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SYNTHESIS OF A NOVEL SERIES OF BIOACTIVE BENZIMIDAZOLE AND BENZOTHIAZOLE AMIDES

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ABSTRACT: A series of substituted benzothiazole and benzimidazole amides (**7a-h**) has been synthesized through the reaction of 2-amino benzothiazole and /benzimidazoles with substituted pyridine acid chloride derivatives in good yields. All the synthesized compounds were characterized by ^{1}H NMR, Mass, IR and CHN analysis.

Keywords: 2-Aminobenzothiazoles; 2-aminobenzimidazoles; bioactive compounds.

INTRODUCTION

Developing countries are mostly affected by health problems due to microbial infections. Further, emergence of bacterial resistance to large number of antibacterial agents such as glycopeptides, sulfonamides, β-lactams, nitroimidazoles, quinolones, tetracyclins, chloramphenicol and macrolides is becoming a major concern. Therefore, the demand for developing novel and potent antibacterial agents remains an attractive field in current research. For last few decades, continuous efforts have been carried out on the structural modifications on the existing scaffolds for the identification of novels antibacterial agents. On the basis of the above development of new hetero moieties, our group and other various research groups are intensively involved in antimicrobial research in finding biologically active pharmacophores by combining different heterocyclic core moieties.

Aminobenzothiazoles are interesting class of heterocyclic compounds possessing a variety of biological properties including antibacterial and antifungal [i-iii], anti-HIV [iv, v], hypertension [vi], anticancer [vii], anti-inflammatory [viii], anti-convulsant [ix], antiinflammation [x] and antidepressant activities [xi, xii]. In the past few years, these ring systems have attracted much interest for the development of potent antibacterial agents either by the structural modification of this scaffold or by developing hybrid compounds. On the other hand, benzimidazoles also display diverse biological activities such as antibacaterial, antifungal and anticancer etc. During past few years various attempts have been made for the developments of benzimidzoles with remarkable pharmacological potentialities. In last few years it was reported that benzothiazole, its bioisosters and derivatives had antimicrobial activities against Gram-negative, Gram-positive bacteria (e.g., *Enterobacter*, *Pseudomonas*

aeruginosa, *E. coli*, and *Staphylococcus epidermidis* etc.) and the yeast (e.g., *Candida albicans*) [xvi]. Furthermore, sulfur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds. Therefore, various benzothiazole compounds are of considerable interest for their diverse pharmaceutical uses and play a vital role in the synthesis of fused heterocyclic systems.

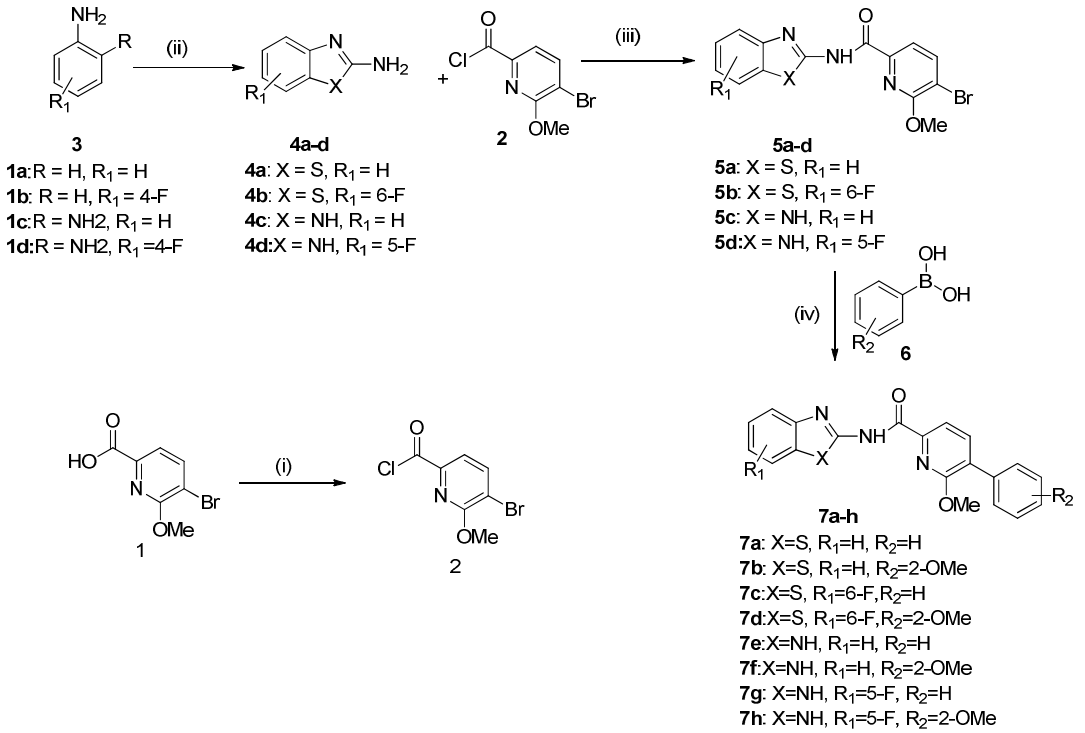
In view of the above findings and in continuation to our previous work to develop new heterocyclic bioactive compound, we herein report the synthesis of benzothiazole and benzimidazole derivatives which are expected to have antibacterial and antifungal properties.

RESULTS AND DISCUSSION

Chemistry

The preparation of 2-amino benzothiazoles (**4a-b**) was carried out by the action of ammonium thiocyanate and bromine on substituted anilines (**3**) to afford substituted 2-aminobenzothiazoles (**4a-b**) as reported in the literature [xiii] (Scheme1). Similarly, 2-amino benzimidazoles (**4c-d**) were synthesized by the reaction of Benzene-1, 2-diamine (**3**) with cyanogens bromide. Compounds (**4a-d)** were coupled with (**2)** coming from acid **(1)** using triethylamine to afford (**5a-d)** finally, compounds (**5a-d)** were reacted with aryl boronic acids (**6)** using Suzuki reaction [xiv, xv] to accomplish the final targets **(7a-h)**.

Scheme 1



Reaction and condition: Scheme 1 (i) CO_2Cl_2, DCM, DMF, RT, 1h; (ii) Ammonium thiocyanate, Br_2, DCM, RT, 16h (for **4a-b**) and (iia) cyanogen bromide, acetonitrile/water, 0^oC-RT,16h (for **4c-d**); (iii) TEA, DCM,0^oC,30 min; (iv) $Pd(PPh_3)_4$, K_2CO_3,Toluene:EtOH:H_2O,16 h,110^oC.

CONCLUSION

In summary, we have reported the synthesis of novel 6-methoxy-5-phenyl-pyridine-2-carboxylic acid benzothiazol-2-ylamide derivatives (**7a-h**) with moderate to good yields. The synthesis of these novel series of compounds involves various synthetic steps which are straightforward. All the compounds are expected to show antimicrobial properties and may emerge as a valuable lead series with great potential to be used as antibacterial and antifungal agents, and as promising candidates for their efficacy evaluation.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

EXPERIMENTAL SECTION

Materials and Methods

All reagents and solvents were used as purchased without further purification. Crude products were purified by column chromatography on silica gel of 60–120 mesh. NMR spectra were recorded on a Varian 400 MHz and 500 MHz spectrometer for ^{1}H NMR. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

Chemistry

Synthesis of 2-amino benzothiazole (4a-b)

To a mixture of aniline **3** (2.0 g, 0.021 mol), ammonium thiocyanate (6.5 g, 0.086 mol), bromine (2.2 mL, 0.043 mol) in DCM (20 mL), stirred for 16 h at room temperature. After completion of the reaction, water was added to the reaction mixture and the product was extracted in DCM (3x50 mL). The solvent was evaporated under vacuum to afford the crude product and purified by column chromatography using a gradient of hexane–EtOAc (3:7-4:6) to give compounds (**4a-b)**.

2-Amino-benzothiazole (**4a)**

Off-white solid; yield : 75%, mp: 126-128 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 6.98-7.00 (m, 1H, Ar-H), 7.18-7.20 (m, 1H, Ar-H), 7.32-7.34 (m, 1H, Ar-H), 7.40-7.42 (s, 2H, NH_2),7.60-7.62 (m, 1H, Ar-H); MS: m/z (%) 150.8 [M^+], UPLC purity (99.89%).

2-Amino-6-fluoro-benzothiazole (**4b)**

Yellow solid; yield : 78%, mp: 145-147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.22 (s, 2H, NH_2),7.02-7.04 (m, 1H, Ar-H), 7.32 (m, 1H, Ar-H), 7.44-7.48 (m, 1H, Ar-H); MS: m/z (%) 168.8 [M^+], UPLC purity (99.23%).

Synthesis of 2-amino benzimidazole (4c)

To a stirred solution of Benzene-1,2-diamine **3** (2.85 g, 0.026 mol) in acetonitrile (20 mL) and water (4 mL) at 0 ^{o}C, was added cyanogen bromide (6.45 mL, 0.032 mol), the reaction mixture was stirred for 16 h at room temperature. After completion of the reaction, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100mL) and shaken the resulting solid was filtered off, was washed with water and dried under reduced pressure to gave compound (**4c-d)**.

2-Amino-benzimidazole (**4c)**

Off-white solid; yield : 72%, mp: 229- 231°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.58-4.60 (broad s, 2H, NH_2) 7.08-7.10 (m, 2H, Ar-H), 7.32-7.34 (m, 2H, Ar-H), 10.60-10.65 (broad s, 1H, NH); MS: m/z (%) 133.85 (M+ACN], HPLC purity (99.98%).

2-Amino-5-fluoro-benzimidazole (4d)

Yellow solid; yield : 78%, mp: 232-234 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.54-4.56 (broad s, 2H, NH_2) 7.10-7.12 (m, 1H, Ar-H), 7.32-7.34 (m, 2H, Ar-H), 10.62-10.66 (broad s, 1H, NH);MS: m/z (%) 151.84 [M^+], UPLC purity (99.05%).

Synthesis of N-(benzo[d]thiazol-2-yl)-5-bromo-6-methoxypicolinamide and N-(1H-benzo[d]imidazol-2-yl)-5-bromo-6-methoxypicolinamide (5)

To a solution of **5-bromo-6-methoxy picolinic acid 1** (325 mg, 0.00140 mol) in DCM (6 ml), cooled to 0 ^{0}C, was added oxalyl chloride (0.180 mL, 0.00210 mol) and DMF (0.1 mL) the mixture was stirred for 1h at room temperature. The solvents were evaporated under vacuum to afford the (335 mg) of crude product **2** (yellow solid), A solution of compound **4** (200 mg, 0.0013 mol) in DCM (8 mL), cooled to 0^{o}C, was added TEA (0.561 mL, 0.004 mol) followed by crude compound **2** (333 mg, 0.0013 mol) in DCM (2 mL) and the mixture was stirred for 30 min at 0^{0}C, rection was quenched with sat $NaHCO_3$sol (20mL), extracted with ethyl acetate,washed with brine solution(20mL), dried over Na_2SO_4, concentrated under reduced pressure and which was further purified by column chromatography using Hexane–EtOAc (8:2–6:4) to obtained compound **5**.

N-(Benzo[d]thiazol-2-yl)-5-bromo-6-methoxypicolinamide (5a)

Off-white solid; yield: 66%, mp: 190-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.20 (s, 3H, OCH_3),7.37-7.39 (m, 1H, Ar-H), 7.42-7.44 (m, 1H, Ar-H), 7.80-7.84 (m, 3H, Ar-H), 8.06-8.08 (m, 1H, Ar-H),10.76-10.78 (s, 1H, NH); MS: m/z (%) 365.8 [M^{+2}], UPLC purity (98.61%).

5-Bromo -N-(6-fluorobenzo[d]thiazol-2-yl)-6-methoxypicolinamide (5b)

Pale yellow solid; yield: 63%, mp: 186-188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.18 (s, 3H, OCH_3), 7.18-7.20 (m, 1H, Ar-H), 7.56-7.58 (m, 1H, Ar-H), 7.78-7.82 (m, 2H, Ar-H), 8.06-8.08 (m, 1H, Ar-H), 10.70 (s, 1H, NH); MS: m/z (%) 383.9[M^{+2}], UPLC purity (95.10%).

N-(1H-Benzo[d]imidazol-2-yl)-5-bromo-6-methoxypicolinamide (5c)

Off-white solid; yield : 68%, mp: 210-212°C ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.15 (s, 3H, OCH_3),7.25 (m, 2H, Ar-H), 7.45 (m, 1H, Ar-H), 7.62 (m, 1H, Ar-H), 7.80 (d, 1H, Ar-H), 8.06 (d, 1H, Ar-H) 10.42 (broad s, 1H, NH), 11.02 (broad s, 1H, NH); MS: m/z (%) 348.7 [M^{+2}], UPLC purity (98.9%).

5-Bromo-N-(5-fluoro-1H-benzo[d]imidazol-2-yl)-6-methoxypicolinamide (5d)

Pale yellow solid; yield: 66%, mp: 218-220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.16 (s, 3H, OCH_3), 7.26-7.18 (m, 1H, Ar-H), 7.46-7.52 (m, 1H, Ar-H), 7.64-7.71 (m, 1H, Ar-H), 7.84 (d, 1H, Ar-H, J = 7.98 Hz),8.08 (d, 1H, Ar-H)10.44 (broad s, 1H, NH), 11.05 (Broad s, 1H, NH); MS: m/z (%) 366.7 [M^{+2}], UPLC purity (98.2%).

Synthesis of N-(R-benzo[d]thiazol-2-yl)-6-methoxy 5-(Substituted)picolinamide and N-(R-benzo[d]imidazol-2-yl)-6-methoxy5-(Substituted)picolinamide (7)

To a stirred solution of compound **5** (50 mg, 0.00013 mol) and compound **6** (25.1 mg, 0.0002 mol) in Toluene:EtOH:water (2:1:0.5) 1.5 mL were added $Pd(PPh_3)_4$ (79.3 mg, 0.000068 mol) and K_2CO_3 (38.0 mg, 0.00027 mol) and heated to 110^{o}C for 16 h in sealed tube. After completion of the reaction as monitered by TLC and LCMS, water was added to the reaction mixture and extracted with ethylacetate. The organic extracts were dried over Na_2SO_4, evaporated *in vacuo* to afford the crude product, which was further purified by column chromatography using a gradient system of Hexane–EtOAC (9:1-7:3) to give the desired compound **7**.

6-Methoxy-5-phenyl-pyridine-2-carboxylic acid benzothiazol-2-ylamide (7a)
Off-white solid; yield : 72%, mp: 196-198 mn ^{o}C, IR (KBr, cm-1) : 3350 (N-H), 1602 (C=N), 1698 (C=O),1520, 1140, 850; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.15 (s, 3H, OCH_3),7.24 (m, 1H, Ar-H), 7.38-7.50 (m, 4H, Ar-H), 7.62 (m, 2H, Ar-H), 7.85-7.90 (m, 3H, Ar-H), 8.05 (m, 1H, Ar-H) 10.95 (broad s, 1H, NH); MS: m/z (%) 361.9 [M^+], HPLC purity (97.72%); Anal. Calcd. for $C_{20}H_{15}N_3O_2S$: C, 66.46; H, 4.18; N, 11.63; Found C, 66.42; H, 4.17; N, 11.59.

6-Methoxy-5-(2-methoxy-phenyl)-pyridine-2-carboxylic acid benzothiazol-2-ylamide (7b)
Off-white solid; yield : 75%, mp: 199-202°C IR (KBr, cm-1) : 3365 (N-H), 1601 (C=N), 1698 (C=O), 1240, 880 ;^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.80(s, 3H, OCH_3),4.15 (s, 3H, OCH_3),7.00-7.10(m, 2H, Ar-H),7.25-7.30(m, 1H, Ar-H), 7.32-7.44 (m, 2H, Ar-H), 7.48-7.50 (m, 1H, Ar-H),7.80(d, 1H, Ar-H),7.85-7.90(m, 2H, Ar-H) 8.01 (d, 1H, Ar-H) 10.90 (broad s, 1H, NH),; MS: m/z (%) 391.8 [M^+], HPLC purity (99.06%); Anal. Calcd. for $C_{21}H_{17}N_3O_3S$: C, 64.43; H, 4.38; N, 10.73; Found C, 64.46; H, 4.39; N, 10.75.

6-Methoxy-5-phenyl-pyridine-2-carboxylic acid (6-fluoro-benzothiazol-2-yl)-amide (7c)
Off-white solid; yield :69%, mp: 200-202°C IR (KBr, cm-1) : 3444 (N-H), 2957, 1609 (C=N), 1697 (C=O),1160, 910; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.12 (s, 3H, OCH_3),7.20 (m, 1H, Ar-H), 7.40-7.50 (m, 3H, Ar-H), 7.55-7.58 (m, 1H, Ar-H), 7.60(m, 2H, Ar-H),7.78(m, 1H, Ar-H),7.85 (d, 1H, Ar-H), 8.02 (d, 1H, Ar-H) 10.92 (broad s, 1H, NH); MS: m/z (%) 379.9 [M^+],HPLC purity (97.99%), Anal. Calcd. For $C_{20}H_{14}FN_3O_2S$: C, 63.31; H, 3.72; N, 11.08; Found C, 63.34; H, 3.74; N, 11.10.

6-Methoxy-5-(2-methoxy-phenyl)-pyridine-2-carboxylic acid (6-fluoro-benzothiazol-2-yl)-amide (7d)
Off-white solid; yield : 70%, mp: 196-198°C IR (KBr, cm-1) : 3328 (N-H), 1612 (C=N), 1650 (C=O),1220, 860; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.78 (s, 3H, OCH_3) 4.15 (s, 3H, OCH_3),7.22 (m, 1H, Ar-H), 7.42-7.52 (m, 2H, Ar-H), 7.56-7.58 (m, 1H, Ar-H), 7.62 (m, 2H, Ar-H), 7.78(m, 1H, Ar-H),7.85 (d, 1H, Ar-H), 8.02 (d, 1H, Ar-H) 10.92 (broad s, 1H, NH); MS: m/z (%) 409.9 [M^+], HPLC purity (99.01%); Anal. Calcd. for $C_{21}H_{16}FN_3O_3S$: C, 61.60; H, 3.94; N, 10.26;. Found C, 61.62; H, 3.95; N, 10.29.

6-Methoxy-5-phenyl-pyridine-2-carboxylic acid (1H-benzoimidazol-2-yl)-amide(7e).
Off-white solid; yield : 74 %, mp: 194-198°C; IR (KBr, cm-1) : 3369 (N-H), 1627 (C=N), 1679 (C=O),1230, 820; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 4.12 (s, 3H, OCH_3),7.12(m, 2H, Ar-H), 7.42-7.50 (m, 5H, Ar-H), 7.60 (m, 2H, Ar-H), 7.90 (d, 1H, Ar-H), 8.02 (d, 1H, Ar-H),11.38 (broad s, 1H, NH), 12.40 (broad s, 1H, NH); MS: m/z (%) 344.9 [M^+],HPLC purity (98.99%); Anal. Calcd. for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27. Found C, 69.78; H, 4.69; N, 16.32.

6-Methoxy-5-(2-methoxy-phenyl)-pyridine-2-carboxylicacid(1H-benzoimidazol-2-yl)-amide(7f)
Off-white solid; yield : 70%, mp: 196-198°C; IR (KBr, cm^{-1}) : 3347 (N-H), 1630 (C=N), 1686 (C=O),1270, 810; ^{1}H NMR (500MHz, DMSO- d_6) δ:3.75(s,3H,OCH_3), 4.02 (s, 3H, OCH_3),7.02 (m, 1H, Ar-H), 7.15 (m, 3H, Ar-H), 7.22 (m, 1H, Ar-H), 7.40 (m, 1H, Ar-H), 7.7 (m, 2H, Ar-H),7.92 (m, 2H, Ar-H), 11.35 (broad s, 1H, NH), 12.40 (broad s, 1H, NH); MS: m/z (%) 375.0[M^+],HPLC purity (97.42%); Anal. Calcd. for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96. Found C, 67.32; H, 4.84; N, 14.90.

6-Methoxy-5-phenyl-pyridine-2-carboxylic acid (5-fluoro-1H-benzoimidazol-2-yl)-amide(7g)
Off-white solid; yield : 71%, mp: 200-202°C ,IR (KBr, cm^{-1}) : 3356 (N-H), 1609 (C=N), 1675 (C=O),1220, 810; ^{1}H NMR (500 MHz, DMSO- d_6) δ: 4.02 (s, 3H, OCH_3),7.14 (m, 1H, Ar-H), 7.30 (m, 3H, Ar-H), 7.34 (m, 1H, Ar-H), 7.56 (m, 1H, Ar-H), 7.86 (m, 2H, Ar-H), 8.05

(m, 2H, Ar-H), 11.36 (broad s, 1H, NH), 12.40 (broad s, 1H, NH); MS: m/z (%) 362.9 [M^+], HPLC purity (97.24%); Anal. Calcd. for $C_{21}H_{17}FN_4O_3$: C, 64.28; H, 4.37; N, 14.28. Found C, 64.24; H, 4.35; N, 14.24.

6-Methoxy-5-(2-methoxy-phenyl)-pyridine-2-carboxylic acid (5-fluoro-1H-benzoimidazol-2-yl)-amide(7h)

Off-white solid; yield :67%, mp: 204-206°C, IR (KBr, cm^{-1}) : 3357 (N-H), 16110 (C=N), 1656 (C=O), 1210, 830; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.75 (s, 3H,OCH_3), 4.02 (s, 3H,OCH_3), 7.16 (m, 1H, Ar-H), 7.28 (m, 2H, Ar-H), 7.32 (m, 1H, Ar-H), 7.60 (m, 1H, Ar-H), 7.85 (m, 2H, Ar-H), 8.04 (m, 2H, Ar-H), 11.35 (broad s, 1H, NH), 12.40 (broad s, 1H, NH), MS: m/z (%) 393.0 [M^+], HPLC purity (98.20%); Anal. Calcd. for $C_{21}H_{17}FN_4O_3$: C, 64.28; H, 4.37; N, 14.28. Found C, 64.32; H, 4.38; N, 14.32.

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