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SYNTHESIS OF NOVEL CHLORO-3-ETHOXYBENZYL-PIPERIDIN-4-AMINO BENZO[*d*] OXAZOLE-5-SULPHANAMIDE

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Abstract: Novel 2-(1-(chloro-3-ethoxybenzyl)piperidin-4-amino)benzo[d]oxazole-5-sulphan amide **(10)** prepared from 1-(4-chloro-3-ethoxybenzyl)piperidin-4-amine **(6)** and 2-(methyl thio) benzo[d]oxazole-5-sulphanamide **(9).** The intermediates were prepared by simple and efficient methods in good yields. All structures of the newly synthesized compounds were confirmed by IR, NMR, mass spectral studies and elemental analysis.

Keywords: Benzoxazoles, piperidine, 4-chloro-3-hydroxybenzoic, Thiophosgene

INTRODUCTION

Benzoxazoles have found broad applications in medicinal chemistry and pharmacology, material chemistry, organometallic and coordination chemistry. Benzoxazoles are found in a variety of natural products [I] and are important targets in drug discovery [II]. Recent observations suggest that substituted benzoxazoles and related heterocycles, possess potential activity with lower toxicities in the chemotherapeutic approach in human beings [III, IV]. Literature survey revealed that targets containing benzoxazole moiety, either isolated from plants or accessed by total synthesis, have remarkable biological activities [V] such as antimicrobial [VI], antihistaminic [VII], antiparasitics [VIII], herbicidal [IX], antiviral [X], antiallergic [XI]. Also, much attention has been paid to benzoxazoles because they have a number of optical applications such as photoluminescents [XII], whitening agents [XIII] and in dye lasers [XIV]. They are also used as intermediates for several therapeutic materials [XV, XVI]. Many naturally occurring piperidine compounds have been experimentally proved excellent antibacterial agents [XVII] as like black pepper (*Piper nigrum Longum*), the main source of piperidine, showed 75% bactericidal inhibition against different generas of bacteria obtained from oral cavity [XVIII, XIX]. Various derivatives of piperidine molecule are used as antimicrobial agents [XX, XXI], some of the molecules like Bamipine and Diphenylpyraline, both containing piperidine ring shows strong H_1-receptor antagonistic activity [XXII] and urease inhibition activity [XXIII].

We therefore synthesized the compound 2-(-1-(chloro-3-ethoxybenzyl) piperidin-4-ylamino) benzo*[d]*oxazole-5-sulphanamide in this 3-ethoxy-4-chlorobenzylpiperidine moiety was

connected to the 5-substituted benzo[*d*]oxazole moiety at its 2-position, to combine different pharmacophores on one scaffold **(Figure-1)**.

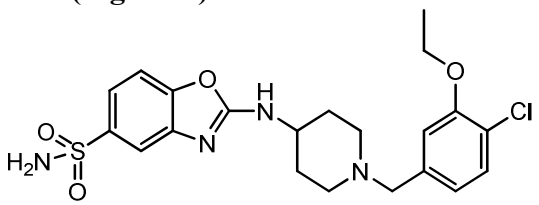


Figure-1

EXPERIMENTAL SECTION

General methods: Melting points were recorded on a Stuart SMP30 melting point apparatus and were uncorrected. Column chromatography was performed using silica–gel (100–200 mesh size) purchased from Thomas Baker, and thin layer chromatography (TLC) was carried out using aluminium sheets pre-coated with silica gel 60F254 purchased from Merck. IR spectra (KBr) were obtained using a PerkinElmer Spectrum100 FTIR Spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker WM-400 spectrometer in DMSO-d6 with TMS as an internal standard. Mass spectra (ESI) were carried out on a JEOL SX-102 spectrometer. CHN analysis was done by Carlo Erba EA 1108 automatic elemental analyzer. The chemicals and solvents used were of commercial grade and were used without further purification unless otherwise stated.

Synthesis of ethyl-4-chloro-3-ethoxybenzoate 2:

To a solution of compound 4-chloro-3-hydroxybenzoic acid **1** (10g, 57.94 mmol) in anhydrous DMF (50 mL) was added K_2CO_3 (16.01g, 155.89 mmol), then stirred for 10 minutes and added the Ethyl Iodide (36.13g, 231.76 mmol). Stirred for overnight at room temperature, the reaction was monitored by TLC, after completion of the reaction concentrated under *vacuo* obtained crude which was dissolved in DCM and filtered. The DCM layer was concentrated on rota evaporation to get compound **2**.

Yield: 75.0%; IR (KBr, cm^{-1}): 775, 1252, 1738, 3196 and 2998. ^{1}H NMR (DMSO-d$_6$, 400 MHz): ð 1.30-1.39 (sex, 6H, 2XCH$_3$), 4.15-4.21 (q, 2H, -CH$_2$), 4.29–4.34 (q, 2H, -CH$_2$), 7.51-7.59 (m, 3H, Ar-H) ppm. ^{13}C NMR (DMSO-d$_6$, 100 MHz): ð 14.8, 15.2, 61.2, 64.5, 116.4, 129.2, 129.4, 132.4, 134.0, 154.2, 166.7 ppm. ESI–MS (m/z): 229 (M+1). Anal. Calcd for $C_{11}H_{13}ClO_3$: C, 57.78; H, 5.73; Found: C, 57.72; H, 5.69.

Synthesis of (4-chloro -3- ethoxyphenyl) methanol 3:

Compound ethyl-4-chloro-3-ethoxybenzoate **2** (43.85 mmol) was dissolved in THF (235 mL) and cooled to 0°C, then added the 2M solution of LAH (3.32g, 87.71 mmol) in THF slowly for 30 minutes, then quenched with saturated ammonium chloride solution and extracted with ethylacetate, dried with anhydrous sodium sulfate, concentrated under vacum to get compound **3**.

Yield: 89%; IR (KBr, cm^{-1}): 778, 1254, 3340, 3198 and 3012. ^{1}H NMR (DMSO-d$_6$, 400 MHz): ð 1.42-1.43 (t, 3H, -CH$_3$), 4.06-4.12 (q, 2H, -CH$_2$), 4.34–4.47 (q, 2H, -CH$_2$), 6.86-6.90 (dd, 1H,Ar-H), 7.06-7.09 (dd, 1H, Ar-H), 7.32-7.34 (m, 1H, Ar-H) ppm. ^{13}C NMR (DMSO-d$_6$, 100 MHz): ð 15.4, 64.2, 116.9, 128.9, 132.0, 132.4, 152.4, 153.9 ppm. ESI–MS (m/z): 187 (M+1). Anal. Calcd for $C_9H_{11}ClO_2$: C, 57.92; H, 5.94; Found: C, 57.87; H, 5.91.

Synthesis of 4-chloro-3-ethoxybenzaldehyde 4:

Compound (4-chloro-3-ethoxyphenyl) methanol **3** (9g, 48.38 mmol) was dissolved in DCM (216 mL) and added the TEMPO (755mg,4.83 mmol) and BAIB (15.57g, 48.38 mmol) at ambient temperature then stirred for 6 h at ambient temperature, after completion of reaction, washed with 0.1M solution of sodiumthiosulfate, then separated the organic layer and concentrated on rot evaporation to get crude, then purified by column chromatography with neutral Alumina.(5% E A+ Hexane) to get the corresponding compound **4**.

Yield: 89.8%; IR (KBr, cm^{-1}): 778, 1248, 1695, 3194 and 3010. ^{1}H NMR (DMSO-d_6, 400 MHz): ð 1.35-1.40 (t, 3H, -CH_3), 4.19-4.24 (q, 2H, -CH_2), 7.67-7.74 (m, 3H, Ar-H), 9.97 (s, 1H, -CHO) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): ð 15.2, 62.9, 114.9, 122.8, 129.4, 132.4, 139.4, 152.6 ppm. ESI–MS (m/z): 185 (M+1). Anal. Calcd for $C_9H_9ClO_2$: C, 58.55; H, 4.91; Found: C, 58.50; H, 4.89.

Synthesis of tertiary butyl-1-(4-chloro-3-ethoxybenzyl)piperidin-4-ylcarbamate 5:

A mixture of 4-chloro-3-ethoxybenzaldehyde **4** and tert-butyl piperidin-4-ylcarbamate was dissolved in DCM cooled to 0°C and added acetic acid then allowed to room temperature and stirred for 1 h at this temperature. Then sodium triacetoxy borohydride was added, stirred for 16 h at ambient temperature washed with saturated sodium bicarbonate solution and the organic layer was removed under vacuo to give the corresponding compound **5**.

Yield: 56.3%; IR (KBr, cm^{-1}): 775, 1250, 1672, 3342, 3197 and 3017. ^{1}H NMR (DMSO-d_6, 400 MHz): ð 1.03(s, 9H,-$(CH_3)_3$), 1.32-1.39 (t, 2H,-CH_2), 1.53-1.58 (t, 2H,-CH_2), 1.84-1.87 (t,2H,-CH_2), 2.55-2.83 (t,2H,-CH_2), 3.46 (m, 1H,-CH), 4.05-4.10 (m, 4H, -CH_2), 6.83-7.33 (m, 3H, Ar-H), 8.07 (s, 1H, -NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): ð 15.6, 29.8, 31.2, 50.2, 52.5, 64.4, 65.8, 80.2, 115.4, 122.9, 123.4, 132.2, 139.4, 153.9, 156.5 ppm. ESI–MS (m/z): 369 (M+1). Anal. Calcd for $C_{19}H_{29}ClN_2O_3$: C, 61.86; H, 7.92; N, 7.59, Found: C, 61.80; H, 7.89; N, 7.55.

Synthesis of 1-(4-chloro-3-ethoxybenzyl) piperidin-4-amine 6:

To a solution of compound **5** (24.39 mmol) in trifluroacetic acid (TFA) (9 mL) and stirred for 4 h at ambient temperature, then concentrated on rota evaporation, then washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and concentrated on rota evaporation to give compound **6**.

Yield: 92%; IR (KBr, cm^{-1}): 775, 1256, 3074, 3195 and 3328, ^{1}H NMR (DMSO-d_6, 400 MHz): ð 1.37-1.41 (t, 2H,-CH_2), 1.58-1.62 (t, 2H,-CH_2), 1.84-1.88 (t,2H,-CH_2), 2.53-2.80 (t,2H,-CH_2), 3.48 (m, 1H,-CH), 4.12-4.15 (m, 4H, -CH_2), 6.85-7.38 (m, 3H, Ar-H), 8.22 (s, 1H, -NH_2) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): ð 15.2, 33.2, 48.2, 52.4, 65.2, 66.6, 115.9, 122.4, 123.1, 132.9, 139.8, 152.4 ppm. ESI–MS (m/z): 267 (M+1). Anal. Calcd for $C_{14}H_{21}ClN_2O$: C, 62.56; H, 7.88; N, 10.42, Found: C, 62.52; H, 7.81; N, 10.39.

Synthesis of 2-mercaptobenzo[d]oxazole-5-sulphanamide 8:

A solution of compound 3-amino-4-hydroxybenzensulfonamide **7** (46.16 mmol) in anhydrous THF (500 mL) was added slowly Thiophosgene (6.31 g, 54.93 mmol) at room temperature for 1h, then stirred at ambient temperature for 6 h. Then the reaction mixture was quenched with saturated ammonium chloride solution and extract with ethylacetate, dried with anhydrous Na_2SO_4 and concentrated by evaporation under reduced pressure to give compound **8**.

Yield: 97%; IR (KBr, cm^{-1}): 1172, 1353, 2580, 3072, 3194 and 3428. ^{1}H NMR (DMSO-d_6, 400 MHz): ð 7.16-7.33 (m, 3H, Ar-H), 14.18 (s, 1H,-SH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): ð 111.9, 118.6, 122.8, 133.2, 142.7, 156.2, 181.6 ppm. ESI–MS (m/z): 230 (M+1). Anal. Calcd for $C_7H_6N_2O_3S_2$: C, 36.51; H, 2.63; N, 12.17, Found: C, 36.49; H, 2.58; N, 12.12.

Synthesis of 2-(methylthio)benzo[d]oxazole-5-sulphanamide 9:

To a stirred solution of compound **8** (31.2 mmol) in anhydrous DMF (85 mL) was added K_2CO_3 (8.64 g, 62.5 mmol), and methyl iodide (3.10 g, 21.8 mmol), then stirred for 4 h at ambient temperature, filtered the solid and concentrated on rota evaporation to get crude. The crude filtered through neutral alumina to get pure compound **9.**

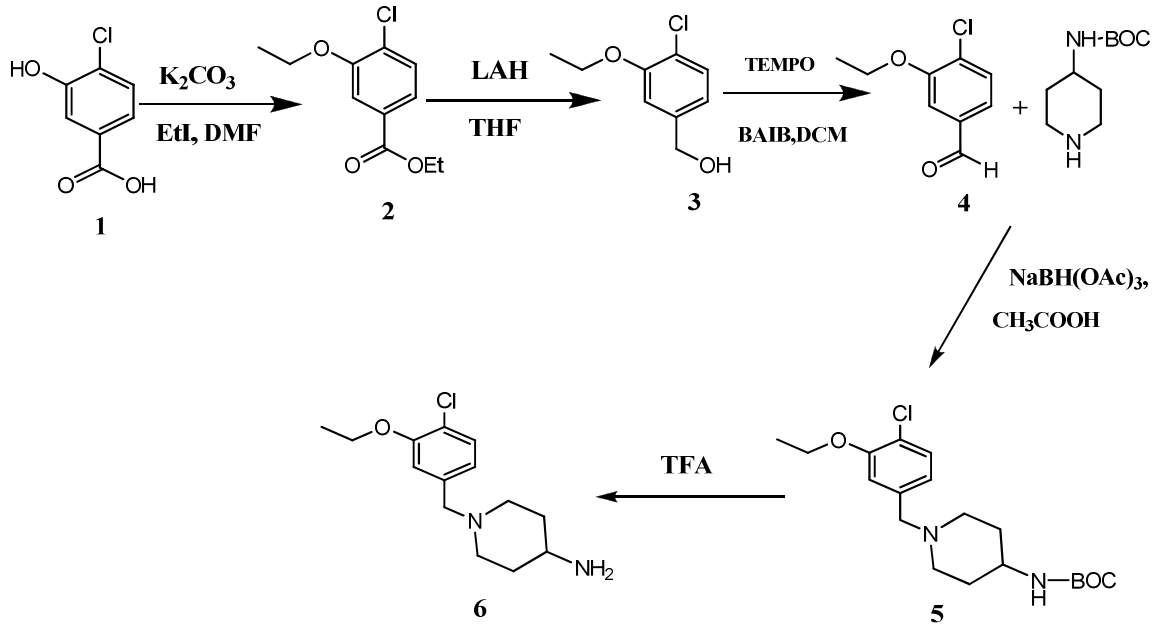
Yield: 39.0%; IR (KBr, cm^{-1}): 1170, 1358, 3076, 3199, 3272 and 3430 ^{1}H NMR (DMSO-d_6, 400 MHz): ð 2.72-2.88 (s, 3H,-SCH_3), 7.87-8.02 (m, 3H, Ar-H), 8.08 (s, 2H,-NH_2) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): ð 111.9, 118.6, 122.8, 133.2, 142.7, 156.2, 181.6 ppm. ESI–MS (m/z): 245(M+1). Anal. Calcd for $C_8H_8N_2O_3S_2$: C, 39.33; H, 3.30; N, 11.47, Found: C, 39.31; H, 3.28; N, 11.42.

Synthesis of 2-(-1-(chloro-3-ethoxybenzyl)-piperidin-4-ylamino)benzo*[d]*oxazole-5-sulphanamide 10:

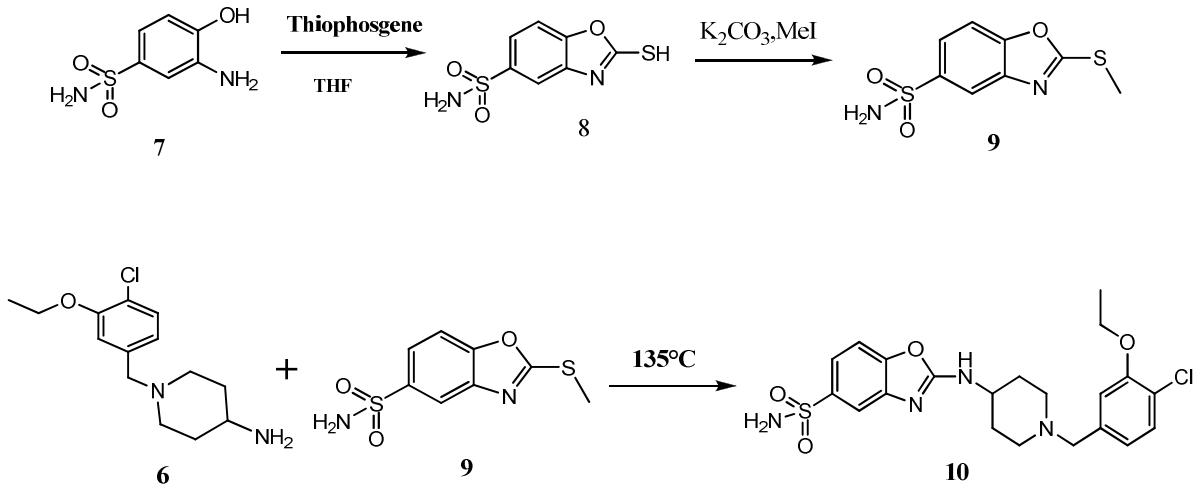
A mixture of compounds 2-(methylthio)benzo[d]oxazole-5-sulphanamide **9** (2 g, 8.19 mmol) and compound 1-(4-chloro-3-ethoxybenzyl) piperidin-4-amine **6** (2.64 g, 9.82 mmol) was in sealed tube and heated to 135°C for 24 h, then cooled to room temperature, dissolved in ethyl acetate and concentrated by evaporation under reduced pressure and the crude material was purified with column chromatography on neutral alumina eluting with a gradient of 2% methanol in ethyl acetate providing the title compound.

Yield: 55%; IR (KBr, cm^{-1}): 1177, 1352, 3079, 3196, 3280 and 3428. ^{1}H NMR (DMSO-d_6,400 MHz): ð 1.29-1.35 (t, 3H,-CH_3), 1.52-1.60 (m, 2H,-CH_2), 1.95-1.96 (t,2H,-CH_2), 2.05-2.11 (t,2H,-CH_2), 2.78-2.81(m, 2H,-CH_2), 3.46-3.49 (t, 2H,-OCH_2), 3.58-3.59 (m, 1H,-CH), 4.08-4.13 (t, 2H, -CH_2), 7.20-7.29 (m, 2H, Ar-H), 7.32-7.35 (m,1H, Ar-H), 7.45-7.50 (m, 2H, Ar-H), 8.21-8.23 (m, 1H, -NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): ð 15.9, 31.2, 52.4, 53.9, 57.2, 65.7, 66.2, 111.8, 118.7, 122.4, 122.7, 123.2, 132.6, 137.9, 139.2, 142.6, 152.4, 152.7, 163.2 ppm. ESI–MS (m/z): 465 (M+1). Anal. Calcd for $C_{21}H_{25}ClN_4O_4S$: C, 54.25; H, 5.42; N, 12.05, Found: C, 54.21; H, 5.37; N, 11.98.

Scheme-1:



Scheme-2:



RESULTS AND DISCUSSION

A convenient method for the synthesis of 2-(-1-(chloro-3-ethoxybenzyl)-piperidin-4-ylamino)benzo*[d]*oxazole-5-sulphanamide **10 i**s shown in **Scheme-1 & 2.** The compound 1-(4-chloro-3-ethoxybenzyl) piperidin-4-amine **6** was synthesized by condensation of 4-chloro-3-ethoxybenzaldehyde **4** and tert-butyl piperidin-4-ylcarbamate under Sodium Triacetoxy Borohydride ($NaBH(OAc)_3$) in acetic acid. The compound 2-(methylthio)benzo[d]oxazole-5-sulphanamide **9** prepared from 3-amino-4-hydroxybenzensulfonamide **7** by treated with thiophosgene than followed by reacted with methyl iodide. The title compound **10** was prepared from condensation of compounds 1-(4-chloro-3-ethoxybenzyl) piperidin-4-amine **6** and 2-(methylthio)benzo[d]oxazole-5-sulphanamide **9** by heated at 135^0 C in sealed tube. The synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis.

CONCLUSIONS

In conclusion, we have developed a simple and efficient method for the synthesis of a novel 2-(-1-(chloro-3-ethoxybenzyl)-piperidin-4-ylamino)benzo[d]oxazole-5-sulphanamide from 1-(4-chloro-3-ethoxybenzyl) piperidin-4-amine and 2-(methylthio)benzo[d]oxazole-5-sulphanamide in good yields. Further research and applications of the reactions are in progress in our laboratories. We believe that this method is highly useful for the synthesis of biologically potent highly substituted benzoxazole derivatives.

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