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Research Article

Synthesis of Azo-Bridged Benzothiazole-Phenyl Ester Derivatives via Steglich Esterification

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Abstract

We synthesized the five compounds of azo bridged ethoxybenzothiazole substituted phenyl ester derivatives by using Dicyclo Hexyl Carbodiimide (DCC) and a catalytic amount of Dimethyl amino pyridine (DMAP) as a nucleophile. All the compounds structures were confirmed by IR, NMR and mass spectrum. The synthesized compounds were screened for antioxidant property by DPPH radical scavenging method. (E)-4-[(6-ethoxy benzothiazol-2-yl) diazenyl] phenyl 2-methyl benzoate (B1) and (E)-4-[(6-ethoxy benzothiazol-2-yl) diazeny]) phenyl 4-fluoro benzoate (B5) showed comparable activities.

Keywords:*Benzothiazole, Esterification, DCC, DMAP, antioxidant, DPPH.*

1. Introduction

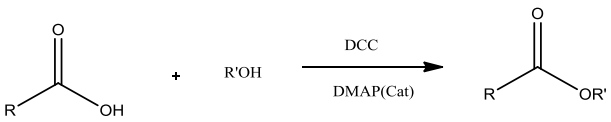
Benzothiazole is one of the most important heterocyclic compounds containing nitrogen and sulpher as hetero atoms, which has received overwhelming response owing to its diversified molecular design and remarkable optical and biological properties (Patel *et al*, 2010). Different substituted benzothiazoles showed antitumor activity, mainly the 2-(4-Amino phenyl) derivatives had in-vitro antitumor activity for a new series of alkyl-, halo-, cyano-, alkoxy- and hydroxy- substituted 2-(4-amino phenyl) benzothiazoles (Bradshaw *et al*, 1998 *;* Choi *et al*, 2006). Some 2- substituted benzothiazoles like 4-(2- substituted benzothiazoles) - 5- mercapto- 3- (substituted)-1, 2, 4-triazole derivatives were examined against *E. coli* and *S. aureus* for antibacterial activity and *Candida albicans*, *Aspergillus nigerfor* antifungal activity. Most of the substituted benzothiazole compounds showed promising results for both the activities (Alang *et al*, 2010; Rajeeva *et al*, 2009). Some of the derivatives of 2- hydrazine benzothiazoles were evaluated for anti-tubercular activity and showed good results (Katz L., 1958).

Antimalarial activity of 2- substituted-6- Nitro and 6-Amino benzothiazoles and their anthranillic acid derivatives were carried on strains of *P. falciparum*. The results showed potency towards the antimalarial activity of clinical and biological properties (Hout *et al*, 2004).

1.1 Introduction to Synthetic work

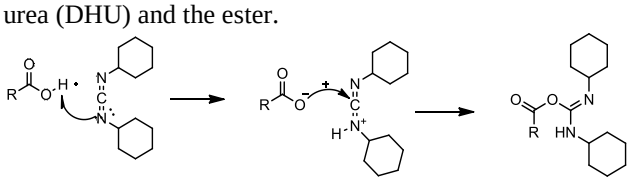
1.1.1 Steglich Esterification

Steglich *et al* in 1978 introduced a new method for esterification. It is a mild reaction, which allows the conversion of sterically hindered complex alcohol and carboxylic acid to esters. Here 0.05 – 0.1 % mole of DMAP was used as catalyst and MDC or DMF was used as a solvent. The reaction mixture was stirred for 5- 10 hrs.

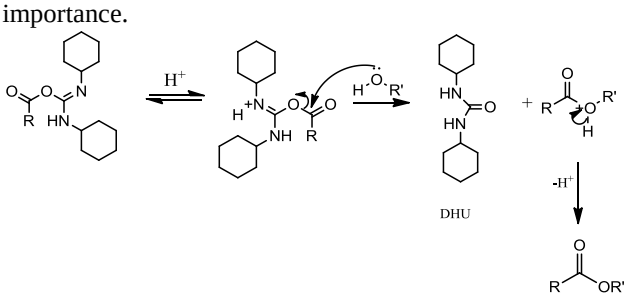


1.1.2Mechanism of the Steglich Esterification

DCC (dicyclo hexyl carbodiimide) and the carboxylic acids are able to form an O-acylisourea intermediate, which offers reactivity similar to the corresponding carboxylic acid anhydride.The alcohol now adds to the activated carboxylic acid to form the stable dicyclo hexyl urea (DHU) and the ester.



In practice, the efficient conversion of acid to esters, the addition of catalytic amount DMAP takes place with more importance.



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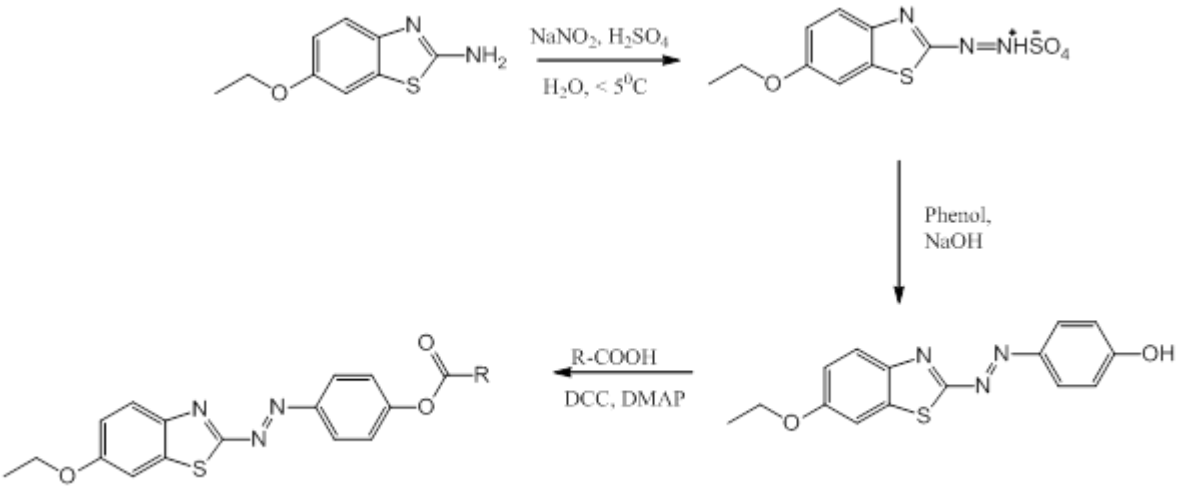


Scheme 1. synthesis of benzothiazole ester Derivatives

DMAP is stronger nucleophile than the alcohol, so it accelerates the reaction rate and act as an acyl transfer reagent, subsequent reactions with alcohol gives the ester (Christian *et al*., 2005).

2 Material and Methods

The raw materials were purchased from Sigma Aldrich and Alfa Asera, all the glass wares were rinsed with acetone and dried in hot air oven. 100 mL two necked round bottomed flasks were used for synthesis. Melting points were determined by open capillary method and were uncorrected. The monitoring of reaction was carried out by Thin Layer Chromatography (TLC), using aluminium plate, coated with silica, obtained from Merck, by using appropriate solvent mixtures. Elemental analysis was performed on Thermo Finningan FLASHEA1112CHN analyzer. The IR spectra (KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. NMR spectra were recorded on a Agilent 400 MHz instruments using TMS as internal standard. Mass spectra were recorded on LC– MS-Aglilent 1100 series with MSD (Ion trap) using 0.1 % aqueous TFA in acetonitrile system on C18-BDS column for 5 min. duration. Ionization mode was EI for all the compounds.

3 Experimental Procedures

3.1 Reaction scheme
Synthetic method is as shown in scheme 1.

3.1.1. Synthesis of (E)-4-[(6-ethoxy benzothiazol-2-yl) diazenyl] phenol

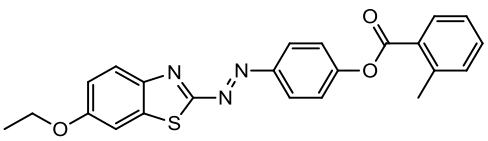
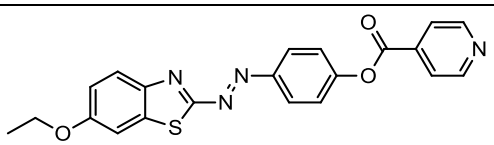
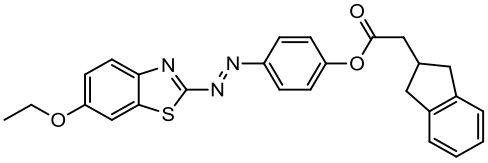
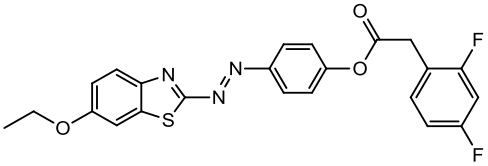
2-Amino-6-ethoxy benzothiazole (2.0 g, 0.0128 mol) was dissolved in sulphuric acid (50 %, 20 mL), the resulting mixture was cooled to 0 ^{0}C. Sodium nitrite (1.06 g, 0.0153 mol) in 15 mL of water was added drop-wise to the cold mixture, and stirred for 1hr at the same temperature. Phenol (0.9 mL, 0.0121 mol) was cooled to 0 ^{0}C and to that diazotized salt solution was added drop-wise, maintain the temperature below 5 ^{o}C, the mixture was stirred for 1hr (Prajapati *et al.,* 2006). The pH was increased by 7-8 by adding aqueous 5 % NaOH solution and stirred for 1 hr. The reaction mixture was diluted with water, the precipitate was collected by filtration and dried.

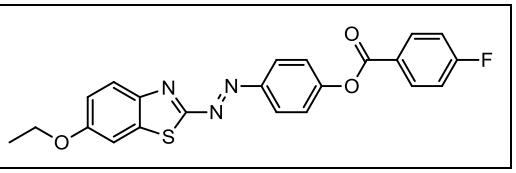
Yield (2.0 g, 67 %) and MP 286-287 ^{0}C

FT-IR (cm^{-1}): 3300 (-OH), 3030 (C-H, aromatic), 1605 (C=N), 1578 (C-C, aromatic), 1458 (N=N), 1379 (C-N), 1296 (C-O), 1234, 1194, 1139, 1060 (benzothiazole), 898, 645 (C-S-C).

^{1}H NMR (500 MHz, $CDCl_3$), δ 8.03-7.98 (q, 3H), 7.30-7.29 (d, *J* = 2.0 Hz, 1H), 7.12-7.09 (q, 1H), 7.00-6.98 (d, *J* = 9.5 Hz, 2H), 4.15-4.11 (q, 2H), 1.49-1.46 (t, 3H).

Table 1 List of compounds synthesized along with structures

Comp Id	Structure
B1	
B2	
B3	
B4	

B5	

3.1.2 General procedure for the synthesis of Benzothiazole ester

A mixture of substituted carboxylic acid (1.2 mol) and DCC (1.2 mol) in MDC (10 mL) was cooled to 0 ^{0}C, to that (E)-4-[(6-ethoxy benzothiazol-2-yl) diazenyl] phenol (1.0 mol) and DMAP (0.6 mol) was added, the resulting suspension stirred for 10 hrs. The completion of the reaction was confirmed by TLC. After completion of the reaction, it was filtered and filtrate was quenched to water and extracted with MDC. The organic layer was washed with 10 % aqueous sodium bicarbonate solution and brine solution, dried over sodium sulphate and evaporated to dryness to get crude material. The crude material was purified by column chromatography using silica gel (60-120 mesh) and pet ether and ethyl acetate as a solvents.

3.1.3 Synthesis of (E)-4-[(6-ethoxy benzothiazol-2-yl) diazenyl] phenyl 2-methyl benzoate (B1)

A mixture of 2-methyl benzoic acid (0.19 g, 0.0014 mol) and DCC (0.28 g, 0.0014 mol) in MDC (10 mL) were cooled to 0 ^{0}C, to that, (E)-4-[(6-ethoxy benzothiazol-2-yl) diazenyl] phenol (0.35g, 0.0016 mol) and DMAP (0.085 g, 0.0007 mol) were added, the resulting suspension was stirred for 10 hrs. The completion of the reaction was confirmed by TLC. After completion of the reaction, it was quenched to water (10 mL) and extracted with MDC (2×10 mL). The organic layer was washed with 10 % aqueous sodium bicarbonate solution (10 mL) and brine solution (10 mL), dried over sodium sulphate and evaporated to dryness, to get crude material. The crude material was purified by column chromatography using silica gel (60-120 mesh) and using 10 % ethyl acetate in pet ether as eluent, evaporated the eluent to get pure material as orange solid (0.2 g, 78 %).
Melting point: 140-141 ^{0}C

FT-IR (cm^{-1}): 2950 (C-H), 1750 (-C=O), 1620 (-C=N), 1570 (C-H aromatic), 1450 (N=N), 1210 (C-N), 1075 (C-O-C), 1139, 1060 (benzothiazole), 890, 645 (C-S-C).

^{1}H NMR (500 MHz, $CDCl_3$), δ 8.19-8.17 (d, *J* = 11.0 Hz, 1H), 8.17-8.14 (m, 2H), 8.08-8.06 (d, *J* = 9.0 Hz, 1H),7.54-7.53 (q, 1H), 7.513-7.51(d, *J* =1.0 Hz, 2H), 7.46-7.38 (m, 2H), 7.38-7.32 (m, 1H), 7.15-7.13 (q, 1H), 4.16-4.14 (m, 2H), 2.71 (s, 3H), 1.51-1.48 (t, 3H).

^{13}C NMR (400 MHz, $CDCl_3$), δ 175.9, 165.2, 158.5, 149.4, 144.3, 140.0, 136.7, 133.8, 132.6, 130.5, 129.2, 126.7, 124.7, 122.3, 120.5, 114.9, 106.1, 64.2, 21.8, 14.8.
LCMS: Experimentally found *m/z* 418.1 for [M^++1] peak and calculated for $C_{23}H_{19}N_3O_3S$, 417.11, elemental analysis for $C_{23}H_{19}N_3O_3S$, calculated C, 66.17; H, 4.59; N, 10.07 % and found C, 66.14; H, 4.56; N, 10.15 %.

3.1.4 Synthesis of (E)-4-[(6-ethoxy benzothiazol-2-yl) diazenyl] phenyl isonicotinate (B2)

A mixture of isonicotinic acid (0.04 g, 0.00033 mol) and DCC (0.102 g, 0.00049 mol) in MDC (10 mL) were cooled to 0 ^{0}C, to that, (E)-4-[(6-ethoxy benzothiazol-2-yl) diazenyl] phenol (0.1 g, 0.00033 mol) and DMAP (0.020 g, 0.0001 mol) were added, the resulting suspension was stirred for 10 hrs. The completion of the reaction was confirmed by TLC. After completion of the reaction, it was filtered and quenched to water (10 mL) and extracted with MDC (2×10 mL). The organic layer was washed with 10 % aqueous sodium bicarbonate solution (10 mL) and brine solution (10 mL), dried over sodium sulphate and evaporated to dryness to get crude material. The crude material was purified by recrystallisation with ethanol, the red color needle shape crystals were filtered and dried & weighed (0.38 g, 92 %) to get title compound.
Melting point: 180-182 ^{0}C

FT-IR (cm^{-1}): 2980 (C-H), 1800 (C=O), 1630 (C=N), 1550 (C-H Aromatic), 1450 (N=N), 1280 (C-N), 1150, 1060 (benzothiazole), 885, 640 (C-S-C).

^{1}H NMR (400 MHz, $CDCl_3$), δ 8.91-8.89 (d, *J* = 6.0 Hz, 2H), 8.17-8.15 (d, *J* = 8.8 Hz, 2H), 8.08-8.06 (d, *J* = 8.8 Hz, 2H), 8.04-8.03 (d, *J* = 5.6 Hz, 2H), 7.47-7.45 (d, *J* = 8.8 Hz, 2H), 7.32-7.31 (d, *J* = 2.4 Hz, 1H), 7.16-7.12 (dd, *J* = 2.4 Hz), 4.16-4.13 (m, 2H), 1.58-1.47 (t, 3H).

^{13}C NMR (400 MHz, $CDCl_3$), δ 172.6, 167.3, 154.2, 150.6, 149.4, 140.6, 138.9, 136.2, 130.5, 127.2, 124.7, 123.1, 122.3, 115.4, 106.2, 64.6, 15.1.

LCMS: Experimentally found *m/z* 405.3 for [M^++1] peak, calculated for $C_{21}H_{16}N_4O_3S$ 404.09, elemental analysis for $C_{26}H_{23}N_3O_3S$, calculated C, 62.36; H, 3.99; N, 13.85 % and found C, 62.38; H, 4.01; N, 13.89%

3.1.5 Synthesis of (E)-4-[(6-ethoxy benzothiazol-2-yl) diazenyl] phenyl 2-(2, 3-dihydro-1H-inden-2-yl) acetate (B3)

A mixture of 2-(2,3-dihydro-1H-indane-2-yl) acetic acid (0.26 g, 0.0015 mol) and DCC (0.276 g, 0.00134 mol) in MDC (10 mL) was cooled to 0 ^{0}C, to that (E)-4-[(6-ethoxy benzothiazol-2-yl) diazenyl] phenol (0.4g, 0.00134 mol) and DMAP (0.164 g, 0.00134 mol) were added and the resulting suspension was stirred for 10 hrs. The completion of the reaction was confirmed by TLC. After completion of the reaction, it was filtered and filtrate was quenched with water (20 mL) and extracted with MDC (2×20 mL). The organic layer was washed with 10 % aqueous sodium bicarbonate solution (20 mL) and brine solution (15 mL), dried over sodium sulphate and evaporated to dryness to get crude material. The crude material was purified by column chromatography using silica gel (60:120 mesh) and 5 % Ethyl acetate in pet ether as solvent system. The solvent was evaporated and recrystallized from ethanol. The red color needle shape crystals were filtered and dried & weighed (0.32 g, 55 %) to get title compound.

Melting point: 160-161 ^{0}C

FT-IR (cm^{-1}): 2960 (C-H), 1775 (C=O), 1580 (C=N), 1510 (C-H aromatic), 1470 (N=N), 1150 (C-N), 820 (C-F), 1170, 1050 (benzothiazole), 895, 650 (C-S-C).

^{1}H NMR (400 MHz, $CDCl_3$), δ 8.05-8.03 (m, 3H), 7.35-7.28 (m, 4H), 7.13-7.10 (dd, *J* = 2.4, 2.4 Hz, 1H), 6.93-6.87 (m, 2H), 4.16-4.10 (q, 2H), 3.93 (s, 2H), 1.49-1.46 (t, 3H).

^{13}C NMR (400 MHz, $CDCl_3$), δ 173.1, 168.4, 159.1, 154.1, 149.4, 147.4, 136.4, 132.2, 132.1, 132.06, 132.0, 125.9, 125.3, 122.4, 116.9, 111.7, 111.6, 111.5, 111.0, 104.8, 104.4, 104.1, 64.17, 34.2, 34.1, 14.7.

LCMS: Experimentally found *m/z* 458.1for [M$^+$+1] peak and calculated for $C_{26}H_{23}N_3O_3S$ 457.15, elemental analysis for $C_{26}H_{23}N_3O_3S$, calculated C, 68.25; H, 5.07; N, 9.18; O, 10.49; S, 7.01 % found C, 68.23; H, 5.08; N, 9.21 %

3.1.6 Synthesis of (E)-4-[(6-ethoxy benzothiazol-2-yl) diazenyl] phenyl 2-(2, 4-difluoro phenyl) acetate (B4)

A mixture of 2-(2,4-difluoro phenyl) acetic acid (0.057 g, 0.00034 mol) and DCC (0.103 g, 0.0005 mol) in MDC (10 mL) was cooled to 0 ^{0}C, to that (E)-4-[(6-ethoxy benzothiazol-2-yl) diazenyl] phenol (0.1g, 0.0003 mol) and DMAP (0.020 g, 0.00016 mol) were added, the resulting suspension was stirred for 10 hrs. The completion of the reaction was confirmed by TLC. After completion of the reaction, it was filtered and filtrate was quenched with water (10 mL) and extracted with MDC (2×10 mL). The combined organic layer was washed with 10 % aqueous sodium bicarbonate solution (10 mL) and brine solution (10 mL), dried over sodium sulphate and evaporated to dryness to get crude material. The crude material was purified with column chromatography by using silica gel (60:120 mesh) and 8 % Ethyl acetate in pet ether as solvent system. The solvent was evaporated and recrystallized from chloroform. The red color needle shape crystals were filtered and dried & weighed (0.125 g, 80 %) to get title compound.

Melting point: 141-142 ^{0}C

FT-IR (cm^{-1}): 2975 (C-H), 1780 (-C=O), 1610 (C=N), 1530 (C-H Aromatic), 1475 (N=N), 1200 (C-N), 1155, 1070 (benzothiazole), 910, 660 (C-S-C).

^{1}H NMR (400 MHz, $CDCl_3$), δ 8.10-8.03 (q, 3H), 7.31-7.26 (m, 3H), 7.25-7.23 (m, 2H), 7.19-7.16 (m, 2H), 7.14-7.11 (m, 1H), 4.17-4.11 (q, 2H), 3.28-3.22 (q, 2H), 3.05-3.02 (t, 1H), 2.81-2.75 (m, 4H), 1.50-1.47 (t, 3H), 7.31-7.26 (m,3H).
^{13}C NMR (400 MHz, $CDCl_3$), δ 173.3, 170.9, 159.3, 154.4, 149.5, 147.5, 142.5, 136.5, 126.6, 126.0, 125.5, 124.7, 122.7, 117.2, 105.0, 64.3, 40.19, 39.1, 36.2, 14.9.
LCMS: Experimentally found *m/z* 454.0 for [M$^+$+1] peak and calculated for $C_{23}H_{17}F_2N_3O_3S$ 453.10, elemental analysis for $C_{23}H_{17}F_2N_3O_3S$, calculated C, 60.92; H, 3.78; N, 9.27 % found C, 60.90; H, 3.79; N, 9.25 %.

3.1.7 Synthesis of (E)-4-[(6-ethoxy benzothiazol-2-yl) diazeny]) phenyl 4-fluoro benzoate (B5)

A mixture of p-fluoro benzoic acid (0.095 g, 0.00068 mol) and DCC (0.15 g, 0.00073 mol) in MDC (10 mL) was cooled to 0 ^{0}C, to that (E)-4-[(6-ethoxy benzothiazol-2-yl) diazenyl] phenol (0.2 g, 0.00068 mol) and DMAP (0.061 g, 0.00054 mol) were added, the resulting suspension was stirred for 10 hrs. The completion of the reaction was confirmed by TLC. After completion of the reaction, it was filtered and filtrate was quenched with water (10 mL) and extracted with MDC (2×10 mL). The organic layer was washed with 10 % aqueous sodium bicarbonate solution (10 mL) and brine solution (10 mL), dried over sodium sulphate and evaporated to dryness to get crude material. The crude material was purified by recrystallisation from ethanol, the red color needle shape crystal was filtered and dried & weighed (0.2 g, 71 %) to get title compound.

Melting point: 167-168 ^{0}C

FT-IR (KBr cm^{-1}): 2940 (C-H), 1770 (-C=O), 1590 (C=N), 1560 (C-H Aromatic), 1455 (N=N), 1220 (C-N), 1155, 1070 (benzothiazole), 910, 660 (C-S-C), 850 (C-F).

^{1}H NMR (400 MHz, $CDCl_3$), δ 8.01-7.99 (t, *J* = 4.0, 8.2 Hz, 1H), 8.08-8.06 (d, *J* = 8.8 Hz, 2H), 7.45-7.43 (d, *J* = 7.2 Hz, 2H), 7.30-7.29 (d, *J* = 2.0 Hz, 1H), 7.12-7.09 (q, 1H), 7.32-7.30 (d, *J* = 7.6 Hz, 2H), 7.00-6.98 (d, *J* = 9.5 Hz, 2H), 4.15-4.11 (q, 2H), 1.49-1.46 (t, *J* =7.0, 14.0, 3H).
^{13}C NMR (400 MHz, $CDCl_3$), δ 16 7.4, 164.2, 162.6, 155.2, 150.6, 143.6, 136.8, 133.5, 130.2, 131.3, 126.3, 125.9, 124.6, 116.8, 115.7, 107.4, 65.1, 14.8.

LCMS: Experimentally found *m/z* 421.9 for [M$^+$+1] peak and calculated for $C_{23}H_{19}N_3O_3S$ 421.09, elemental analysis for $C_{22}H_{16}FN_3O_3S$, calculated C, 62.70; H, 3.83; N, 9.97 % found C, 62.73; H, 3.85; N, 10.10 %

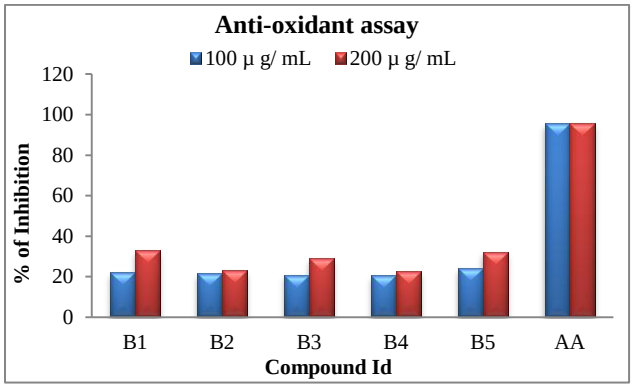
3.2 Antioxidant Assay

3.2.1 Free radical scavenging ability by DPPH radical assay (1, 1-diphenyl-2-picryl hydrazyl)

DPPH radical scavenging activity of purified compound was determined (Raj *et al*.,2013) for 200 µg/mL and 100 µg/mL concentrations of test sample in an aliquot of 100 µL were mixed with 100 µL of 40 µM methanolic solution of DPPH (Himedia, Mumbai, India) in a 96-well micro titer plate. The decrease in absorbance at 517 nm was recorded after the incubation for 15 min. at room temperature. The absorbance of the DPPH solution without sample was used as the control. The Ascorbic Acid (AA, Himedia, Mumbai) was used as a standard to compare the activity. Appropriate blank readings at 517 nm were recorded for each tested dilutions. The assay was carried out in triplicate. The percentage inhibition of the DPPH radical by the samples was calculated according to the formula and it is shown in the graph 1.

Percentage of inhibition = $[(A_C - A_S)/A_C)] \times 100$

where A_C is the absorbance of the control and A_S is the absorbance of the sample/standard at 15 min.



Graph 1 Antioxidant oxidant activity of the synthesized compounds

4. Result and Discussions

The synthesis of heterocyclic esters by Steglichesterfication reaction was monitored by TLC and it was confirmed by recording the Melting of the solid and IR spectrum. Then, it was characterized through the LCMS, ^{1}H NMR and ^{13}C NMR spectrum. Presence of ethoxy and methyl groups in synthesized compounds, were suspected to have antioxidant activity. So, synthesized compounds were screened for antioxidant activity by DPPH radical scavenging method and percentage of absorbance of DPPH radical scavenging was studied for 200 µg/mL and 100 µg/mL, in which B1 and B5 compounds had comparable activity.

Conclusions

Synthesis of esters from bulky phenol group and substituted carboxylic acid were achieved by Steglich esterification method. The antioxidant study reveals that, benzothiazoles containing methyl and fluoro substitutions on ester phenyl groups show comparable results.

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