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Design and Synthesis of New Arylsulfonamide and Arylamide Derivatives for the Platelet Aggression Inhibitor

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Abstract: A series of arylsulfonamide and arylamide derivatives have been prepared from anisole in good yields. The structures of those compounds were confirmed by ^{1}H-NMR and MS analysis. Their activities against platelet aggregation were tested *in vitro* by using the Born test on rabbits.

Keywords: Arylsulfonamide, arylamide, synthesis, platelet aggregation, inhibitor.

Thromboxane A_2 (TXA_2) is known to exhibit the activities of stimulation of platelet function and smooth muscle contraction, including platelet aggregation, vasoconstriction, and bronchoconstriction. Several cardiovascular, renal, and pulmonary diseases are generally associated with an overproduction of TXA_2 by the action of thromboxane synthase on the prostaglandin endoperoxide PGH2[1,2]. Effective pharmaceuticals to treat these disorders can be resulted from (a) inhibitors of thromboxane synthase and (b) antagonists of thromboxane receptor. The second class of agents are believed to be useful for preventing the agonist effects of PGH2, which is accumulated from the inhibition of TXA_2[3,4]. Therefore, the majority of recent efforts have been focusing on searching for agents, which could have dual effects: inhibition of the thromboxane synthase and antagonist property of the thromboxane receptor.

It has been reported that arylsulfonamide and arylamide derivatives have the activity of thromboxane synthase inhibitor and thromboxane receptor antagonist. There are examples from using compound **1**, HN-11 500, DT-TX30, EK112, and picotamide **2**[5-8]. The arylsulfonamido and arylamido moieties are the feature for the biological activities of those compounds (**Figure 1**)[9,10]. On the basis of picotamide structure, we became interested in the synthesis of the related compounds, which also carried amide **3** or sulfonamide fundionalities **4**. The preliminary studies were conducted by attaching the sulfonamido or amido group to the 1,3-position of the picotamide aryl ring to form new derivatives for their antiplatelet studies.

Here, we present an efficient synthetic strategy for the generation of new arylsulfonamide and arylamide derivatives from convenient starting materials (**Scheme**

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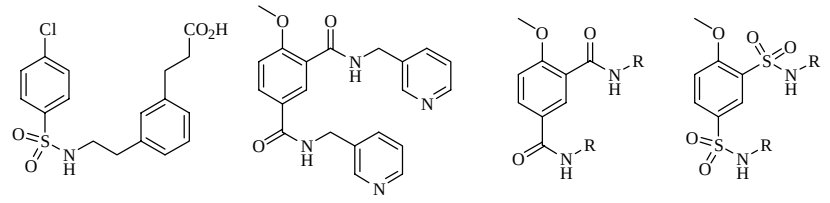
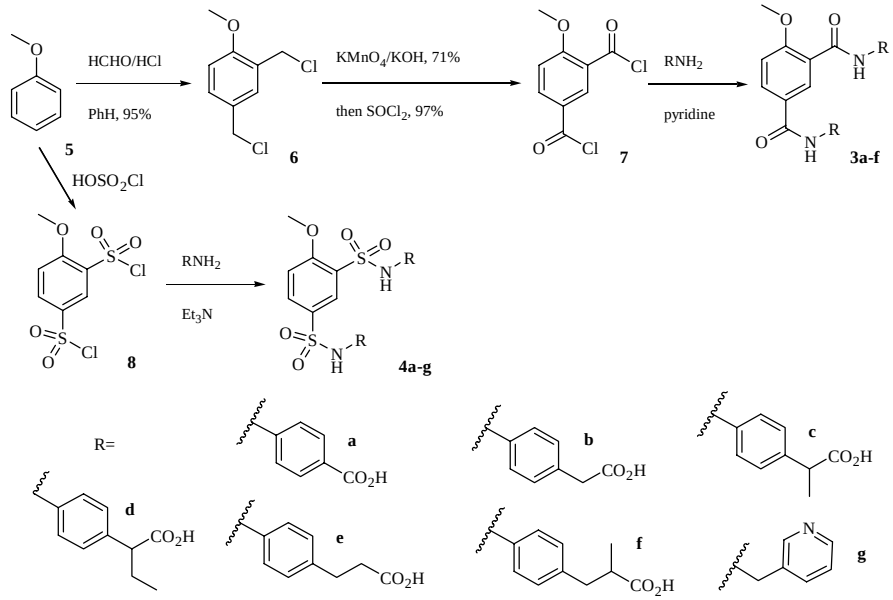
1). The reactions of anisole **5** with $HOSO_2Cl$ or HCHO/HCl give 4-methoxy-1,3-disubstituted benzene derivatives **6** or **8** respectively. Compounds of **6** or **8** are eventually converted to the desired products **3** and **4**. The reported approach is available for synthesizing a number of related compounds and has the potential for conducting the combinatorial chemistry on this project.

Figure 1 Chemical structure of 3[3-(2-{[(4-chlorophenyl)sulfonyl]amino}ethyl)phenyl propanoic acid **1**, picotamide **2**, and new arylamide and arylsulfonamide derivatives **3-4**



Scheme 1 Synthesis of arylamides **3** and arylsulfonamides **4**



General procedure

The detailed procedure of the final step for the desired analogs **4** is reported as the followings: To a mixture of amine (**a-g**, 10 mmol) in ethyl acetate (20 mL) and dry pyridine (8 mL) was slowly added disulfonyl chloride (**8**, 5 mmol). After reluxing the mixture for 4-8 h (monitored by TLC), the solution was evaporated under reduced pressure. The normal workup and evaporation of the organic phase produced a residue, which was crystallized from MeOH to give compound (**4**, 93%).

The design and synthesis of total 13 compounds of arylsulfonamide and arylamide derivatives were reported here. All of the obtained compounds have not previously been prepared and their structures were confirmed by HRMS (EI) and ^{1}H-NMR spectroscopy[11]. These 13 compounds were also tested *in vitro* against platelet aggregation. The structures and percentage inhibition of platelet aggregation (ADP) values of the synthesized compounds were listed in **Table 1.**

Table 1 The analytical and biological data of the synthesized compounds *

Cpd	Molecular formula	MS (e/m) M-1	Yield(%)	Mp °C	*%Inhibition platelet aggregation(ADP)*
3a	$C_{23}H_{18}N_2O_7$	433.7	69 %	294-296	60.53
3b	$C_{25}H_{22}N_2O_7$	461.7	71 %	191-192	78.32
3c	$C_{27}H_{26}N_2O_7$	489.6	71 %	234-235	53.05
3d	$C_{27}H_{26}N_2O_7$	490.0	61 %	258-260	58.34
3e	$C_{29}H_{30}N_2O_7$	517.8	80 %	142-143	55.15
3f	$C_{29}H_{30}N_2O_7$	517.7	61%	203-204	49.75
4a	$C_{21}H_{18}N_2S_2O_9$	505.0	76 %	158-159	64.36
4b	$C_{23}H_{22}N_2S_2O_9$	533.2	90 %	123-124	79.16
4c	$C_{25}H_{26}N_2S_2O_9$	562.3	93 %	202-204	65.93
4d	$C_{25}H_{26}N_2S_2O_9$	561.7	71 %	134-135	71.22
4e	$C_{27}H_{30}N_2S_2O_9$	590.0	74 %	94.5-96	68.75
4f	$C_{27}H_{30}N_2S_2O_9$	589.3	75 %	95-96	38.19
4g	$C_{19}H_{20}N_2S_2O_9$	449.4	63%	155-156	62.33
picotamide					58.37

* Concentration of controlled drug (picotamide): 1×10^{-4} mol/L
Concentration of inducer (ADP sodium phosphate): 5 μ mol/L

The obtained result showed that the majority of compounds exhibited certain activity against platelet aggregation *in vitro*, in which compound **3b** and **4b** possess better activities than the controlled agent (picotamide). The further bioassays of these compounds in cell culture and on animal model will be under investigation.

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11. Compound **3b**, $C_{25}H_{22}N_2O_7$, HRMS (EI): 461.7, ^{1}H-NMR (DMSO- d_6, δppm): 12.30 (s, 2H, COOH), 10.23 (s, 1H, -NH-), 10.22 (s, 1H, -NH-), 8.26 (s, 1H, Ar-H), 8.14 (d, 1H, Ar-H), 7.70 (m, 4H, Ar-H), 7.31 (d, 1H, Ar-H), 7.22 (m, 4H, Ar-H), 3.96 (s, 3H, -OCH_3), 3.53 (s, 4H, -CH_2-). Compound **4b**, $C_{23}H_{22}N_2S_2O_9$, HRMS (EI): 533.2 and ^{1}H-NMR (DMSO- d_6, δppm): 12.29 (s, 2H, -COOH), 10.27 (s, 1H, -NH-), 10.25 (s, 1H, -NH-), 8.22 (d, 1H, Ar-H), 7.81 (q, 1H, Ar-H), 7.07 (m, 4H, Ar-H), 6.95 (m, 4H, Ar-H), 3.90 (s, 3H, OCH_3), 3.45 (s, 2H, -CH_2-), 3.43 (s, 2H, -CH_2-).

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