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Synthesis, antidiabetic activity and *in silico* studies of benzo[*b*]thiophene based small molecule α-amylase inhibitors

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Highlights

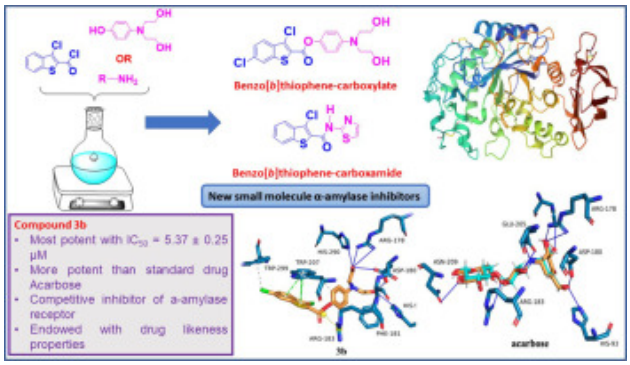
- Benzo[b]thiophene based small molecule α-amylase inhibitors.
- Significant antidiabetic activity with IC_{50} ranging from 5.37 to 29.89 μM.
- Compound **3b** more potent than acarbose with IC_{50} of 5.37 μM.
- Competitive inhibitor of α-amylase having Ki of 1.76 μM.
- Safer antidiabetic agent endowed with drug-likeness properties.

Abstract

Benzo[*b*]thiophene has been implicated as molecular framework in the drug discovery against broad spectrum of biological targets. In the antidiabetic drug regime, benzo[*b*]thiophene based SGLT2 and ALR2 inhibitors have been recently developed but their potential towards α-amylase inhibition remained unexplored to date. In this context, a series of novel small molecule benzo[*b*]thiophene-2-

carboxylic acid derivatives **(3a-p)** was synthesized, characterized, and evaluated for antidiabetic activity as α-amylase inhibitors. We found that, all benzo[*b*]thiophene derivatives exhibited significant α-amylase inhibition with IC_{50} value ranging from 5.37 ± 0.25 μM to 29.89 ± 0.68 μM. The SAR studies showed benzo[*b*]thiophene carboxylate bearing bis(2-hydroxyethyl)amino group (**3b**) was most potent with IC_{50} of 5.37 ± 0.25 μM compared to standard drug Acarbose (IC_{50} = 6.40 ± 0.14 μM). Further, the enzyme inhibition mechanism study regarded **3b** as competitive inhibitor of α-amylase with Ki value of 1.76 μM. A detailed *in silico* study was also performed in order to estimate binding properties, drug likeness and predict toxicity profile of these agents. It was demonstrated that novel small molecule benzo[*b*]thiophene derivative (**3b**) can effectively bind through H-bonding, hydrophobic and π-stacking interactions within α-amylase active site. Moreover, drug likeness and toxicity prediction studies suggested compound **3b** as potential & safter α-amylase inhibitor. Overall, our present study disclosed a novel class of benzo[*b*]thiophene based α-amylase inhibitors and opened a template for further lead optimization and development.

Graphical abstract



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Introduction

According to the International Diabetes Federation (IDF), the number of people with diabetes is steadily increasing, with 415 million currently affected globally. As estimated, by 2040, the diabetes mellitus (DM) cases could rise to 642 million [1]. Diabetes mellitus (DM) is a long-term metabolic disease associated with the persistence of high blood glucose level (hyperglycemia) condition which often leads to other health issues such as heart diseases, nerve damage, eye issues and kidney failure [2]. Thus, efficacious, and safer drug against this global disease remained as key area of research.

In this context, enzyme inhibition-based drug discovery emerged as an effective strategy for metabolic disorders like Diabetes mellitus (DM) [3]. Especially, α-amylase and α-glucosidase has been extensively explored for the treatment of type 2 diabetes (DM2) since both are vital metabolic enzymes for the efficient digestion of carbohydrates and glycogen to provide free glucose for absorption [4]. Of these, the enzyme amylase, which is secreted by the salivary glands, hydrolyze the α-(1,4)-D-glycosidic bonds found in carbohydrates and disintegrate into smaller components like glycogen and monosaccharides, which the body would then absorb further [[5], [6], [7], [8]]. Hence, suppressing the α-amylase enzyme there by reducing the postprandial glycaemia proved to be an

effective treatment option for DM2 [[9], [10], [11], [12]]. Presently, the FDA-approved α-amylase/glucosidase inhibitors such as Acarbose, Voglibose, and Miglitol (Fig. 1) are being used in the clinics to treat DM2 [13,14]. Nevertheless, a number of side effects, including diarrhea, flatulence, skin reactions, abdominal pain, and abnormal liver functions, are associated to these antidiabetic medications [15]. Consequently, development of effective and safter α-amylase inhibitors remained as main areas of research in the antidiabetic regime.

Thiophenes are extensively explored bioactive scaffolds among the sulfur containing heterocycles providing plethora of new lead molecules for the drug design and discovery in last two decades [[16], [17], [18], [19]]. This resulted in several clinical drugs based on thiophene framework for the treatment of various types of diseases with high therapeutic potency [[20], [21], [22]]. Particularly, the benzo[*b*]thiophene-2-carboxylic acid derivatives (amide and ester) demonstrated broad spectrum of biological activities including anticancer, antifungal, antibacterial, anti-inflammatory and antidiabetic [[23], [24], [25], [26], [27], [28], [29], [30]]. For instance, benzo[b]thiophene carboxamide-benzimidazole conjugate (**A**) (Fig. 2) showed potent antiproliferative activities against HeLa cells with IC_{50} in low micromolar range [31]. Similarly, quinazolinone-benzothiophene conjugate (**B**) found to be potential candidate against mycobacterium tuberculosis H37Rv strain [32] while benzo[b]thiophene carboxamide (**C**) exhibited potent anti-inflammatory activity as COX-2 inhibitor. Furthermore, hybrid of quinoxaline-benzo[b]thiophene moiety **(D**) reported as potent and selective aldose reductase (ALR2) inhibitor [33]. Recently, benzo[b]thiophene based drug candidates viz. Ipragliflozin (**E**) has been approved for the treatment of DM2 which is selective inhibitor of sodium-glucose cotransporter-2 (SGLT2) [34]. Thus, there is considerable renewed interest towards synthesis of novel benzo[*b*]thiophene based antidiabetic agents.

In the quest of searching novel and safer antidiabetic agents, currently a number of heterocycles such as isatin, coumarin, chromene, indole, benzimidazole and triazole have been extensively used as core skeletons for the development of α-glucosidase/α-amylase inhibitors [[35], [36], [37], [38], [39]]. However, potential of benzo[*b*]thiophene scaffolds towards a-amylase inhibition is yet to explore. Hence, inspired by the aforementioned therapeutic applications of benzo[*b*]thiophenes and our continuous research efforts towards the development of new leads as antidiabetic agents [40], we sought to utilize bioactive benzo[*b*]thiophene framework and develop a library of small molecule α-amylase inhibitors. For this purpose, a series of novel benzo[*b*]thiophene-2-carboxylic acid derivatives have been synthesized by incorporating functionalized aromatic or aliphatic (cyclic/acyclic) units through amide or ester linkages and evaluated for their inhibition potential against α-amylase enzyme along with *in silico* studies. The present study revealed new benzo[*b*]thiophene analogs as potent and competitive α-amylase inhibitors along with favorable drug-likeness profile which is reported herein.

Section snippets

Chemistry

All the chemicals and reagent were used for the experiment, were purchased from Loba Chemie. Pvt Ltd., Sigma Pvt. Ltd. & Meark India Ltd. (Mumbai, India). and were used without further purification. The reactions were monitored through TLC using E. Merck 0.25 mm silica gel plates and spots were

visualized through UV light. The uncorrected melting points of the compounds were measured in one end open capillary method. The characterization of synthesized compound was carried out by FT-IR …

Synthesis and characterization

The targeted benzo[*b*]thiophene-2-carboxylic acid derivatives were synthesized as shown in Scheme 1. Initially the required intermediates 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride (**1a-c)** were synthesized by reported synthetic method from cinnamic acid as starting material [41]. The intermediate 2,2′-((4-hydroxyphenyl)azanediyl)bis(ethan-1-ol) **(2a)** was prepared by our earlier reported method from 4-amino phenol and 2-chloroethanol [42]. Then, the coupling reaction of 3-chlorobenzo[*b* …

Conclusion

In conclusion, a new series of small molecule benzo[*b*]thiophenes was discovered with potent α-amylase inhibition efficacy. The targeted benzo[*b*]thiophene-2-carboxylic acid analogues **(3a-p)** were synthesized in excellent yields and characterized by various spectroscopy methods like ^{1}H & ^{13}C NMR, FT-IR and elemental analysis. All benzo[*b*]thiophene derivatives revealed to have excellent inhibition profile against the targeted α-amylase with IC_{50} value ranging from 5.37 ± 0.25 μM to 29.89 ± 0.68 μM. …

CRediT authorship contribution statement

Rupal J. Joshi: Methodology, Conceptualization. **Monil P. Dholariya:** Methodology, Formal analysis, Data curation. **Savankumar R. Chothani:** Methodology, Investigation. **Chirag A. Chamakiya:** Data curation. **Hardik L. Varu:** Validation, Software. **Manisha B. Karmur:** Visualization. **Deepika Maliwal:** Validation, Software. **Raghuvir R.S. Pissurlenkar:** Software, Validation. **Atul H. Bapodra:** Supervision, Project administration. **Anilkumar S. Patel:** Methodology, Formal analysis, Data curation. **Naval P. Kapuriya:** …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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