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EFFICIENT SYNTHESIS OF 6-(4-HYDROXY-1-ALKYL-1*H*-BENZO[*d*]IMIDAZOL-6-YL) PYRIMIDINE-2,4(1*H*, 3*H*)-DIONES

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A convenient synthesis of 6-(4-hydroxy-1-alkyl-1*H*-benzo[*d*]imidazol-6-yl) pyrimidine-2,4(1*H*, 3*H*)-diones **7** was achieved through a seven-step procedure starting from 5-bromo-1,3-difluoro-2-nitrobenzene. The structures of compounds **1-7** are assigned on the basis of their elemental analysis and spectral (IR, ^{1}H NMR and MS) data.

KEYWORDS: pyrimidine and imidazole,

INTRODUCTION

The nitrogen containing heterocyclic systems are very interesting because of their physico-chemical properties with relevance to the design of new drugs of pharmaceutical importance. Synthetic compounds which contain pyrimidine skeleton such as imatinib, zidovudine and trimethoprim are important drugs used as anticancer, antiviral and antibiotic (chart 1) agents. The pyrimidine derivatives are also have been found to exhibit a wide range of pharmacological activities, such as anticancer[1], anti-bacterial[2], anti-inflammatory[3], antiproliferative[4], anti-cancer[5], leishmanicidal[6], antifungal[7],anti-convulsant[8], cycotoxic[9], anti-tubercular[10], anti-oxidant[11]and diuretic[12] activities. These compounds are also used as hypnotic drugs for the nervous system[13], calcium-sensing receptor antagonists [14] and antagonists of the human A2A adenosine receptor [15].

Imidazole derivatives have attracted considerable attention owing to their effective biological activity and extensive use[16-20]. Palladium catalyzed organic transformations are the traditional methods to assemble these compounds for the formation of carbon-carbon bonds.

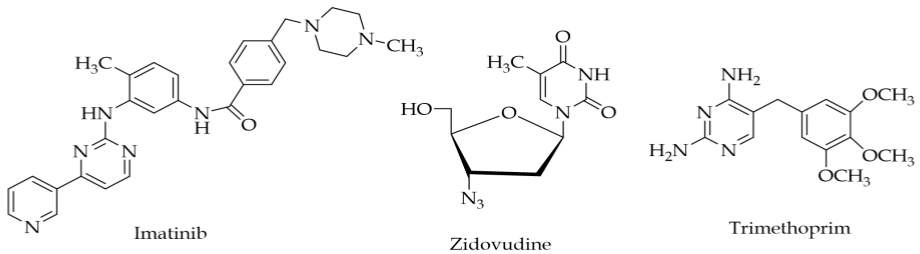

Chart 1: Chemical structures of imatinib, zidovudine and trimethoprim

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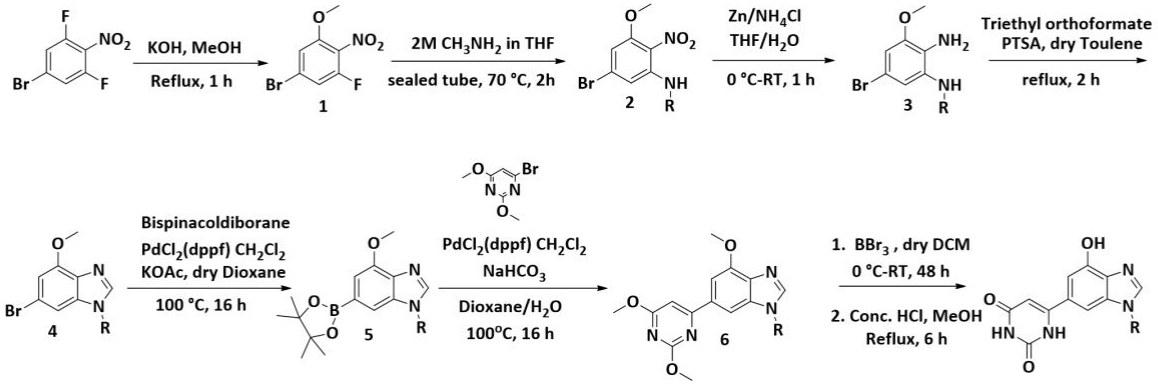
Substituted pyrimidines are already well established as key cores in medicinal chemistry, along with that the sulfonamides have lot of biological significance and in connection with present search on the design and synthesis of substituted pyrimidines linked to imidazole in a single molecular frame work. It was envisaged that these two active pharmacophores, if linked together, would generate novel molecular templates which are likely to exhibit interesting biological properties. The increasing incidence of bacterial and fungal resistance to a large number of antimicrobial agents has prompted studies on the development of new potential antimicrobial compounds. An attempt was made to synthesize novel 6-(4-hydroxy-1-alkyl-1*H*-benzo[*d*]imidazol-6-yl) pyrimidine-2,4(1*H*, 3*H*)-diones **7.**



R=	-CH_3	-CH_2CH_3

Scheme-I

MATERIALS AND METHODS:

Melting points were determined using a Cintex melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed by using Merck silica gel 60 F254 precoated plates (0.25 mm) and column chromatography was performed by using Silica gel (particle size 100-200 mesh). IR spectra (KBr) were recorded on a Perkin-Elmer BX series FTIR spectrometer. ^{1}H NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer. Mass spectra were determined on Agilent LC-1100 (LC-MS) series instrument. Elemental analyses were performed on a Carlo Erba 106 and Perkin Elmer model 240 analyzers. All the chemicals and reagents used in present investigation were purchased from Sigma Aldrich Chemical Company.

SYNTHESIS AND CHARACTERIZATION

Synthesis of 5-Bromo-1-fluoro-3-methoxy-2-nitrobenzene 1: To a stirred solution of 5-bromo-1, 3-difluoro-2-nitrobenzene (3 g, 12.60 mmol) in MeOH (30 mL) was added KOH (635 mg, 11.34 mmol) and stirred the reaction mixture at reflux temperature for 1 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT; the solvent was concentrated under reduced pressure. The obtained residue was dissolved in

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water (30 mL), extracted with DCM (3x20 mL). The combined organic layer was washed with brine (20 mL), dried over *anhydrous* sodium sulphate and concentrated under reduced pressure. The crude compound was purified by column chromatography (silica gel 230-240 mesh, eluted with pet ether) to afford 5-bromo-1-fluoro-3-methoxy-2-nitrobenzene **1** as off white solid (2.7 g, 85.7% yield).

The structures of the products **1-7** have been elucidated on the basis of IR, ^{1}H NMR, and MS spectral data. Elemental analyses were satisfactory and confirm elemental composition and purity of newly synthesized compounds **1-7.**

5-Bromo-1-fluoro-3-methoxy-2-nitrobenzene 1: IR (KBr) $_{max}$ (cm^{-1}): 3035, 2928, 2855, 1668, 1591, 1556, 1454, 1394, 1351, 1239, 1168, 1131, 1101,908; ^{1}H NMR (400 MHz, DMSO-d_6): 7.57 (dd, J = 9.4, 1.8 Hz, 1H), 7.50 (br-s, 1H), 3.96 (s, 3H); LC-MS: *m/z* 248.6 $(M+H)^+$. Anal. Calcd for $C_7H_5BrFNO_3$: C 33.63%, H 2.02%, N 5.60%. Found: C 33.75%, H 2.04%, N 5.63%.

Synthesis of 5-Bromo-3-methoxy-*N*-alkyl-2-nitroaniline 2: To a stirred solution of 5-bromo-1-fluoro-3-methoxy-2-nitrobenzene (1.2 g, 4.8 mmol) in THF (10 mL) was added 2M Methylamine in THF (9.6 mL, 19.2 mmol) and stirred the reaction mixture in a seal tube at 70 °C temperature for 2 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT, solvent was concentrated under reduced pressure to afford 5-bromo-3-methoxy-*N*-alkyl-2-nitroanilines **2.**

5-Bromo-3-methoxy-*N*-methyl-2-nitroaniline 2a: Yellow solid, 96% yield; IR (KBr) $_{max}$ (cm^{-1}): 3357, 3321, 3254, 3030, 2922, 1658, 1593, 1557, 1454, 1394, 1351, 1239, 1135, 1114, 941; ^{1}H NMR (400 MHz, DMSO-d_6): 6.60 (d, J = 1.8 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 6.48 (m, 1H), 3.81 (s, 3H), 2.72 (d, J = 4.7 Hz, 3H); LC-MS: *m/z* 259.85 $(M+H)^+$. Anal. Calcd for $C_8H_9BrN_2O_3$: C 36.80%, H 3.47%, N 10.73%. Found: C 36.91%, H 3.48%, N 10.75%.

5-Bromo-3-methoxy-*N*-ethyl-2-nitroaniline 2b: Yellow solid, 92% yield; IR (KBr) $_{max}$ (cm^{-1}): 3384, 3354, 3241, 3034, 2933, 1641, 1595, 1567, 1452, 1354, 1323, 1241, 1142, 1111, 932; ^{1}H NMR (400 MHz, DMSO-d_6): 6.51 (d, J = 1.8 Hz, 1H), 6.54 (d, J = 1.8 Hz, 1H), 6.42 (m, 1H), 3.31 (q, 2H), 2.40 (t, 3H), 2.70 (d, J = 4.7 Hz, 3H); LC-MS: *m/z* 274.0 $(M+H)^+$. Anal. Calcd for $C_9H_{11}BrN_2O_3$: C 39.29%, H 4.03%, N 10.18%. Found: C 39.35%, H 4.05%, N 10.19%.

Synthesis of 5-Bromo-3-methoxy-N^1- alkylbenzene-1, 2-diamine 3: To a stirred solution of 5-bromo-3-methoxy-N-methyl-2-nitroaniline (1.2 g, 4.59 mmol) in THF/H_2O (30 mL, 2:1 v/v) was added Zn dust (3 g, 45.97 mmol), NH_4Cl (1.2 g, 22.98 mmol) at 0 °C and stirred the reaction mixture at RT for 1 h. The progress of the reaction was monitored by TLC. The reaction mixture was filtered through a pad of celite, celite pad washed with

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EtOAc (20 mL), combined organic layer was washed with water (20 mL), and aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layer was dried over *anhydrous* sodium sulphate and concentrated under reduced pressure. The crude compound was purified by column chromatography (silica gel 230-400 mesh, eluted with 15% EtOAc in Pet ether) to afford 5-bromo-3-methoxy-N1-alkylbenzene-1, 2-diamines **3.**

5-Bromo-3-methoxy-*N*^{1}-methylbenzene-1,2-diamine 3a: Brown solid, 85% yield; IR (KBr) $_{max}$ (cm^{-1}): 3009, 2951, 1667, 1595, 1550, 1451, 1114, 930; ^{1}H NMR (400 MHz, DMSO-d_6): 6.43 (d, J = 2.1 Hz, 1H), 6.22 (d, J = 2.0 Hz, 1H), 4.93 (br-s, 1H), 4.12 (s, 2H), 3.72 (s, 3H), 2.68 (d, J = 3.7 Hz, 3H); LC-MS: *m/z* 230.02 $(M+H)^+$. Anal. Calcd for $C_8H_{11}BrN_2O$: C 41.58%, H 4.80%, N 12.12%. Found: C 41.63%, H 4.82%, N 12.15%.

5-Bromo-3-methoxy-*N*^{1}-ethylbenzene-1,2-diamine 3b: Brown solid, 80% yield; IR (KBr) $_{max}$ (cm^{-1}):3021, 2954, 1669, 1590, 1552, 1457, 1117, 938; ^{1}H NMR (400 MHz, DMSO-d_6): 6.47 (d, J = 2.1 Hz, 1H), 6.21 (d, J = 2.0 Hz, 1H), 4.95 (br-s, 1H), 4.08 (s, 2H), 3.41 (q, 2H), 2.43(t, 3H), 2.70 (d, J = 3.7 Hz, 3H); LC-MS: *m/z* 244.02 $(M+H)^+$. Anal. Calcd for $C_9H_{13}BrN_2O$: C 44.10%, H 5.35%, N 11.43%. Found: C 44.25%, H 5.37%, N 11.46%.

Synthesis of 6-Bromo-4-methoxy-1-alkyl-1*H*-benzo[d]imidazole 4: To a stirred solution of 5-bromo-3-methoxy-N1-methylbenzene-1, 2-diamine (900 mg, 3.89 mmol) in Toluene (15 mL) was added Triethyl orthoformate (634 mg, 4.28 mmol), PTSA (50 mg, catalytic amount) and stirred the reaction mixture at reflux temperature for 2 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT; the solvent was concentrated under reduced pressure. The obtained residue was dissolved in water (20 mL), extracted with EtOAc (3x20 mL). The combined organic layer was washed with brine (10 mL), dried over *anhydrous* sodium sulphate and concentrated under reduced pressure. The crude compound was purified by column chromatography (silica gel 230-240 mesh, eluted with 2% MeOH in DCM) to afford 6-bromo-4-methoxy-1-alkyl-1*H*-benzo[d]imidazoles **4.**

6-Bromo-4-methoxy-1-methyl-1*H*-benzo[d]imidazole 4a: White solid, 85% yield; IR (KBr) $_{max}$ (cm^{-1}): 2972, 2874, 1670, 1581, 1553, 1463, 1351 1140, 1131; ^{1}H NMR (400 MHz, DMSO-d_6): 8.07 (s, 1H), 7.42 (d, J = 1.8 Hz, 1H), 6.85 (d, J = 1.8 Hz, 1H), 3.93 (s, 3H), 3.77 (s, 3H); LC-MS: *m/z* 239.90 $(M+H)^+$. Anal. Calcd for $C_9H_9BrN_2O$: C 44.84%, H 3.76%, N 11.62%. Found: C 44.96%, H 3.77%, N 11.66%.

6-Bromo-4-methoxy-1-ethyl-1*H*-benzo[d]imidazole 4b: White solid, 82% yield; IR (KBr) $_{max}$ (cm^{-1}): 2998, 2881, 1677, 1556, 1545, 1460, 1370, 1140, 1134; ^{1}H NMR (400 MHz, DMSO-d_6): 8.09 (s, 1H), 7.40 (d, J = 1.8 Hz, 1H), 6.87 (d, J = 1.8 Hz, 1H), 3.77 (s, 3H); 3.71(q, 2H), 2.57(t, 3H); LC-MS: *m/z* 254.10 $(M+H)^+$. Anal. Calcd for $C_{10}H_{11}BrN_2O$: C 47.08%, H 4.35%, N 10.98%. Found: C 47.25%, H 4.37%, N 10.97%.

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Synthesis of 4-Methoxy-1-alkyl -6-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1*z*-benzo[d]imidazole 5: To a stirred solution of 6-bromo-4-methoxy-1-methyl-1H-benzo[d]imidazole (800 mg, 3.31 mmol) in Dioxane (15 mL) was added Bis (pina-colato)diborane (843 mg, 3.31 mmol), Potassium acetate (976 mg, 9.95 mmol) and the reaction mixture was degassed with Argon gas. After 10 min $PdCl_2$ (dppf) CH_2Cl_2 (135 mg, 0.16 mmol, Catalyst) was added and stirred the reaction mixture at 100 °C for 16 h. The reaction mixture was cooled to RT; filtered through a pad of celite with EtOAc (30 mL); organic layer was washed with water (20 mL). Aqueous layer was extracted with EtOAc (2x 20 mL).The combined organic layer was dried over *anhydrous* sodium sulphate and concentrated under reduced pressure. The crude compound was purified by column chromatography (Florisil silica gel 60-100 mesh, eluted with 1-2% MeOH in DCM) to afford 4-methoxy-1-alkyl-6-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1H-benzo[d]imidazoles **5.**

4-Methoxy-1-methyl-6-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1*H*-benzo[d]imidazole 5a: Pale yellow, 52% yield; IR (KBr) $_{max}$ (cm^{-1}): 2968, 2903, 2889, 1657, 1586, 1557, 1470, 1352, 1151, 1131; ^{1}H NMR (400 MHz, DMSO-d_6): 8.11 (s, 1H), 7.47 (s, 1H), 6.93 (s, 1H), 3.93 (s, 3H), 3.83 (s, 3H), 1.31 (s, 12H); LC-MS: *m/z* 274.02 $(M+H)^+$. Anal. Calcd for $C_{14}H_{18}BrN_2O_3$: C 55.81%, H 3.90%, N 21.70%. Found: C 55.93%, H 3.91%, N 21.74%.

4-Methoxy-1-ethyl-6-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1*H*-benzo[d]imidazole 5b: Pale yellow, 61% yield; IR (KBr) $_{max}$ (cm^{-1}): 2974, 2908, 2854, 1654, 1588, 1561, 1475, 1354, 1131; ^{1}H NMR (400 MHz, DMSO-d_6): 8.12 (s, 1H), 7.42 (s, 1H), 6.97 (s, 1H), 3.93 (s, 3H), 3.77(q, 2H), 2.67(t, 3H), 1.34 (s, 12H); LC-MS: *m/z* 302.12 $(M+H)^+$. Anal. Calcd for $C_{16}H_{23}BrN_2O_3$: C 63.60%, H 7.67%, N 9.27%. Found: C 63.68%, H 7.68%, N 9.29%.

Synthesis of 6-(2, 6-Dimethoxypyrimidin-4-yl)-4-methoxy-1-alkyl-1*H*-benzo[d]imidazole 6: To a stirred solution of 4-methoxy-1-methyl-6-(4, 4, 5, 5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole (500 mg, 1.73 mmol), 4-bromo-2, 6-dimethoxypyrimidine (456 mg, 2.08 mmol) in Dioxane/water (10 mL, 4:1 v/v) was added $NaHCO_3$ (292 mg, 3.47 mmol) and the reaction mixture was degassed with Argon gas. After 10 min $PdCl_2$ (dppf) CH_2Cl_2 (71 mg, 0.08 mmol, catalyst) was added and stirred the reaction mixture at 100 °C for 16 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT; the catalyst was filtered through a pad of celite with EtOAc (30 mL); organic layer was washed with water (20 mL). Aqueous layer was extracted with EtOAc (2x 20 mL).The combined organic layer was dried over *anhydrous* sodium sulphate and concentrated under reduced pressure. The crude compound was purified by column chromatography (silica gel 230-400 mesh, eluted with 1-2% MeOH in DCM) to afford 6-(2,6-dimethoxypyrimidin-4-yl)-4-methoxy-1-alkyl-1H-benzo[d]imidazoles **6.**

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6-(2,6-Dimethoxypyrimidin-4-yl)-4-methoxy-1-methyl-1*H*-benzo[d]imidazole 6a: Yellow liquid, 80.5% yield; IR (KBr) $_{max}$ (cm^{-1}): 2951, 1663, 1574, 1555, 1475, 1367, 1142, 1112; ^{1}H NMR (400 MHz, DMSO-d_6): 8.43 (s, 1H), 8.09 (s, 1H), 7.28 (d, J = 1.3 Hz, 1H), 6.85 (d, J = 1.3 Hz, 1H), 4.00-3.90 (m, 9H), 3.81 (s, 3H); LC-MS: *m/z* 301.0 $(M+H)^+$. Anal. Calcd for $C_{15}H_{16}N_4O_3$: C 59.99%, H 5.37%, N 8.66%. Found: C 60.07%, H 5.39%, N 8.71%

6-(2,6-Dimethoxypyrimidin-4-yl)-4-methoxy-1-ethyl-1*H*-benzo[d]imidazole 6b: Yellow liquid, 84% yield; IR (KBr) $_{max}$ (cm^{-1}): 2971, 1674, 1571, 1545, 1474, 1377, 1154, 1142; ^{1}H NMR (400 MHz, DMSO-d_6): 8.47 (s, 1H), 8.04 (s, 1H), 7.28 (d, J = 1.3 Hz, 1H), 6.87 (d, J = 1.3 Hz, 1H), 4.02-3.92 (m, 9H), 3.71(q, 2H), 2.61(t, 3H) ; LC-MS: *m/z* 315.10 $(M+H)^+$. Anal. Calcd for $C_{16}H_{18}N_4O_3$: C 61.13%, H 5.77%, N 17.82%. Found: C 61.28%, H 5.79%, N 17.87%.

Synthesis of 6-(4-Hydroxy-1-alkyl-1H-benzo[d]imidazol-6-yl) pyrimidine-2, 4(1*H*, 3*H*)-Dione 7:

To a stirred solution of 6-(2, 6-dimethoxypyrimidin-4-yl)-4-methoxy-1-methyl-1H-benzo[d]imidazole (200 mg, 0.66 mmol) in dry DCM (10 mL) was added BBr_3 (0.3 mL, 3.33 mmol)at 0 °C and stirred the reaction mixture at RT for 48 h. The progress of the reaction was monitored by LCMS. The reaction mixture was concentrated under reduced pressure. The residue was washed with diethyl ether (3x10 mL) and dried under vacuum to afford 6-(6-hydroxy-2-methoxypyrimidin-4-yl)-1-alkyl-1H-benzo[d]imidazol-4-oles as crude brown solid. This crude compound (140 mg, 0.51 mmol) in MeOH (5 mL) was added Conc. HCl (5 mL) at RT and stirred the reaction mixture at reflux temperature for 6 h. The progress of the reaction was monitored by LCMS. The reaction mixture was cooled to RT and concentrated under reduced pressure. The obtained solid was purified by prep HPLC to afford 6-(4-hydroxy-1-alkyl-1H-benzo[d]imidazol-6-yl) pyrimidine-2, 4(1*H*, 3*H*)-Diones **7**.

6-(4-Hydroxy-1-methyl-1*H*-benzo[*d*]imidazol-6-yl) pyrimidine-2, 4(1*H*, 3*H*)-Dione 7a: White solid, 66% yield; IR (KBr) $_{max}$ (cm^{-1}): 3385, 3452, 2964, 1671, 1558, 1541, 1487, 1374, 1147, 1118; ^{1}H NMR (400 MHz, DMSO-d_6): 11.33 (s, 1H, D_2O exchangeable), 11.28 (d, J = 5.6 Hz, 1H, D_2O exchangeable), 10.86 (br-s, 1H, D_2O exchangeable), 9.15 (s, 1H), 7.70 (d, J = 5.9 Hz, 1H), 7.42 (s, 1H), 7.18 (s, 1H), 3.95 (s, 3H); LC-MS: *m/z* 259.07 $(M+H)^+$. Anal. Calcd for $C_{12}H_{10}N_4O_3$: C 55.81%, H 3.90%, N 21.70%. Found: C 55.93%, H 3.92%, N 21.74%.

6-(4-Hydroxy-1-ethyl-1*H*-benzo[*d*]imidazol-6-yl) pyrimidine-2, 4(1*H*, 3*H*)-Dione 7b: White solid, 66% yield; IR (KBr) $_{max}$ (cm^{-1}): 3365, 3445, 2974, 1665, 1545, 1542, 1484, 1375, 1142, 1123; ^{1}H NMR (400 MHz, DMSO-d_6): 11.37 (s, 1H, D_2O exchangeable), 11.24 (d, J = 5.6 Hz, 1H, D_2O exchangeable), 10.82 (br-s, 1H, D_2O exchangeable), 9.11 (s, 1H), 7.72 (d, J = 5.9 Hz, 1H), 7.45 (s, 1H), 7.20 (s, 1H), 3.82(q, 2H), 2.74(t, 3H);

LC-MS: *m/z* 273.05 $(M+H)^+$. Anal. Calcd for $C_{13}H_{12}N_4O_3$: C 57.35%, H 4.44%, N 20.58%. Found: C 57.48%, H 4.46%, N 20.55%.

CONCLUSION

In conclusion, we have synthesized a novel series of derivatives **7**. All the synthesized compounds were characterized by IR, ^{1}H NMR, and mass spectrometry analysis. The advantages of this protocol include a simple reaction set-up not requiring specialized equipment, non-toxicity of the reagents, mild reaction conditions and high product yields with excellent purity.

CONFLICT OF INTEREST:

The authors declare no conflict of interest, financial or otherwise.

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