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Synthesis, crystal structure and antidiabetic activity of substituted (*E*)-3-(Benzo [*d*]thiazol-2-ylamino) phenylprop-2-en-1-one

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ABSTRACT

A novel series of substituted (*E*)-3-(Benzo [*d*]thiazol-2-ylamino)phenylprop-2-en-1-onewere synthesized starting from 2-aminobenzothiazole and 1-aryl-3,3-bis- (methylsulfanyl)-2-propen-1-onesin the presence of a catalytic amount of sodium hydride in THF. The synthesised compounds' structures were confirmed by IR, Mass spectrometry, ^{1}H NMR, ^{13}C NMR and HRMS spectral data. These compounds were evaluated for their antidiabetic activity, and most of the derivatives of (*E*)-3-(Benzo [*d*]thiazol-2-ylamino) phenylprop-2-en-1-one displayed significant antidiabetic activity.

1. Introduction

A variety of heterocyclic compounds can be synthesised using 2-aminobenzothiazoles, as the functional group NH_2 is suitably situated in the moiety. A literature survey reveals that several derivatives of 2-aminobenzothiazoles have useful biological activity i.e. antibacterial [1], antifungal [2], antimalarial [3], antitubercular [4], antihelmintic [5], viral infection [6] as well as antitumour activity [7–13].The antidiabetic properties shown by benzothiazole derivatives i.e. *N*-(6-chlorobenzothiazol-2-yl)-2-(substituted amino) acetamide were reported by Mariappan et al. [14] Furthermore, 2-arylsulfonylaminobenzothiazole derivatives were prepared and subjected for evaluation of their in vitro activity against protein tyrosine phosphatase 1B (PTP-1B) by Gabriel and co-workers [15]. Pattan et al. reported antidiabetic activity of 2-amino[5′(4-sulphonylbenzilidine)-2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole [16]. Recently, the synthesis of nine ethyl 2-(6-substituted benzo[*d*]thiazol-2-ylamino)-2-oxoacetate derivatives and their protein tyrosine phosphatase 1B inhibitory activities were studied by Gabriel et al. [17] Protein tyrosine phosphatase 1B inhibitors like Ertiprotafib are found to have immense adverse effects [18]. Hereby, there is a need to search for alternate targets. However, till date there are no detailed reports on the study of the benzothiazole derivatives on the inhibition of the enzymes taking part in the carbohydrate metabolism. α-amylase and α-glucosidases are the key players in the postprandial hyperglycaemia observed in case of non insulin dependent diabetes mellitus (NIDDM). Hence inhibition of these enzymes can act as a potent target that can serve as a powerful strategy in the treatment of NIDDM [19].

In continuation of our on-going research into antidiabetic herein we report the synthesis, characterization and antidiabetic activity of (*E*)-3-(Benzo [*d*]thiazol-2-ylamino)phenylprop-2-en-1-onestarting from 2-aminobenzothiazole and 1-aryl-3,3-bis-(methylsulfanyl)-2-propen-1-ones. In the synthesis the catalytic system employed was a small amount of sodium hydride in THF. These compounds were screened for their antidiabetic activity by using α-amylase

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inhibition assay as well as glucosidase inhibition assay with murine pancreatic, small intestinal and liver extracts and also the pure α-glucosidase.

2. Results and discussion

2.1. Chemistry

A novel series of substituted (*E*)-3-(Benzo[*d*]thiazol-2-ylamino) phenylprop-2-en-1-one (**3**, **a**–**l**) was prepared using mild base i.e. NaH through substitution reaction of suitably functionalized α-aroylketene dithioacetals (AKDTAs) (**1**, **a**–**f**) with 2-aminobenzothiazole (**2**, **a**–**d**) in THF(Scheme 1). The precursors, α-aroylketene dithioacetals (AKDTAs) (**1**, **a**–**f**) were prepared from readily available substituted acetophenone, carbon disulfide, and an alkylating agent, using literature procedures [20,21].

The IR spectrum shows the carbonyl stretching vibrations were below 1600 cm^{-1}due to the characteristic conjugation effect of the amino group. In ^1H NMR spectra, *S*,*N*-ketals showed a characteristic NH proton at δ 15.2 ppm, assigned to the $-NH_2$ group. The amino group participated in a strong hydrogen bonding with the oxygen of the carbonyl group (NH–O═C). The ^{13}C NMR spectrum showed a signal for the carbonyl carbon of the ketone near δ 185. Furthermore, crystals of (*E*)-1-(4-Chlorophenyl)-3-(6-ethoxybenzo[*d*] thiazol-2-ylamino)-3-(methylthio)-prop-2-en-1-one suitable for X-ray analysis were grown by vapour diffusion of MeOH into a $CHCl_3$ solution. The structure of the compound **3h** was confirmed from X-ray crystallographic analysis [CCDC 885525] and the configuration is *E* (Fig. 1).

2.2. Biology

The antidiabetic activities were examined by the standard α-amylase inhibition and glucosidase inhibition assay. The activity results expressed as IC_{50} are summarised in Table 1. The IC_{50}values were the average of three independent measurements. The protease inhibitor used was phorbol-12-myristate-13-acetate.

The α-amylase inhibition activity was carried out by using reported method with a slight modification. The (*E*)-3-(Benzo [*d*] thiazol-2-ylamino) phenylprop-2-en-1-one derivatives tested, as compare to acarbose (IC_{50} = 35.5 μM). These derivatives showed significant level of inhibition. The α-amylase inhibition activity study revealed that the derivatives **3c** (IC_{50} = 15.87 μM), **3e** (IC_{50} = 16.32 μM), **3f** (IC_{50} = 16.87 μM), **3d** (IC_{50} = 17.84 μM) and **3h** (IC_{50} = 17.85 μM) showed excellent inhibition. Furthermore, the derivatives **3i** (IC_{50} = 19.85 μM), **3b** (IC_{50} = 18.88 μM), **3k** (IC_{50} = 18.63 μM) and **3j** (IC_{50} = 18.35 μM) were found to be superior as compared to **3a** derivative whereas less potent to **3c**, **3e**, **3f**, **3d** and **3h** derivatives. In case of the **3a** derivative (IC_{50} = 20.59 μM) showed moderate activity similar to that of the **3i** derivatives.

In *vitro* efficacy of compounds was evaluated for their antidiabetic activity using glucosidase inhibition assay. The results are tabulated in Table 1. Compounds **3b** (IC_{50} = 19.93 μM) and **3c** (IC_{50} = 18.04 μM) were shows excellent inhibition of murine pancreatic glucosidase where as derivatives **3c** (IC_{50} = 20.85 μM), **3d** (IC_{50} = 21.72 μM), **3j** (IC_{50} = 23.51 μM) and **3k** (IC_{50} = 23.16 μM) exhibited moderate inhibition. Furthermore activities shown by compounds **3a** (IC_{50} = 26.94 μM), **3f** (IC_{50} = 24.71 μM) and **3h** (IC_{50} = 26.49 μM) are moderate. The derivatives **3g** and **3i** exhibited a further reduced level of activity as compare to **3a**, **3f** and **3h**.

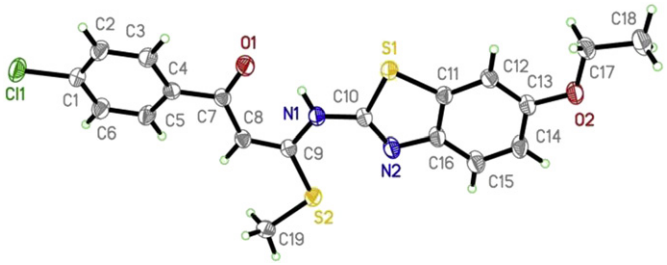


Fig. 1. Single crystal X-ray structure of **3h** (*E*-isomer).

Inhibitory activity of synthesised compounds against murine intestinal glucosidase is as shown in Table 1. Compound **3h** (IC_{50} = 14.72 μM) showed excellent activity. However compounds **3b** and **3f** were showed reduced activity. The derivatives **3a** (IC_{50} = 29.99 μM) and **3k** (IC_{50} = 29.29 μM) were found to be inferior inhibitor for the intestinal glycosidase. Furthermore, the compound **3e** showed no inhibition where as rest of the derivatives **3c** (IC_{50} = 31.88 μM), **3d** (IC_{50} = 31.88 μM), **3g** (IC_{50} = 44.50 μM), **3i** (IC_{50} = 32.14 μM) and **3j** (IC_{50} = 49.36 μM) showed very little inhibition. While acarbose failed to show any inhibition.

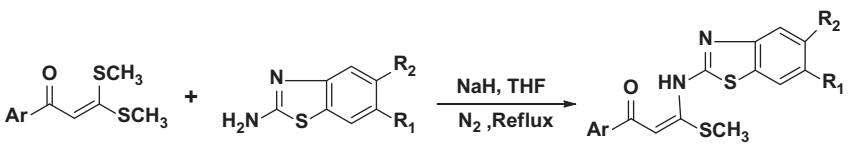
In the inhibition of murine liver glucosidase a variation was observed among the tested compounds. The derivatives **3c** (IC_{50} = 15.74 μM), **3d** (IC_{50} = 15.39 μM), **3f** (IC_{50} = 16.74 μM) and **3g** (IC_{50} = 15.03 μM) showed excellent inhibitory activity. Whereas compound **3h** (IC_{50} = 17.36) showed significant activity. The acarbose exhibited inhibitory activity in micro-molar range (IC_{50} = 0.99 μM). Furthermore, the derivatives **3a** (IC_{50} = 22.49 μM), **3i** (IC_{50} = 21.66 μM) and **3k** (IC_{50} = 21.38 μM) exhibited moderate activity as compare to **3c**, **3f**, **3g** and **3h**. In case of **3b** (IC_{50} = 24.21 μM) and **3j** (IC_{50} = 24.19 μM) observed inhibition is reduced as compare to **3a**, **3i** and **3k** while **3e** shows no inhibition.

α-glucosidase (E.C. 3.2.1.20) inhibitory activity against pure enzyme showed compound **3a** (IC_{50} = 21.05 μM) to selectively inhibit the pure enzyme. Other derivatives tested failed to show inhibition unlike acarbose (IC_{50} = 102 μM) which was used as a standard inhibitor against pure alpha glucosidase indicating the selectivity of the compounds towards the α-amylase and the crude murine glucosidases.

3. Experimental section

3.1. Chemistry

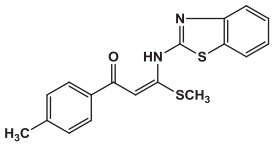
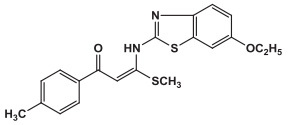
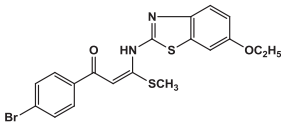
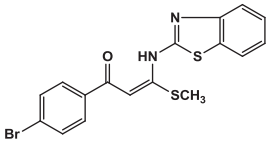
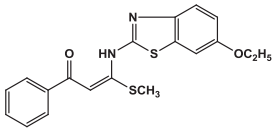
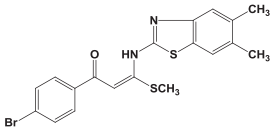
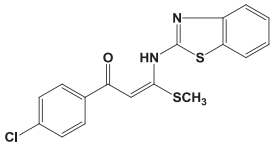
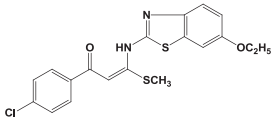
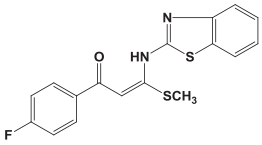
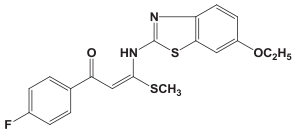
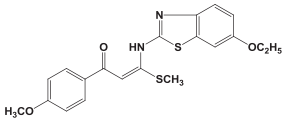
Melting points of compounds were determined by a Kofler micro melting point apparatus and were uncorrected. IR spectra



1 (a-f) 2 (a-d) 3 (a-k)

Scheme 1. General synthetic pathway for the preparation of compounds **3a**–**k**; **Ar** = C_6H_5, 4-$CH_3C_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4; 4-$OCH_3C_6H_4$; R_1 = H, 6-OC_2CH_3, 6-CH_3; R_2 = H, 5-CH_3.

Table 1
Enzyme inhibition activity of compounds **3a**–**k**. The results summarized are the mean values of $n = 3$ for IC_{50} values; NI – No inhibition.

Sr. No.	Code	Structure	Enzyme inhibition IC_{50} values (μM)			
			Porcine pancreatic α-amylase	Murine pancreatic glucosidase	Murine intestinal glucosidase	Murine liver glucosidase
1.	**3a**		20.59	26.94	29.99	22.49
2.	**3b**		18.88	19.93	23.50	24.21
3.	**3c**		15.87	20.85	31.88	15.74
4.	**3d**		17.84	21.72	45.31	15.39
5.	**3e**		16.32	18.04	NI	NI
6.	**3f**		16.87	24.71	25.85	16.74
7.	**3g**		20.33	32.35	44.50	15.03
8.	**3h**		17.85	26.49	14.72	17.36
9.	**3i**		19.85	33.57	32.14	21.66
10.	**3j**		18.35	23.51	49.36	24.19
11.	**3k**		18.63	23.16	29.29	21.38
12.	**Acarbose**		35.50	>100	NI	>100

were recorded on a Thermo Nicolet Nexus 670 spectrometer using KBr pellets. ^{1}H NMR spectra were recorded on AVANCE 300 MHz spectrometer using tetramethylsilane (TMS) as an internal standard and a^{13}C NMR (75 MHz) Varian instrument. Mass spectra were recorded on VG-7070H Micromass at 200 °C, 70 eV.

*3.1.1. Typical procedure for synthesis of substituted (E)-3-(Benzo [d] thiazol-2-ylamino) phenylprop-2-en-1-one(**3**, **a**–**l**)*

In a 100 mL two neck round bottom flask, of which one neck is fitted with a reflux condenser, the mixture of 0.01 mol of substituted 2-aminobenzothiazole (**2**, **a**–**d**), 0.02 mol sodium hydride under N_2 atmosphere in 5–10 mL of dry THF was added through the other neck, and the reaction mixture was stirred at room temperature for 10–15 min. Into the reaction mixture 0.01 mol 1-aryl-3,3-bis-(methylsulfanyl)-2-propen-1-ones (**1**, **a**–**f**) i.e. aroyl ketene dithioacetal in 10 mL dry THF was added and the mixture was refluxed. Progress of the reaction was monitored by TLC (hexane: EtOAc, 8:2). After completion of the reaction, the reaction mixture was poured into crushed ice (250 mL of ice-water) with vigorous stirring and then stirred at room temperature for another 30 min. The reddish or yellow precipitate formed was filtered, washed with cold water and dried. The crude product was recrystalized from MeOH or $CHCl_3$: MeOH. The recrystalized product was characterized by various spectroscopic techniques.

*3.1.2. (E)-3-(Benzo [d]thiazol-2-ylamino)-3-(methylthio)-1-p-tolylprop-2-en-1-one (**3a**)*

IR (KBr υ_{max}/cm^{-1}): 3143, 3059, 2989, 2922, 2852, 2744, 2299, 1595, 1568, 1556, 1489, 1454, 1315, 1255, 1182, 1076, 837, 754, 694; Mass [ESI, 70 eV] *m*/*z* (%): 341 (100), 342 (26), 343 (12), 376 (29); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.42 (s, 3H, $ArCH_3$), 2.53 (s, 3H, SCH_3), 6.04 (s, 1H, CH=C), 7.17–7.23 (m, 3H, PhH), 7.34–7.39(m, 1H, PhH), 7.68–7.71 (d, J = 7.5 Hz, 1H, PhH), 7.76–7.80 (m, 3H, PhH), 15.16 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 15.8, 21.5, 92.4, 120.9, 121.4, 123.9, 125.7, 126.1, 127.3, 128.3, 129.2, 132.1, 136.2, 142.4, 151.1, 159.2, 164.6, 186.5; HRMS (ESI)*m*/*z*: Calculated for $C_{18}H_{17}-N_2OS_2$: $[M + H]^+$ 341.0767, Found: 341.0782.

*3.1.3. (E)-3-(6-Ethoxybenzo [d] thiazol-2-ylamino)-3-(methylthio)-1-p-tolylprop-2-en-1-one (**3b**)*

IR (KBr υ_{max}/cm^{-1}): 3066, 2985, 2978, 2887, 2860, 2736, 2673, 2609, 2534, 2439, 2277, 2158, 1600, 1539, 1519, 1475, 1456, 1435, 1392, 1303, 1290, 1261, 1222, 1182, 1111, 1056, 933, 819, 758; Mass [ESI, 70 eV] *m*/*z* (%): 385 (100), 386 (29), 387 (15); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.38 (s, 3H, $ArCH_3$), 1.42–1.47 (t, 3H, CH_2-CH_3), 2.52 (s, 3H, SCH_3), 4.01–4.08 (q, 2H, CH_3-CH_2), 5.96 (s, 1H, CH=C), 6.93–6.96 (dd, J = 2.4 and J = 6.6 Hz 1H, PhH), 7.16–7.17(d, J = 2.4 Hz, 1H, PhH), 7.55–7.58 (d, d, J = 8.4 Hz, 2H, PhH), 7.65–7.68 (d, J = 8.8 Hz, 1H, PhH), 7.74–7.77 (d, J = 8.4 Hz, 2H, PhH), 15.16 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 14.1, 15.1, 20.8, 91.3, 104.4, 114.5, 121.3, 126.6, 128.5, 132.0, 135.6, 141.6, 144.6, 155.5, 156.3, 164.0, 185.5; HRMS (ESI)*m*/*z*: Calculated for $C_{20}H_{21}-N_2O_2S_2$: $[M + H]^+$ 385.1033, Found: 385.1044.

*3.1.4. (E)-1-(4-Bromophenyl)-3-(6-ethoxybenzo[d]thiazol-2-ylamino)-3-(methylthio)prop-2-en-1-one (**3c**)*

IR (KBr υ_{max}/cm^{-1}): 3149, 2997, 2895, 2735, 2571, 2534, 2297, 1876, 1602, 1573, 1543, 1504, 1483, 1456, 1427, 1319, 1284, 1261, 1224, 1074, 1058, 920, 883, 817, 758; Mass [ESI, 70 eV] *m*/*z* (%): 449 (82), 451 (82); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.42–1.47 (t, 3H, CH_2-CH_3), 2.52 (s, 3H, SCH_3), 4.01–4.08 (q, 2H, CH_3-CH_2), 5.96 (s, 1H, CH=C), 6.93-6.96 (dd, J = 2.4 and 6.6 Hz, 1H, PhH), 7.16–7.17 (d, J = 2.4 Hz, 1H, PhH), 7.55–7.58 (d, J = 8.4 Hz, 2H, PhH), 7.65–7.68 (d, J = 8.8 Hz, 1H, PhH), 7.74–7.77 (d, J = 8.4 Hz, 2H, PhH), 15.16 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 14.8, 15.8, 64.1, 91.6, 105.1, 115.3, 122.2, 126.4, 128.8, 129.8, 131.7, 133.4, 137.9, 145.2, 156.3, 156.7, 165.8, 185.0; HRMS (ESI)*m*/*z*: Calculated for $C_{19}H_{18}BrN_2O_2S_2$: $[M + H]^+$ 448.9989, Found: 448.9993.

*3.1.5. (E)-3-(Benzo [d]thiazol-2-ylamino)-1-(4-bromophenyl)-3-(methylthio)prop-2-en-1 one (**3d**)*

IR (KBr υ_{max}/cm^{-1}): 3159, 3061, 2985, 2920, 2829, 2717, 2659, 2619, 2482, 1591, 1568, 1564, 1537, 1489, 1463, 1436, 1423, 1328, 1278, 1259, 1224, 1178, 1076, 935, 842, 804, 657; Mass [ESI, 70 eV] *m*/*z* (%): 405 (98), 407 (100), 408 (25); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.53 (s, 3H, SCH_3), 5.98 (s, 1H, CH=C), 7.22–7.25 (dd, J = 1.8 & 7.2 Hz, 1H, PhH), 7.36–7.39 (t, J = 6.3 and 7.2 Hz, 1H, PhH), 7.69–7.71 (d, J = 8.2 Hz,2H, PhH), 7.75–7.79 (m, 3H, PhH); ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 15.9, 92.0, 121.0, 121.6, 124.2, 126.3, 126.6, 128.8, 130.1, 131.7, 137.8, 138.0, 143.6, 165.8, 169.9, 182.7; HRMS (ESI)*m*/*z*: Calculated for $C_{17}H_{14}BrN_2OS_2$: $[M + H]^+$ 404.9713, Found: 404.97130.

*3.1.6. (E)-3-(6-Ethoxybenzo[d]thiazol-2-ylamino)-3-(methylthio)-1-phenylprop-2-en-1-one (**3e**)*

IR (KBr υ_{max}/cm^{-1}): 3149, 3089, 3068, 2974, 2933, 2883, 2841, 2623, 2532, 2285, 2160, 1901, 1600, 1548, 1456, 1438, 1417, 1390, 1301, 1253, 1220, 1111, 1053, 931, 732, 682, 651; Mass [ESI, 70 eV] *m*/*z* (%): 371 (98), 372 (25), 373 (12); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.42–1.46 (t, 3H, CH_2CH_3), 2.52 (s, 3H, SCH_3), 4.01–4.08 (q, 2H, CH_3CH_2), 6.03 (s, 1H, CH=C), 6.92–6.96 (dd, J = 2.2 and 6.0 Hz, 1H, PhH), 7.163–7.169 (d, J = 2.2 Hz, 1H, PhH), 7.39–7.48 (m, 3H, PhH), 7.65–7.68 (d, J = 9.0 Hz,1H, PhH), 7.87–7.89 (m, 2H, PhH), 15.21 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 14.8, 15.7, 64.0, 92.04, 105.0, 115.2, 122.0, 127.2, 128.2, 128.4, 131.6, 133.2, 133.4, 139.0, 145.2, 156.2, 156.9, 165.2, 186.3; HRMS (ESI) *m*/*z*: Calculated for $C_{19}H_{19}N_2O_2S_2$: $[M + H]^+$ 371.0870, Found: 371.0887.

*3.1.7. (E)-1-(4-Bromophenyl)-3-(5,6-dimethylbenzo[d]thiazol-2-ylamino)-3 (methylthio) prop-2-en-1-one (**3f**)*

Yellow solid; IR (KBr υ_{max}/cm^{-1}): 3142, 2976, 2916, 2852, 2648, 2571, 2466, 2283, 1591, 1539, 1531, 1487, 1456, 1433, 1273, 1259, 1224, 1174, 1076, 918, 869, 840, 761; Mass [ESI, 70 eV] *m*/*z* (%): 433 (96), 435 (100); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.43 (s, 3H, $ArCH_3$), 2.35 (s, 3H, $ArCH_3$), 2.51 (s, 3H, SCH_3), 5.95 (s, 1H, CH=C), 7.45 (s, 1H, PhH), 7.54 (s, 1H, PhH), 7.57–7.58 (d, J = 8.4 Hz, 2H, PhH), 7.74–7.76 (d, J = 8.4 Hz, 2H, PhH), 15.15 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 15.8, 20.01, 20.08, 91.5, 121.1, 122.0, 126.4, 128.7, 129.4, 131.0, 131.6, 133.3, 135.5, 137.8, 149.5, 158.0, 165.8, 185.0; HRMS (ESI) *m*/*z*: Calculated for $C_{19}H_{18}BrN_2OS_2$: $[M + H]^+$ 432.9990, Found: 432.9805.

*3.1.8. (E)-3-(Benzo [d]thiazol-2-ylamino)-1-(4-chlorophenyl)-3-(methylthio)prop-2-en-1-one (**3g**)*

IR (KBr υ_{max}/cm^{-1}): 3149, 3070, 3005, 2920, 2848, 2659, 2569, 1591, 1568, 1547, 1537, 1494, 1463, 1435, 1425, 1328, 1282, 1259, 1222, 1089, 846, 765, 756; Mass [ESI, 70 eV] *m*/*z* (%): 361 (100), 363 (42); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.53 (s, 3H, SCH_3), 5.99 (s, 1H, CH=C), 7.21–7.28 (dd, J = 1.5 Hz, 1H, PhH), 7.35–7.42 (m,3H, PhH), 7.69–7.72 (d, J = 7.5 Hz, 1H, PhH), 7.77–7.80 (d, J = 8.3 Hz, 1H, PhH), 7.82-7.85 (d, J = 8.3 Hz, 2H, PhH), 15.19 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 15.9, 92.1, 121.1, 121.6, 126.3, 128.7, 132.2, 138.1, 151.1, 159.0, 165.7, 185.3; HRMS (ESI) *m*/*z*: Calculated for $C_{17}H_{14}N_2OS_2Cl$: $[M + H]^+$ 361.0225, Found: 361.0236.

*3.1.9. (E)-1-(4-Chlorophenyl)-3-(6-ethoxybenzo[d]thiazol-2-ylamino)-3-(methylthio)prop-2-en-1-one (**3h**)*

IR (KBr υ_{max}/cm^{-1}): 3155, 3093, 2974, 2926, 2879, 2763, 2735, 2663, 2574, 2547, 2295, 1602, 1554, 1506, 1489, 1460, 1433, 1284, 1253, 1224, 1178, 1112, 1085, 1056, 920, 813, 761; Mass [ESI, 70 eV] *m*/*z* (%): 405 (100), 407 (42); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm:

1.42–1.47 (t, 3H, OCH_2CH_3), 2.52 (s, 3H, SCH_3), 4.01–4.08 (q, 2H, CH_3CH_2O), 5.96 (s, 1H, CH═C), 6.93–6.96 (dd, J = 2.2 and 6.0 Hz, 1H, PhH), 7.16–7.17 (d, J = 2.2 Hz, 1H, PhH), 7.39–7.42 (d, J = 8.3 Hz, 2H, PhH), 7.65-7.68 (d, J = 9.0 Hz, 1H, PhH), 7.82–7.84 (d, J = 8.3 Hz, 2H, PhH), 15.16 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 14.8, 15.8, 64.0, 91.6105.0, 115.3, 122.1, 128.6, 128.7, 129.7, 133.4, 137.4, 137.9, 145.3, 146.9, 156.30, 156.37, 156.7, 184.8; HRMS (ESI) m/z: Calculated for $C_{19}H_{18}N_2O_2S_2Cl$: $[M + H]^+$ 405.0495, Found: 405.0498.

3.1.10. (E)-3-(Benzo [d]thiazol-2-ylamino)-1-(4-fluorophenyl)-3-(methylthio)prop-2-en-1-one (**3i**)

IR (KBr υ_{max}/cm^{-1}): 3170, 3122, 3059, 2991, 2924, 2873, 2806, 2748, 2611, 1597, 1566, 1543, 1508, 1494, 1456, 1438, 1427, 1319, 1276, 1247, 1186, 1159, 1072, 864, 823, 771, 725; Mass [ESI, 70 eV] m/z (%): 345 (100), 346 (25) 347 (10); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.53 (s, 3H, SCH_3), 5.98 (s, 1H, CH═C), 7.08–7.13 (t, J = 8.3 Hz, 2H, PhH), 7.21–7.24 (t, J = 3.0 and 7.5 Hz, 1H, PhH), 7.35–7.40 (t, J = 7.5 and 8.3 Hz, 2H, PhH), 7.69–7.71 (d, J = 7.5 Hz, 1H, PhH), 7.77–7.79 (d, J = 7.5 Hz, 1H, PhH), 7.89–7.94 (dd, J = 3.0 and 6.0 Hz, 2H, PhH); ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 15.8, 92.0, 115.5, 115.6, 121.0, 121.5, 124.1, 126.2, 129.6, 129.7, 132.1, 135.2, 151.0, 159.0, 165.2, 163.3, 166.7, 185.2; HRMS (ESI)m/z: Calculated for $C_{17}H_{14}FN_2OS_2$: $[M + H]^+$ 345.0518, Found: 345.0531.

3.1.11. (E)-3-(6-Ethoxybenzo[d]thiazol-2-ylamino)-1-(4-fluorophenyl)-3-(methylthio)prop-2-en-1-one (**3j**)

IR (KBr υ_{max}/cm^{-1}): 3057, 2980, 2926, 2879, 2735, 2598, 1602, 1550, 1498, 1460, 1433, 1298, 1255, 1222, 1165, 821, 599; Mass [ESI, 70 eV] m/z (%): 389 (10), 371 (100), 372 (25), 373 (15); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.42–1.46 (t, 3H, OCH_2CH_3), 2.52 (s, 3H, SCH_3), 4.01–4.08 (q, 2H, CH_3CH_2O), 5.96 (s, 1H, CH═C), 6.92–6.96 (dd, J = 2.2 and 8.3 Hz, 1H, PhH), 7.08–7.14 (t, J = 8.3 and 9.0 Hz, 2H, PhH), 7.16–7.17 (d, J = 2.2 Hz, 1H, PhH), 7.65–7.68 (d, J = 8.3 Hz, 1H, PhH), 7.88–7.93 (m, 2H, PhH), 15.13 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 14.8, 15.7, 64.0, 91.6, 105.1, 115.32, 115.36, 115.6, 122.1, 129.5, 129.6, 135.2, 135.3, 145.2, 156.2, 156.8, 163.2, 165.3, 166.6, 184.9; HRMS (ESI)m/z: Calculated for $C_{19}H_{18}FN_2O_2S_2$: $[M + H]^+$ 389.0778, Found: 389.0793.

3.1.12. (E)-3-(6-Ethoxybenzo[d]thiazol-2-ylamino)-1-(4-methoxyphenyl)-3-(methylthio) prop-2-en-1-one (**3k**)

IR (KBr υ_{max}/cm^{-1}): 2980, 2933, 2891, 2833, 2738, 2692, 1600, 1573, 1556, 1516, 1504, 1462, 1431, 1319, 1301, 1244, 1226, 1170, 1172, 1074, 1022, 840, 812, 769; Mass [ESI, 70 eV] m/z (%): 401 (100), 402 (25), 403 (15), 383 (7); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.41–1.46 (t, 3H, OCH_2CH_3), 2.51 (s, 3H, SCH_3), 3.86(s, 3H, OCH_3), 4.00–4.07 (q, 2H, CH_3CH_2O), 5.98 (s, 1H, CH═C), 6.88–6.95 (dd, J = 2.6 and 9.0 Hz, 3H, PhH), 7.15–7.16 (d, J = 2.6 Hz, 1H, PhH), 7.63–7.66 (d, J = 8.8 Hz, 1H, PhH), 7.85–7.88 (d, J = 8.8 Hz, 2H, PhH), 15.19 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 14.8, 15.7, 55.4, 64.0, 91.7, 105.0, 113.7, 115.1, 121.9, 129.3, 130.6, 131.5, 133.3, 145.3, 156.1, 157.1, 162.5, 164.1, 185.5; HRMS (ESI)m/z: Calculated for $C_{20}H_{21}N_2O_3S_2$: $[M + H]^+$ 401.0975, Found: 401.0993.

3.2. Biology

The pharmacological evaluations of the products were carried out in the pharmacological unit, Institute of Bioinformatics and Biotechnology, (University of Pune, INDIA.)

3.2.1. α-Amylase inhibition assay

Benzothiazole derivatives were employed to check the α-amylase inhibitory activity using the Bernfeld method (1955) with a slight modification in the substrate. The 100 μL of porcine pancreatic α-amylase 50 μg ml^{-1} (O.D. 0.4 at 280 nm) was incubated with 100 μL of samples (1 mg ml^{-1}) at 37 °C for 10 min [22]. 500 μL of starch (1%) was added to initiate the α-amylase activity. α-amylase without any compound was used as control. The DNSA assay was employed to estimate reducing sugar at A540 nm and the enzyme units were expressed as micro-molar per minute. Under the used assay conditions, one unit of enzyme was defined as the amount of enzyme required to liberate 1 μM of maltose. The final inhibition shown by different samples were compared with the standard inhibitor, acarbose [19]. The following formula was used to estimate inhibitory activity:

$$\%\ \text{Inhibition} = (A540_{\text{Control}} - A540_{\text{Test}})/A540_{\text{Control}} \times 100$$

3.2.2. Glucosidase inhibition assay with murine pancreatic, small intestinal and liver extracts

Fromthe National Toxicology Centre, Pune, 10-week-old male Swiss mice weighing 20 g were procured. The entire procedure of activity was carried out following the guidelines of the Institutional Animal Ethical Committee. The obtained Swiss mice from the national toxicology centre, Pune, were starved for 12 h. Pancreas, liver and small intestine tissues were excised and homogenized with 10 mM ice cold phosphate buffer containing 6 mM NaCl (1:10 dilution; w/v) and appropriate amount of protease inhibitors. At 10,000 rpm tissue homogenates were centrifuged for 10 min. After 10 min, the supernatant was taken as a source of enzyme and was diluted so as to get an absorbance of 0.4 (at 280 nm). The assay of enzyme inhibition was carried out as described above. The method employed by Bhat et al. was used to calculate percentage inhibition of the samples against pancreatic, small intestinal and liver glucosidases [23].

3.2.3. α-Glucosidase inhibition assay

Glucosidase inhibition assay of benzothiazole derivatives was carried out as per Sanap et al., 2010 [24]. In brief, 100 μL of α-glucosidase (0.1 unit/ml; Sigma Aldrich, USA) was mixed with each of the samples (200 μL) and incubated for 1 h at 37 °C. Enzyme action for α-glucosidase was initiated by addition of 100 μL of 10 mM *p*-nitrophenyl-α-D-glucopyranoside in 100 mM phosphate buffer of pH 6.8 and stopped by adding 2 mL of 0.1 M Na_2CO_3 after an incubation of 10 min at 37 °C. α-Glucosidase inhibitory activity was determined by measuring absorbance of the *p*-nitrophenol released from *p*NPG at 420 nm using Shimadzu Spectrophotometer UV-1601 using the following formula:

$$\%\ \text{Inhibition} = (A420_{\text{Control}} - A420_{\text{Test}})/A420_{\text{Control}} \times 100$$

4. Conclusion

Thus, in the present study, we have synthesized series of novel (*E*)-3-(Benzo [*d*]thiazol-2-ylamino)phenylprop-2-en-1-one starting from 1-aryl-3,3-bis-(methylsulfanyl)-2-propen-1-ones and 2-aminobenzothiazole and screened as new class of antidiabetic agents. The benzothiazole derivatives **3c**, **3e**, **3f**, **3d** and **3h** showed excellent inhibitory activity against α-amylase. We also found that the derivatives **3b**, **3c**, **3d**, **3f**, **3g** and **3h** are promising glycosidase inhibitors. The results of the present investigation indicate the importance of these novel compounds as potential lead candidates.

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