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Design and efficient synthesis of A-278637 derivatives as potential potassium channel opener

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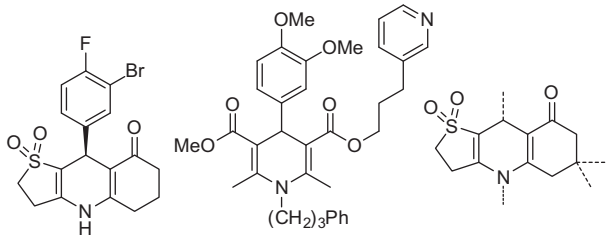
ABSTRACT

A series of thieno[3,2-*b*]quinoline derivatives designed based on A-278637 scaffold, were synthesized efficiently via one-pot three-component reaction under solvent-free and catalyst-free conditions. This work provides a new compound library with potential biological activity for biomedical screening.

Thiophene derivatives are interesting because of their antifungal,[1] antibacterial,[2] anti-acetylcholinesterase,[3] analgesic, antipyretic and antiinflammatory activities.[4] Recently, these compounds have also been reported as Cdc7 kinase inhibitors,[5] NMDA receptor antagonists,[6] and so on. In addition, some synthesized compounds with thienopyridine core unit exhibit antimalarial,[7] and antimicrobial[8] activities. A-278637 (**I**), a preclinical potassium channel opener developed by Abbott, was reported to selectively inhibit spontaneous bladder contractions.[9–14] So the research of its derivatives is of great significance. However, only a few studies on the synthesis and bioactivity of thienoquinoline analogs based on thienopyridine core have been documented in the literature.[8,14] In view of the important biological properties of the thienoquinoline derivatives, it is worthy of modifying this significant scaffold further. Besides, an N-alkylated dihydropyridine derivative, AC394 (**II**), can potentiate the antitumor effect of adriamycin and show antimetastatic activity.[15] So the aryl group was removed and hydrocarbyl substituents were introduced at positions 4, 6 and 9 of A-278637 (**I**), thus the ultimate structure (**III**) was obtained. These modifications may contribute to the bioactivity differences and provide a new compound library with potential biological activity for biomedical screening.



A-278637(I) AC394(II) III

The known synthesis methods of thienoquinoline derivatives had many drawbacks, including multistage procedures, drastic reaction conditions, long reaction time, low yields and the use of catalyst and organic solvents. Recently, the progress in the field of solvent-free reactions is gaining much attention because of their high efficiency and selectivity, easy separation and purification, mild reaction conditions, and eco-friendliness.[16] Many organic reactions and complex transformations have been reported to proceed under solvent-free conditions.[17,18] In addition, by virtue of the convergence of productivity, facile execution, and generally high yield of products, one-pot multicomponent reactions (MCRs) have attracted considerable attention from the point of view of ideal synthesis.[19] Therefore, if a one-pot MCR could be carried out under solvent-free conditions, it may be most efficient and eco-friendly. In continuing our work on the design and efficient synthesis of potential biologically active heterocyclic compounds,[20] herein we

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shall report a simple work-up, three-component and catalyst-free synthesis of a range of new thienoquinoline derivatives, which may prove to be of biological interest (Scheme 1).

The effect of solvent on the reaction was initially examined by reacting 3-fluorophenyl aldehyde (1 mmol) and dihydrothiophen-3(2*H*)-one-1,1-dioxide (1 mmol) with 3-phenylamino-5,5-dimethylcyclohex-2-enone (1 mmol) without catalyst. When the reaction was performed below 50 °C, only trace amount of expected product was obtained in the presence/absence of solvents, as indicated by TLC. So the model reaction was carried out using AcOH, $CHCl_3$, EtOH, DMF and water as solvents at 60 °C to investigate the solvent effect. As can be seen in Table 1, the reaction under solvent-free condition provided the best yield in the shortest reaction time (Table 1, entry 6). So we carried out the solventless reaction to synthesize the desired products.

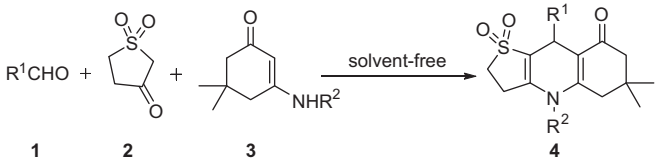
To optimize the temperature for the synthesis, the previous three reagents were reacted under solvent-free condition at temperatures ranging from 60 to 120 °C (Table 2). We found that the yield of **4a** was improved and the reaction time was shortened as the temperature was increased from 60 to 90 °C (Table 2, entries 1–4). The yield plateaued when the temperature was further increased from 100 to 110 °C (Table 2, entries 5–6). Therefore, a reaction temperature of 90 °C was considered to be most suitable.

Based on the optimized reaction conditions (solvent-free, catalyst-free, 90 °C), a series of N-substituted thieno[3,2-*b*]quinoline derivatives were synthesized. The results are summarized in Table 3.

To examine the efficiency and the applicability of this three-component reaction, a series of aldehydes and enaminones were submitted to the optimized reaction conditions. As shown in Table 3, this protocol could be applied not only to aromatic aldehydes with either electron-withdrawing groups (such as nitro or halide groups) or electron-donating groups (such as alkoxyl groups), but also to heterocyclic and aliphatic aldehydes (entry 17 and 18). Particularly noteworthy was the fact that hydrogen atom at position 4 can be substituted with phenyl bearing either electron-donating group (such as a methyl, entry 13–18) or electron-withdrawing group (such as halide groups, entry 19 and 20), or even with alkyl group (such as benzyl, entry 21 and 22), which highlighted the wide scope of this three-component condensation. Therefore, we concluded that the nature of the substituents of the aldehydes and enaminones had no obvious effect on this reaction.

All the products were characterized by IR, ^{1}H NMR and HRMS data.[21] The structure of **4j** was also established by X-ray crystallographic analysis (Fig. 1).[22]

Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of N-substituted thieno[3,2-*b*]quinoline derivatives could be explained by a possible reaction sequence similar to the previous reports, which is presented in Scheme 2.[23] The product **4** may be synthesized via sequential condensation, addition and cyclization. The condensation between aldehyde **1** and



Scheme 1. Synthesis of A-278637 derivatives.

Table 1
Solvent effect on the synthesis of **4a**

Entry	Solvent	*T* (°C)	Time (h)	Yield (%)
1	AcOH	60	20	32
2	$CHCl_3$	60	18	28
3	EtOH	60	18	22
4	DMF	60	16	25
5	H_2O	60	20	36
6	Solvent-free	60	15	52

Table 2
Temperature optimization for the synthesis of **4a**

Entry	*T* (°C)	Time (h)	Yield (%)
1	60	15	52
2	70	12	63
3	80	10	78
4	90	8	85
5	100	7	80
6	110	6	80
7	120	6	68

Table 3
Synthesis of product **4** under solvent-free condition at 90 °C[a]

Entry	Product	R^1	R^2	Time (h)	Yield[b] (%)
1	**4a**	3-FC_6H_4	Ph	8	85
2	**4b**	4-FC_6H_4	Ph	9	80
3	**4c**	3,4-$Cl_2C_6H_3$	Ph	9	78
4	**4d**	3-$NO_2C_6H_4$	Ph	9	80
5	**4e**	4-$NO_2C_6H_4$	Ph	8	83
6	**4f**	3-ClC_6H_4	Ph	8	77
7	**4g**	3-BrC_6H_4	Ph	10	81
8	**4h**	4-ClC_6H_4	Ph	9	84
9	**4i**	4-BrC_6H_4	Ph	9	83
10	**4j**	3-$CH_3OC_6H_4$	Ph	10	78
11	**4k**	2-FC_6H_4	Ph	12	75
12	**4l**	3,4-$(OCH_2O)C_6H_3$	Ph	12	72
13	**4m**	3-FC_6H_4	4-$CH_3C_6H_4$	9	86
14	**4n**	4-FC_6H_4	4-$CH_3C_6H_4$	9	80
15	**4o**	4-BrC_6H_4	4-$CH_3C_6H_4$	9	81
16	**4p**	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	9	76
17	**4q**	*n*-C_3H_7	4-$CH_3C_6H_4$	10	68
18	**4r**	Thiophene-2-yl	4-$CH_3C_6H_4$	10	59
19	**4s**	3-FC_6H_5	4-BrC_6H_4	12	63
20	**4t**	3-FC_6H_4	4-ClC_6H_4	12	65
21	**4u**	4-ClC_6H_4	$C_6H_5CH_2$	15	46
22	**4v**	4-BrC_6H_4	$C_6H_5CH_2$	14	52

[a] General procedure: 1 mmol **1** and 1 mmol **2** were triturated together for 30 min. Then 1 mmol **3** was added and mixed thoroughly. The mixture was kept at 90 °C until completion (monitored by TLC).
[b] Isolated yield.

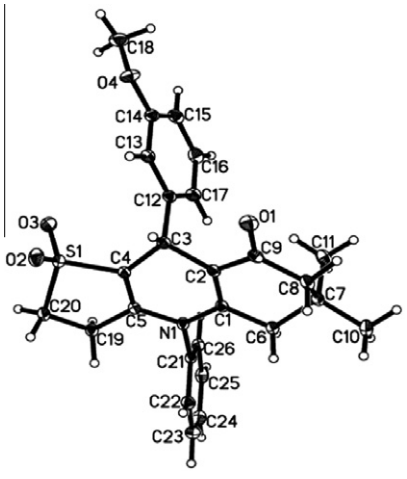
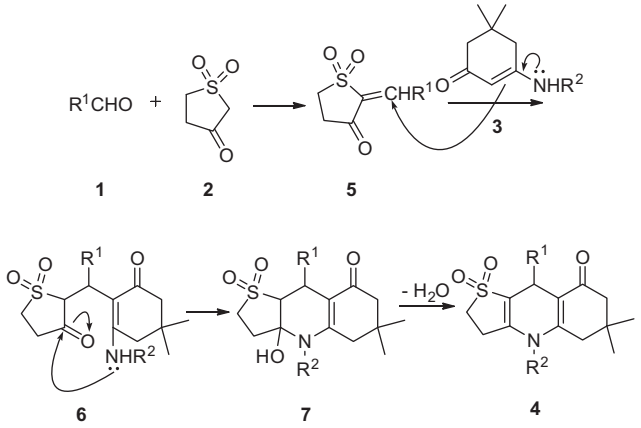


Figure 1. Crystal structure of **4j**.



Scheme 2. A putative reaction mechanism.

dihydrothiophen-3(2*H*)-one-1,1-dioxide **2** leads to intermediate **5**. Michael addition between **5** and **3** can give **6**, which upon intramolecular cyclization and dehydration, would generate the ultimate product.

In summary, we have provided an efficient three-component route using readily available starting materials for the synthesis of a series of thieno[3,2-*b*]quinoline derivatives under solvent-free and catalyst-free conditions. The experimental simplicity, higher yields, short reaction time, eco-friendly and the simple workup procedure, makes the procedure attractive to modify the scaffold of A-278637. The new series of thieno[3,2-*b*]quinoline derivatives may prove to be of biological interest and provide new classes of compounds with potential biological activity for biomedical screening.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.10.127.

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21. The experimental procedures of synthesis and the spectroscopic data of the synthesized compounds are available in Supplementary data.
22. The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed using a Rigaku Saturn diffractometer. Crystal data for **4j**: $C_{26}H_{27}NO_4S$, colorless, crystal dimension $0.20 \times 0.14 \times 0.12$ mm, Monoclinic, space group P_121/n_1, $a = 11.2488(14)$, $b = 14.8013(18)$, $c = 13.3866(16)$ Å, $\beta = 92.747(7)°$, $V = 2226.3(5)$ Å^3, $M_r = 449.55$, $Z = 4$, $D_c = 1.341$ g/cm^3, $\lambda = 0.71070$ Å, μ(Mo Kα) = 0.179 mm^{-1}, $F(0\,0\,0) = 952$, $S = 1.041$, $R_1 = 0.0489$, $wR_2 = 0.1250$. CCDC 790992 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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