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Synthesis, activity evaluation and 3D-QSAR study of some novel derivatives of 4, 5, 6, 7-tetrahydrothieno [3,2-c] pyridine

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Abstract

A series of novel derivatives of 4, 5, 6, 7-tetrahydrothieno [3,2-c] pyridine were synthesized and structurally characterized by ^{1}H NMR and MS. Their *in vivo* anti-platelet aggregation activities were evaluated. A 3D-QSAR was performed using the CoMFA and the CoMSIA. This model provided useful guidelines for novel anti-platelet thienopyridines design.

Keywords: Thienopyridines; Anti-platelet aggregation activities; $P2Y_{12}$ receptors; 3D-QSAR

During the last three decades of the 20th century, an intensive research in antithrombosis was devoted to compounds showing anti-aggregatory potency [1]. Several drugs were explored, except aspirin, among the huge number of synthetic molecules tested, but only few of them were used clinically. Ticlopidine was first used in 1978 and found a broad scope of applications [2]. Another synthetic molecule, clopidogrel (Fig. 1) was explored in 1998 as an anti-platelet drug for prevention or treatment of myocardial infarction and other diseases associated with atherosclerosis [3]. Both clopidogrel and ticlopidine share their chemical structure with thieno- and hydrogenated-pyrido fused heterocycles. Recently, Sankyo developed a novel anti-platelet thienopyridines, prasugrel (Fig. 1), which showed better platelet inhibition activity than clopidogrel in a series of preclinical and clinical studies [4,5].

In this paper, we described the design and synthesis of some novel derivatives of 4, 5, 6, 7-tetrahydrothieno [3,2-c] pyridine based on the following considerations. In our former study, we changed the $COOCH_3$ group in the structure of clopidogrel to CONHN=R group and kept the chlorophenyl group to resulting good activity in initial pharmacology experiment. Since fluorophenyl group in prasugrel contribute to its high activity, compounds **6–30** were designed by

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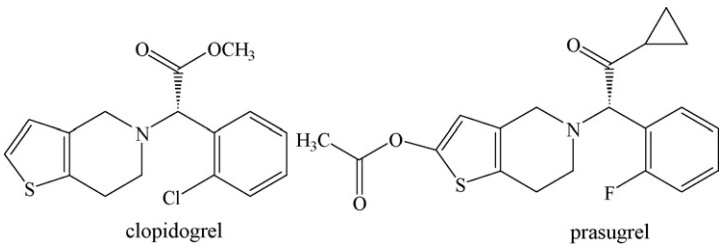


Fig. 1. Chemical structure of clopidogrel and prasugrel.

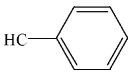
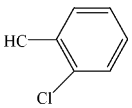
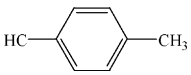
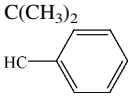
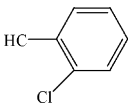
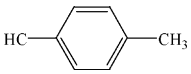
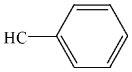
changing the types of halogen atom and its substitute position to benzene ring. These compounds were synthesized and evaluated in order to study the SAR of anti-platelet thienopyridines and to supply useful guidelines for designing of novel compounds.

The structure of the obtained target compounds were shown in Table 1. The compounds were characterized by ^{1}H NMR [6] and MS.

The synthesis route of title derivatives was illustrated in Scheme 1.

The intermediate **1–5** was synthesized following the method by Bousquet [7].

Table 1
The substituents, yields, MS and activity of compounds **6–30**

Compound	R_1	R_2	Total yields (%)	FAB-MS ($m + 1/z$)	Maximum aggregation (%)	Inhibition ratio (%)
Control					54.8 ± 5.8	
Clopidogrel					9.1 ± 3.5	83.4
6	3-Cl	H_2	70	322.2	30.2 ± 4.3	44.9
7	4-Cl	H_2	71	322.2	33.9 ± 6.3	38.1
8	2-F	H_2	73	306.0	26.8 ± 5.6	51.1
9	3-F	H_2	71	306.2	32.4 ± 8.3	40.9
10	4-F	H_2	69	306.0	28.4 ± 8.1	48.2
11	3-Cl	$C(CH_3)_2$	66	362.2	26.3 ± 6.8	52.0
12	3-Cl		52	410.2	43.7 ± 10.0	20.3
13	3-Cl		40	444.0	44.8 ± 11.1	18.2
14	3-Cl		61	424.2	45.5 ± 8.2	17.0
15	4-Cl	$C(CH_3)_2$	68	362.2	22.6 ± 3.9	58.8
16	4-Cl		53	410.0	40.1 ± 4.9	26.8
17	4-Cl		44	444.0	48.3 ± 6.8	11.9
18	4-Cl		63	424.2	36.0 ± 6.9	34.3
19	2-F	$C(CH_3)_2$	70	346.2	14.8 ± 6.2	73.0
20	2-F		60	394.0	30.8 ± 4.1	43.8