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SYNTHESIS, CHARACTERIZATION OF NOVEL BENZOTHIOPHENE

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Abstract

A library of novel benzo[*b*]thiophene have been synthesized regioselectively in good yields through the one-pot domino reactions of thiophenone, malononitrile and aromatic aldehydes in the presence of NaOEt. This transformation presumably involves Knoevenagel condensation–Michael addition–intramolecular Thorpe-Ziegler cyclization–Tautomerization–Elimination sequence of reactions.

Introduction

benzo[*b*]thiophene derivatives are found within the structural core of several biologically active compounds, for example, raloxifene™ is a selective estrogen receptor modulator for the prevention of osteoporosis in postmenopausal women[1] and zileuton™ is an active inhibitor of 5-lipoxygenase used to prevent difficulty in breathing, wheezing and coughing due to asthma and sertaconazole has several known mechanisms of action (**Figure 1**).[2]

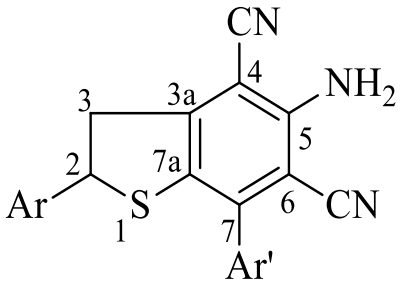

Figure 1. Benzo[*b*]thiophene derivatives synthesized in the present work

Other pharmacological applications of benzo[*b*]thiophene derivatives include estrogen receptor antagonists,[3] antifungal,[4] antiinflammatory[5] and antimitotic[6] agents. The above significance of benzo[*b*]thiophene derivatives has set path to several investigations leading to their synthesis and biological activity studies.[7]

Several other molecular entities containing benzothiophene core are at various stages of development. They include **T588**[8] a cognition enhancing agent with potential application for treating Alzheimer's dementia; **LY353381**[9] an additional SERM from Lilly; **AP521**[10] with potent $5Ht_{1A}$ receptor binding ability; **CI959**[11] an anti-inflammatory agent; and **B428**[12] a urokinase inhibitor. Another structurally interesting compound is **PD144795**[13] an endothelial cell activation inhibitor as a benzothiophene oxide (**Figure 3**).

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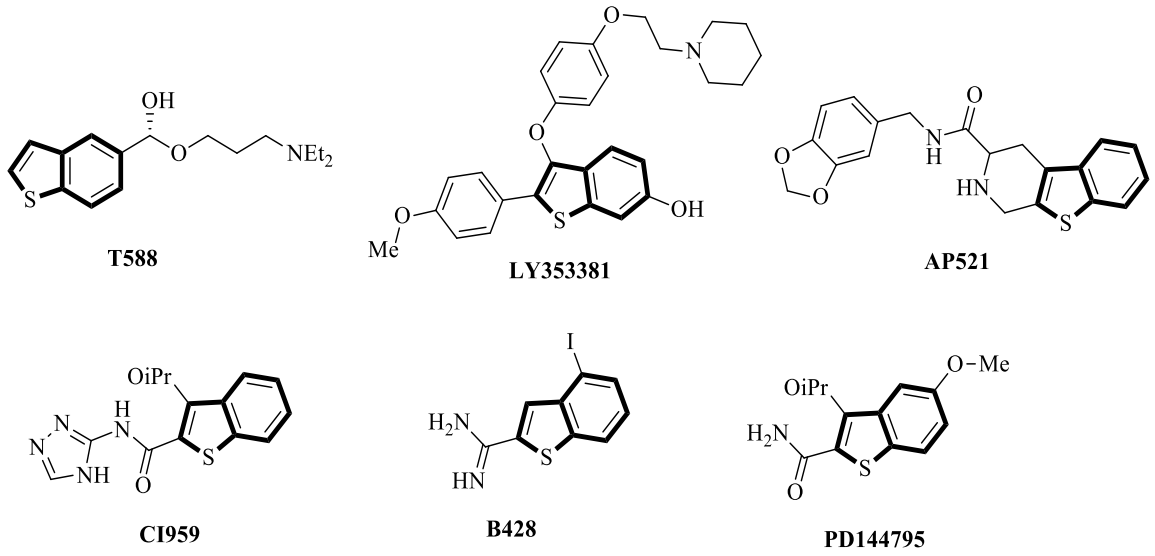
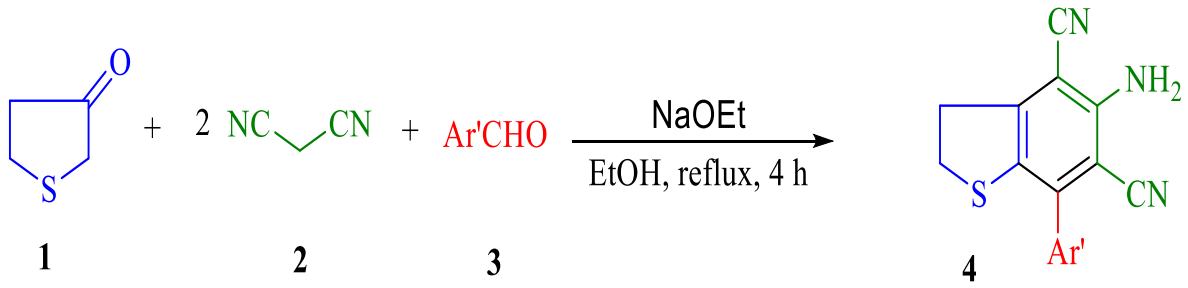


Figure 3. Benzothiophenes Various stages of development

In view of the importance of benzothiophene derivatives, herein we report a domino protocol for the regioselective synthesis of a library of highly functionalized novel 5-amino-2,7-diaryl-2,3-dihydrobenzo[*b*]thiophene-4,6-dicarbonitriles **4** in good yields through the one-pot four-component reactions of 5-aryldihydro-3(2*H*)-thiophenones **1**, malononitrile **2** and aromatic aldehydes **3** in the presence of morpholine (**Scheme 1**).



Scheme 1. Synthesis of 2,3-dihydrobenzo[*b*]thiophene-4,6-dicarbonitriles **4**

Structure elucidation

The structure of all the Benzo[*b*]thiophenes **4** were elucidated unambiguously with the help of one and two-dimensional NMR spectroscopy. As a representative case, the ^{1}H and ^{13}C NMR chemical shift assignment of **4r** are discussed.

In the ^{1}H NMR spectra of **4r**, the 2-CH and the 5-NH_2 protons overlap and appear as a multiplet at 5.01–5.08 ppm. The D_2O exchange experiment reveals that the H-2 appears as a triplet at 5.04 ppm (J = 8.4 Hz) and the latter appears as a broad singlet at 5.08 ppm.

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Table 2. Yield and melting point of Benzo[*b*]thiophene **4**

Entry	Comp	Ar′	Yield of 4 (%)	mp (°C)
1	**4a**	4-MeC_6H_4	79	165-167
2	**4b**	4-MeOC_6H_4	85	167-169
3	**4c**	4-ClC_6H_4	72	175-177
4	**4d**	4-FC_6H_4	73	157-1159

[a] Isolated yield after purification by column chromatography

Conclusions

The present investigation reports a one-pot domino protocol for the regioselective synthesis of novel Benzo[*b*]thiophene via Knoevenagel condensation–Michael addition–intramolecular Thorpe-Ziegler cyclization–Tautomerization–Elimination sequence of reactions.

This four-component reaction results in the formation of four new C–C bonds in a single operation. The structure of all the Benzo[*b*]thiophene was elucidated with NMR and single crystal X-ray studies.

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