** showed antibacterial activity against Gram-positive bacteria MRSA1 and MRSA2. However, they showed no activity against Gram-negative bacteria EC 34, KL 18, and PS 23.

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Compounds **10a**, **12c**, **13**, and **14** exhibited antibacterial activity against only MRSA2. The study on the structure of the compounds **8a-8f**, **9a-9d**, and **10a-10e** (Fig. 1) reveals that the presence of the –CHO group on the aromatic ring assists in exhibiting appreciable activity.

Similarly, pyroglutamates **11a-11f**, derived from cysteine, showed the contribution of the –CHO group to the activity (Fig. 2).

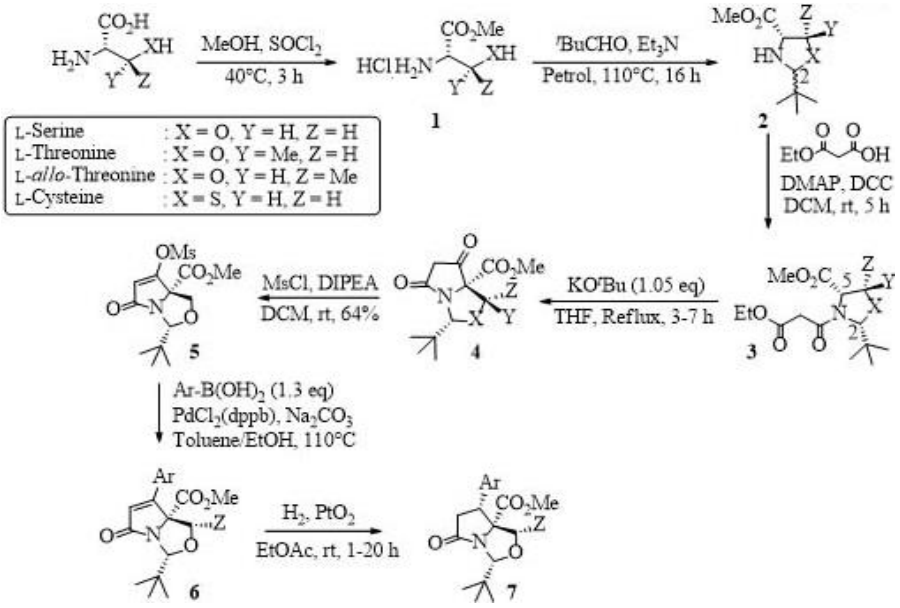
Comparing the structure and activities of **8d**, **10d**, and **11d** supports the previous observation of the antibacterial activity due to the presence of the –CHO group on the aromatic ring. The reduction of the –CHO group to the $–CH_2OH$ group lost the compound's activity, which is evident if we juxtapose the structure and activity of **8d** and **10d**. Again, compounds **8a**, **8b**, and **10a** have similar structures. They differ only in the presence or absence of methyl group at C-4, its stereochemistry, and unsaturation at C-6 (Fig. 1). The activity of **10a** showed moderate antibacterial activity against Gram-positive bacteria MRSA 2, whereas **8a** and **8b** are not active. This result implies that C-4 methyl is unnecessary for activity and provably imposes steric hindrance. Moreover, the presence of unsaturation at C-6 diminishes activity in case of 6(4-methoxyphenyl)- derivatives **8a**, **8b** and **9a**.

Of interest, **12c** showed appreciable activity. Observation of the structures of **11e** and **12c** (Fig. 2 and Fig. 3) showed that the presence of sulfoxide is essential for the antibacterial activity of 4-chlorophenyl pyroglutamate derivatives. Sulfur systems are inactive for all other systems (e.g., 4-methoxyphenyl, phenyl).

Moreover, *N*, *O*-acetaldeprotection of some inactive compounds, e.g., **9b** and **9c**, leads to weakly active compounds **13** and **14**, respectively (Fig. 4). This indicates that the hydrophilicity of compounds increases activity.

Generally, the presence of –CHO on the aromatic ring increases antibacterial activity in every series. In addition, for the 4-chlorophenyl derivative, the replacement of the S atom by sulfoxide increases antibacterial activity. The free NH and OH in pyroglutaminol help to improve activity, probably due to the increased solubility.

Among the compounds studied, pyroglutamates **8d** and **11d** are more potent antibacterial agents, while pyroglutaminols**13** and **14** are weakly active.



Scheme 1. Preparation of highly functionalized pyroglutamates.

Table 1. MIC values for the screening of selected compounds against several pathogens.

Sl No	Compound	Gram-positive bacteria	
		MRSA 1	MRSA 2
1	8a	n. a.	n. a.
2	8b		
3	8c		
4	8d	31.25 µg/mL	15.63 µg/mL
5	8e		
6	8f	n. a.	n. a.
7	9a		
8	9b		
9	9c		
10	9d		
11	10a	n. a.	62.00 µg/mL
12	10b	n. a.	n. a.
13	10c		
14	10d		
15	10e		
16	11a		
17	11b		
18	11c		
19	11d	15.63 µg/mL	15.63 µg/mL
20	11e	n. a.	n. a.
21	11f		-
22	12a		n. a.
23	12b		
24	12c	n. a.	31.25 µg/mL
25	13	n. a.	125.00 µg/mL
26	14	n. a.	125.00 µg/mL

n. a. = not active

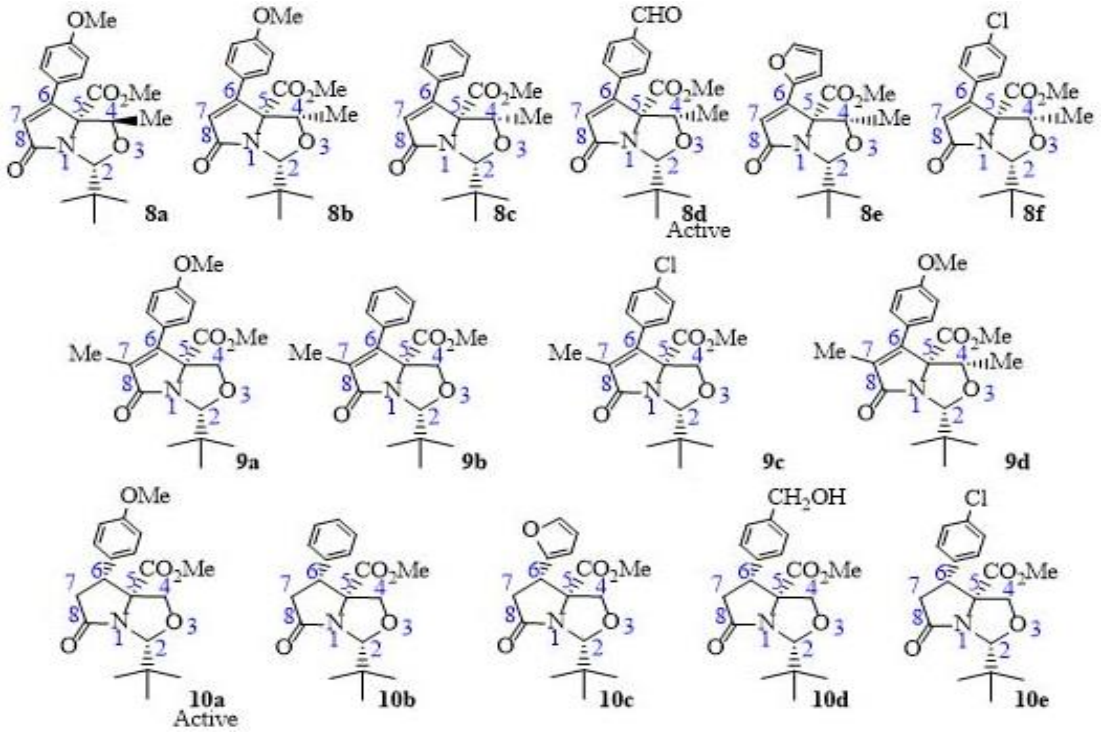


Fig. 1. Pyroglutamates derived from L-Serine, L-Threonine and L-*allo*-Threonine

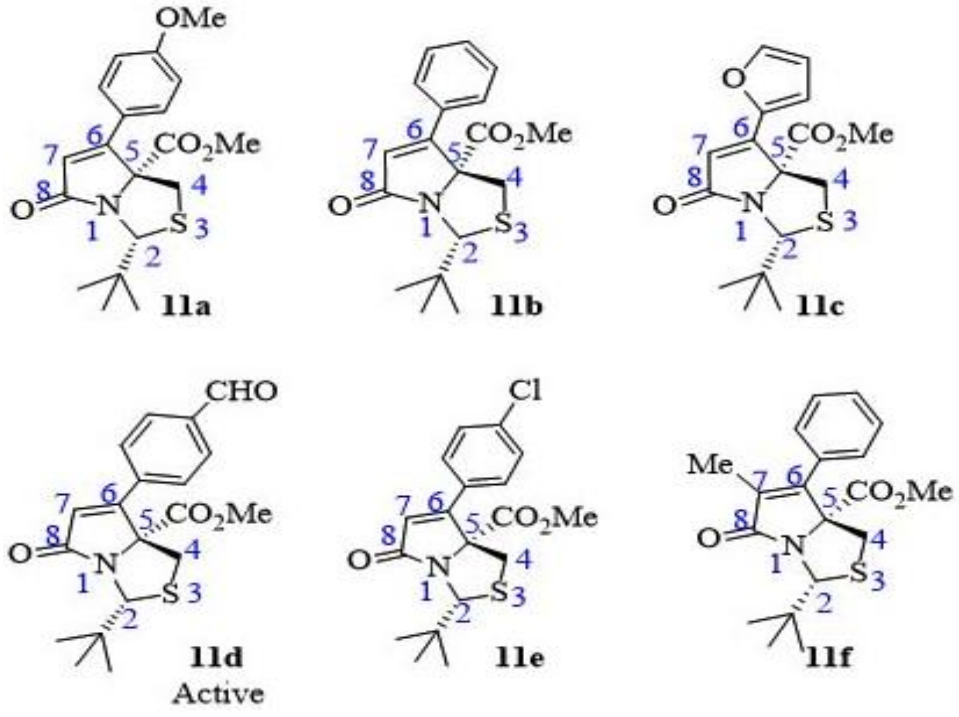


Fig. 2. Pyroglutamates derived from L-Cysteine.

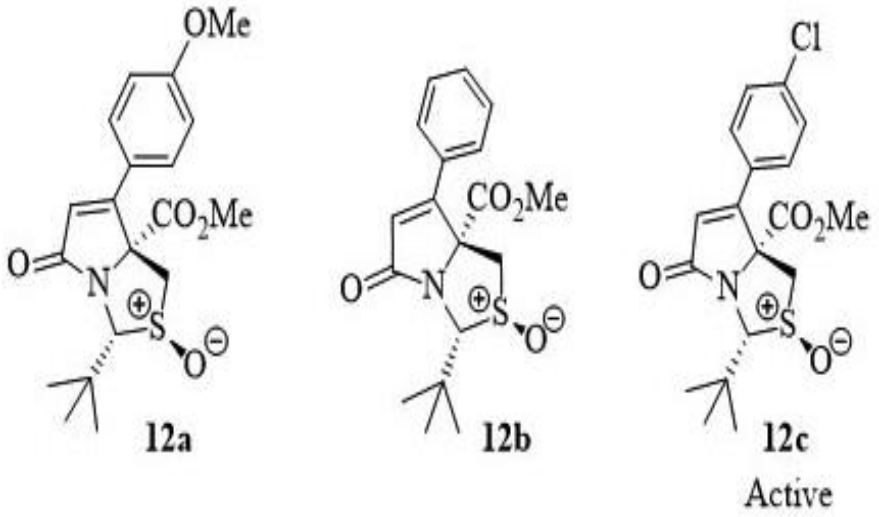


Fig. 3. Sulfoxides.

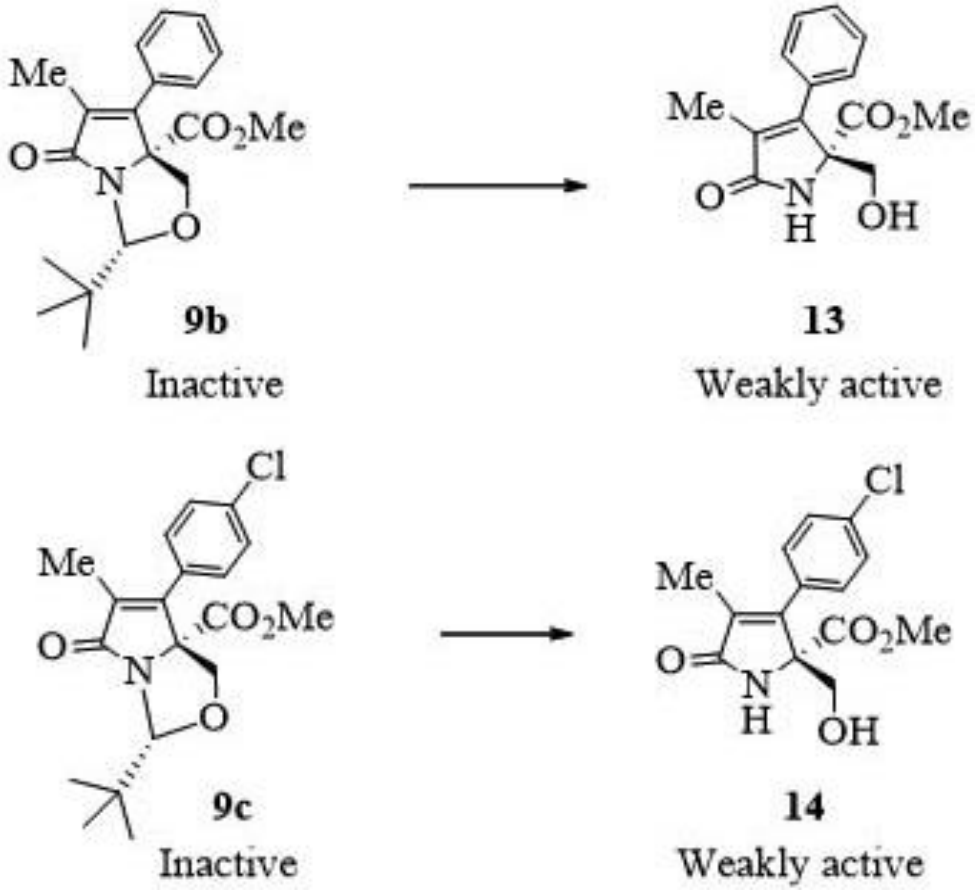


Fig. 4.*N, O*-Acetaldeprotection of pyrrolinones to yield pyroglutaminol.

Conclusion

The Structure-Activity Relationships (SAR) of pyroglutamate derivatives were studied qualitatively. Compounds **8e** and **11d** showed antibacterial activity against Gram-positive bacteria MRSA1 and MRSA2. Compounds **10a**, **12c**, **13**, and **14** exhibited antibacterial activity against only MRSA2. It has been observed that the presence of the –CHO group on the aromatic ring assists in exhibiting appreciable activity. Also, the hydrophilicity of compounds increases activity.

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Conflict of Interest

The writers of this article announce that they have no conflict of interest.

Authors Contribution

Begum, H., with the cooperation of Moloney, M. G., outlined the experiment. Bagum performed the analysis. Furthermore, Begum devised the article manuscript, and Islam, M. R., assessed it.

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