Original Article

Synthesis and Characterization of Novel N-Benzylbenzimidazole Linked Pyrimidine Derivatives as Anticancer Agents

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ABSTRACT

Background: Emergence of resistance to accessible anticancer drugs became a threat to human lives in the recent time. To address this issue, discovery of novel anticancer agents becomes very essential. Benzimidazoles and pyrimidines have been reported to possess potent anticancer activity. **Materials and Methods:** A hybrid approach has been used, in which core structure of potentially active N-benzyl benzimidazole and pyrimidine derivatives are brought together in to a single molecule. The desired compounds were prepared by the condensation of N-benzyl benzimidazole chalcones with guanidine hydrochloride. The synthesized compounds were characterized using spectral studies (IR, ^{1}H, ^{13}C-NMR techniques and mass spectrometry). All the compounds were screened for their anticancer activity against human breast cancer cell line MDA-MB-231. **Results:** The spectral data's are in well agreement with the synthesized compounds 5a-e. Compounds 5b (GI_{50} = 39.6 μM) and 5a (GI_{50} = 84.0 μM) exhibited significant anticancer activity. **Conclusion:** Owing to the anticancer activity, compound 5b can be used as lead structure in the development of yet more potent anticancer agents.

Key words: Chalcone, Benzimidazole, Pyrimidine, Anticancer activity, SRB assay.

INTRODUCTION

In present situation cancer became a cruel reality to human lives due to their resistance to accessible drugs. Thus, discovery of new types of anticancer drugs becomes very critical. Benzimidazoles are exceptionally valuable for the development of anticancer agent as they inhibits several enzymes involved in pathology of cancer including tyrosine kinase,[1] Raf kinase,[2] phosphatidylinositol 3-kinase[3] and insulin-like growth factor I receptor kinase.[4] In addition, N-benzyl substituted benzimidazoles have been synthesized exhibiting potent anticancer activity in which the PPTMB[5] and BPB[6] are examples (Figure 1). The pyrimidine motif is a core structure in numerous biologically active compounds. Some representatives of this heterocycle exhibited anticancer activity.[7-9] Moreover compounds like GNE-477[10] and certinib[11] were reported as potential anticancer agents (Figure 1).

The hybrid of N-benzyl benzimidazole and pyrimidine moieties is anticipated to be a good approach to design promising anticancer agents. Thus in present work an efficient synthesis of some new N-benzyl benzimidazole linked pyrimidine derivatives were synthesized and evaluated against human breast cancer cell line MDA-MB-231.

MATERIALS AND METHODS

Materials and Instrumentation

The chemicals used were procured from Merck (India) and Finar (India). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker

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Avance III 500 MHz (AV 500), spectrometer using TMS as internal standard. The mass spectra were recorded on Varian Inc 410 prostar Binary LC-MS. IR spectra were obtained on a Bruker Alpha-T FT-IR spectrometer. Melting points were determined by open tube capillary method and are uncorrected. Progress of the reaction and purity of the products was checked by TLC under iodine vapors/UV light.

General Method for the Synthesis of 4-(1-benzyl-1H-benzo[d]imidazol-2-yl)-6-(Substituted Phenyl) Pyrimidin-2-amine (5a-e)

Appropriate N-benzyl benzimidazole chalcone **4a-e** (2 mmol) was dissolved in mixture of absolute alcohol (10 ml) and aqueous sodium hydroxide solution (10%, 1 ml). Guanidine hydrochloride (4 mmol) was added to the reaction mixture and the contents were refluxed until completion of reaction (10-12 h). The progress of the reaction was monitored by TLC (Benzene-ethyl acetate, 4:1). The reaction mixture was cooled and the precipitate formed was filtered and washed with rectified spirit.

4-(1-benzyl-1H-benzo[d]imidazol-2-yl)-6-phenylpyrimidin-2-amine (5a)

Yield: 72 %; cream colour solid; m.p. 204-206°C; FTIR (KBr) cm^{-1} 3404 (br, $-NH_2$), 1628 (C=N); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 8.15-8.13 (2H, m, H-2′ and H-6′), 7.97 (1H, s, H-15), 7.80 (1H, d, *J* = 7 Hz, H-4) 7.71 (1H, d, *J* = 7.5 Hz, H-7), 7.54-7.53 (3H, m, H-3′, H-5′ and H-4′), 7.35-7.29 (2H, m, H-5 and H-6), 7.26-7.23 (2H, m, H-3″ and H-5″), 7.20-7.16 (3H, m, H-2″, H-6″ and H-4″), 7.02 (2H, s, $-NH_2$), 6.37 (2H, s, H-10); ^{13}C NMR (125 MHz, DMSO-d_6): 165.49 (C12), 163.86 (C16), 159.18 (C14), 148.21 (C2), 142.52 (C8), 138.46 (C1″), 137.30 (C1′), 137.23 (C9), 131.22 (C4′), 129.28 (C3′ and C5′), 128.98 (C3″ and C5″), 127.74 (C4″), 127.44 (C2″ and C6″), 127.28 (C2′ and C6′), 124.48 (C6), 123.33 (C5), 120.41 (C4), 112.04 (C7), 104.90 (C15), 48.42 (C10); ESI-MS m/z: 378.1 [M+H]..

4-(1-benzyl-1H-benzo[d]imidazol-2-yl)-6-(p-tolyl) pyrimidin-2-amine (5b)

Yield: 62 %; cream colour solid; m.p. 180-182°C; FTIR (KBr) cm^{-1} 3306 ($-NH_2$), 1624 (C=N); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 8.05 (2H, d, *J* = 10 Hz, H-2′ and H-6′), 7.94 (1H, s, H-15), 7.79 (1H, dd, J = 5 Hz, *J* = 10 Hz, H-4), 7.70 (1H, dd, *J* = 5 Hz, *J* = 10 Hz, H-7), 7.35-7.29 (4H, m, H-3′, H-5′, H-5 and H-6), 7.26-7.23 (2H, m, H-3″ and H-5″), 7.19-7.16 (3H, m, H-2″, H-6″ and H-4″), 6.98 (2H, s, $-NH_2$), 6.37 (2H, s, H-10), 2.38 (3H, s, $-CH_3$); ESI-MS m/z: 392.1 [M+H].

4-(1-benzyl-1H-benzo[d]imidazol-2-yl)-6-(4-chlorophenyl)pyrimidin-2-amine (5c)

Yield: 66 %; cream colour solid; m.p. 186--188°C; FTIR (KBr) cm^{-1} 3321 and 3201($-NH_2$), 1627 (C=N); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 8.18 (2H, d, *J* = 8.5 Hz, H-2′ and H-6′), 7.98 (1H, s, H-15), 7.80 (1H, d, *J* = 7 Hz, H-4) 7.77 (1H, d, *J* = 7.5 Hz, H-7), 7.6 (2H, d, *J* = 9 Hz, H-3′ and H-5′), 7.35-7.29 (2H, m, H-5 and H-6), 7.26-7.23 (2H, m, H-3″ and H-5″), 7.20-7.17 (3H, m, H-2″, H-6″ and H-4″), 7.04 (2H, s, $-NH_2$), 6.37 (2H, s, H-10); ^{13}C NMR (125 MHz, DMSO-d_6): 164.19 (C12), 163.81 (C16), 159.37 (C14), 148.05 (C2), 142.49 (C8), 138.44 (C1″), 137.24 (C9), 136.09 (C4′), 136.00 (C1′), 129.35 (C2′ and C6′), 129.10 (C3′ and C5′), 128.98 (C3″ and C5″), 127.75 (C4″), 127.43 (C2″ and C6″), 124.53 (C6), 123.36 (C5), 120.41 (C4), 112.06 (C7), 104.74 (C15), 48.41 (C10); ESI-MS m/z: 411.9 [M+H].

4-(1-benzyl-1H-benzo[d]imidazol-2-yl)-6-(4-bromophenyl)pyrimidin-2-amine (5d)

Yield: 58 %; light yellow colour solid; m.p. 216-218°C; FTIR (KBr) cm^{-1} 3330 and 3205 ($-NH_2$), 1627 (C=N); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 8.10 (2H, d, *J* = 8.5 Hz, H-2′ and H-6′), 7.97 (1H, s, H-15), 7.80 (1H, dd, *J* = 1.5 Hz, *J* = 7.5 Hz, H-4), 7.75-7.70 (3H, m, H-3′, H-5′ and H-7), 7.36-7.29 (2H, m, H-5 and H-6), 7.26-7.23 (2H, m, H-3″ and H-5″), 7.20-7.17 (3H, m, H-2″, H-6″ and H-4″), 7.04 (2H, s, $-NH_2$), 6.36 (2H, s, H-10); ESI-MS m/z: 455.9 [M+H], 457.9 [M+2].

4-(1-benzyl-1H-benzo[d]imidazol-2-yl)-6-(4-fluorophenyl)pyrimidin-2-amine (5e)

Yield: 68 %.; cream colour solid; m.p. 210-212°C; FTIR (KBr) cm^{-1} 3373 and 3294 ($-NH_2$), 1633 (C=N); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 8.23-8.20 (2H, m, H-2′ and H-6′), 7.98 (1H, s, H-15), 7.81 (1H, d, *J* = 7.5 Hz, H-4), 7.71 (1H, d, *J* = 8 Hz, H-7), 7.36-7.29 (4H, m, H-5, H-6, H-3′ and H-5′), 7.25-7.16 (5H, m, H-3″, H-5″, H-2″, H-6″ and H-4″), 7.05 (2H, s, $-NH_2$), 6.38 (2H, s, H-10); ^{13}C NMR (125 MHz, DMSO-d_6): 165.23-163.26 (C4′), 164.37 (C12), 163.80 (C16), 159.25 (C14), 148.16 (C2), 142.52 (C8), 138.45 (C1″), 137.23 (C9), 133.77-133.75 (C2′ and C6′), 129.74-129.67 (C1′), 128.97 (C3″ and C5″), 127.74 (C4″), 127.43 (C2″ and C6″), 124.49 (C6), 123.34 (C5), 120.40 (C4), 116.27 (C3′ and C5′), 116.10 (C5′), 112.03 (C7), 104.69 (C15), 48.42 (C10); ESI-MS m/z: 396.1 [M+H].

Anticancer activity

The *in vitro* cytotoxicity activities (cell viability assay) of the compounds were evaluated by SRB assay[12] against Human breast cancer cell line MDA-MB-231. The cell

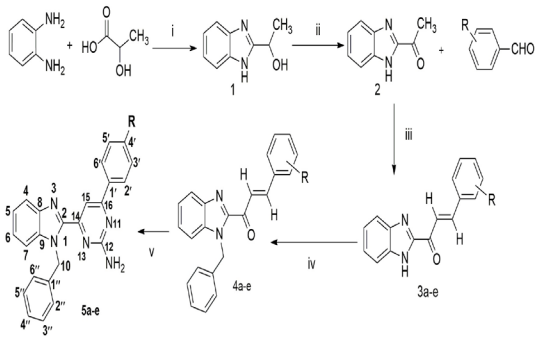
line was grown in RPMI 1640 medium containing 2 mM L-glutamine and 10% fetal bovine serum. Cells were inoculated into 96 well microtiter plates in 90 µL medium at 5000 cells per well and incubated at 37°C, 5% CO_2, 95% air and 100% relative humidity for 24 h. Subsequent to the addition of drugs (0.1–100 µM), the culture plate was incubated for additional 48 h. Cells were fixed *in situ* by slowly adding 25 µL of 10% trichloroacetic acid and then incubated for 60 min at 4°C. After discarding the supernatant, the plate was washed five times with tap water. Finally, 50 µL of sulforhodamine in 1% acetic acid solution was added to each well for staining. The stained cells were solubilized using 10 mM trizma base and the absorbance was noted at a wavelength of 515 nm. The % viability was calculated for each compound at different concentration using the formula: (Absorbance of Test/Absorbance of control) × 100

The GI_{50} (Concentration required to cause 50% inhibition in growth) for the synthesized compounds were calculated from a non-linear sigmoidal dose–response (Variable slope) curve by using GraphPad Prism v.4.03 software.

RESULTS AND DISCUSSION

Synthesis

The desired compounds were prepared as outlined in the (Scheme 1). 2-hydroxyethylbenzimidazole 1 was obtained by condensation of *o*-phenylenediamine with lactic acid under acidic condition. Oxidation of the 1 followed by neutralization with ammonia gave 2-acetylbenzimidazole 2.[13] The required chalcones 3a-e were obtained by claisen-schmidt condensation of 2-acetylbenzimidazole 2 with substituted aromatic aldehydes in presence of NaOH.[14] N-Benzyl substituted benzimidazole chalocones (4a-e) were obtained by nucleophilic substitution reactions of ^{1}H-Benzimidazole chalcones (3a-e) with benzyl chloride.[15] Condensation of the N-benzyl benzimidazole chalcones with guanidine hydrochloride resulted in novel pyrimidine derivatives (5a-e).



compound **5a**; R=H **5b**; R=CH_3 **5c**; R=Cl **5d**; R=Br **5e**; R=F

The scheme of synthesis 1: Synthetic route to 1-benzyl-2-(1-substituted-5-aryl-4,5-dihydro-1H-pyrazol-3-yl)-1H-benzo[d]imidazoles. Reagents and conditions: i) 4N HCl, reflux, 8 h; ii) $K_2Cr_2O_7$, dil. H_2SO_4, r.t., 2h; iii) Ar-CHO, 10 % aq NaOH, ethanol, r.t., 4-8 h; iv) Benzyl chloride, anhydrous K_2CO_3, dry acetone, reflux, 22-26 h; v) Guanidine. HCl, NaOH, EtOH, H_2O, reflux, 10-12 h.

Spectral Study

The structures of synthesized compounds 5a-e were assigned via spectroscopic analysis: IR, ^{1}H-NMR, ^{13}C-NMR and mass spectrometry. The spectral study of compound 5a is described as an example. IR spectrum of compound 5a showed the characteristic peak at 3404 cm^{-1} corresponding to N-H stretching. In ^{1}HMR spectrum of 5a, the doublets due to arylidene protons disappeared, instead a singlet at δ 7.97 is observed due to proton at C15 ensuring the formation of pyrimidine ring. The phenyl protons H-2′ and H-6′ appeared as a multiplet at δ 8.15-8.13. The benzimidazole protons (H-4 and H-7) appeared as two separate doublets at δ 7.80 and 7.71 (J = 7.5 Hz) respectively. One multiplet at δ 7.54-7.53 was attributed to three aromatic protons of phenyl group (H-3′, H-5′ and H-4′). Two benzimidazole protons (H-5 and H-6) were observed as a multiplet at δ 7.35-7.29. Two separate multiples at δ 7.26-7.23 and δ 7.20-7.16 were assigned to aromatic benzyl protons (H-3″, H-5″, H-2″, H-6″ and H-4″). The amino protons appeared as a singlet at δ 7.02. The methylene protons at C10 appeared as a singlet at δ 6.37.

The ^{13}C NMR spectrum of compound 5a, the peaks at δ 165.49, 163.86, 159.18, 104.90 are attributed to pyrimidine carbons (C12, C16, C14 and C15). The peaks at δ 148.21, 142.52, 137.23, 124.48, 123.33, 120.41 and 112.04 are assigned to benzimidazole carbons (C2, C8, C9, C6, C5, C4 and C7). The aromatic benzyl carbons (C1″), (C3″ and C5″), (C2″ and C6″) and (C4″) appeared at δ 138.46, 128.98, 127.44 and 127.74 respectively. The peaks at δ 131.22, 137.30, 127.28 and 129.28 are assigned to (C4′), (C1′), (C2′ and C6′) and (C3′ and C5′) respectively. A peak at 48.42 confirms the presence of methylene carbon (C10). Additionally, ESI-MS spectrum showed a peak at 378.1 (M+H). Hence, the above spectral data are compatible with the structure of desired product 5a.

Anticancer Activity

The *in vitro* anticancer activities (cell viability assay) of compounds were evaluated by SRB assay against Human breast cancer cell line MDA-MB-231. Compounds 5a

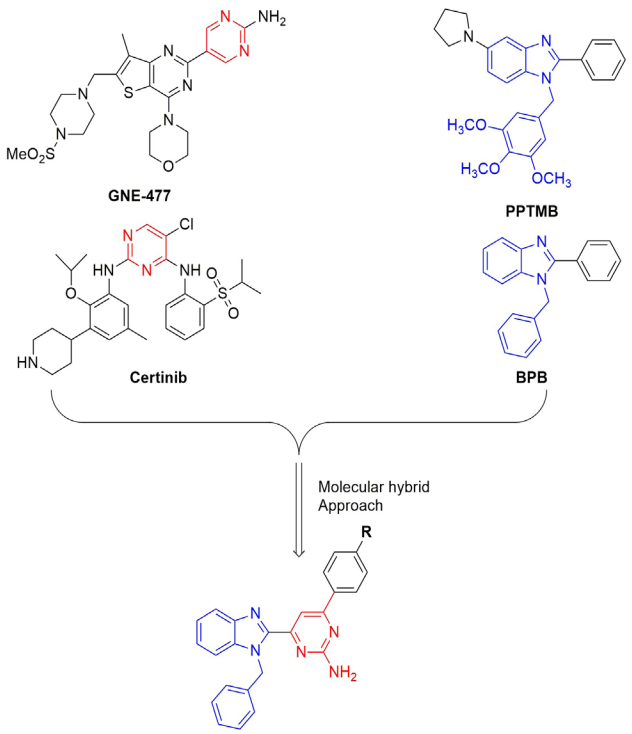


Figure 1: Rational Design of the Benzimidazole Linked Pyrimidine via Hybriding Potent Anticancer Agents.

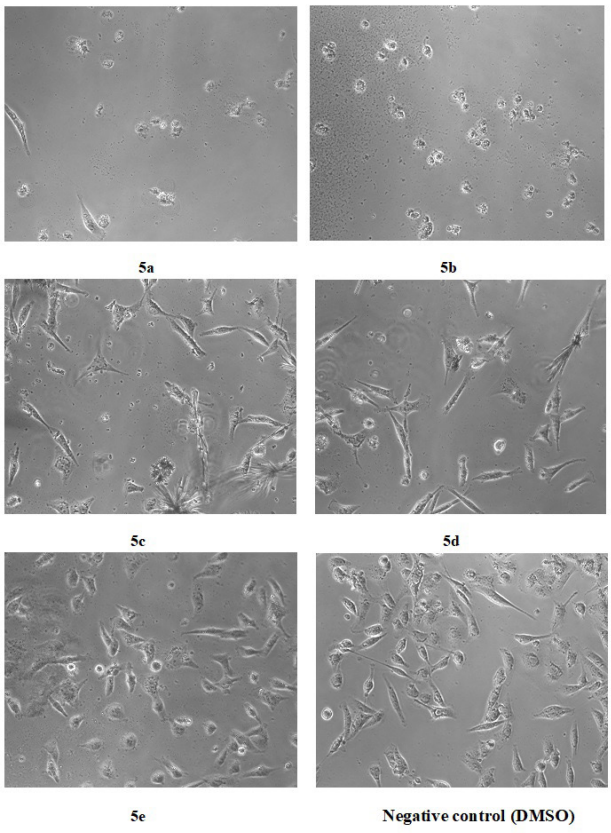


Figure 2: Images of Phase Contrast Microscopy. Cells were treated with 100 µM 5a-e, for 48 h. Negative Control Included cells treated with DMSO.

Table 1: *In vitro* anticancer activity of synthesized compounds 5a-e (GI^{50} µM).

Compound	GI_{50} (µM)
5a	84.0
5b	39.6
5c	>100
5d	>100
5e	>100

Positive control Adriamycin (GI_{50}= 0.04 µM).

(GI_{50} = 84.0 µM) and 5b (GI_{50} = 39.6 µM) exhibited weak activity. Compound 5a-b clearly inhibited the proliferation of Human breast cancer cell line MDA-MB-23 as shown in (Figure 2). All the other compounds found inactive (GI_{50} >100 µM) as compared to standard drug adriamycin. The results obtained from cytotoxicity testing are represented in (Table 1).

CONCLUSION

Five novel benzimidazole derivatives containing pyrimidine ring were synthesized. The structures of new compounds were confirmed by spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and mass spectrometry). Our anticancer study results revealed that the most active compound **5b** possessed GI_{50} value of 39.6 µM. Based on the GI_{50} values presented by the tested compounds, it could be concluded that, presence of electron releasing group on the phenyl ring enhanced the active.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

NMR: Nuclear magnetic resonance spectroscopy; **TMS:** Tetramethylsilane; **DMSO-d_6:** Deuterated Dimethyl Sulfoxide; **LC-MS:** Liquid Chromatography-

Mass spectrometry; **ESI-MS:** Electro spray ionization-Mass Spectrometer; **FT-IR:** Fourier transform infrared spectroscopy; **TLC:** Thin layer chromatography; **UV:** Ultraviolet spectroscopy; **SRB:** Sulforhodamine B; **RPMI:** Roswell Park Memorial Institute.

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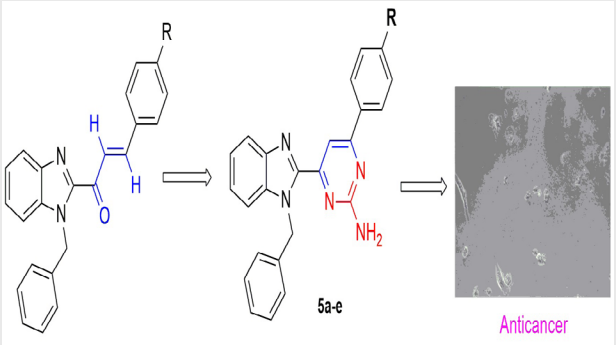
PICTORIAL ABSTRACT



SUMMARY

- Identification of lead molecules against cancer is a vital area of today's research. In this study a new series of N-benzyl benzimidazole and pyrimidine derivatives were synthesized, characterized and evaluated for *in vitro* anticancer activity. Compound 5b showed significant activity. Hence it can be used as a lead structure in the advance of yet more potent anticancer agents.

ABOUT AUTHORS

Dr. Ajaya Kumar Behera was born in Nayagarh District of Odisha, India, in 1962. He received his M.Sc. degree from Utkal University in 1984 and M.Phil. and Ph.D. degrees from Berhampur University in 1990 and 1996, respectively. After working for a few years at Government College, he joined the PG Department of Chemistry, Sambalpur University, in 1997 as Senior Lecturer and became Reader in 2003. His research interest includes synthesis of pharamacologically active heterocycles, spiroheterocycles and natural products.

Dr. Jagadeesh Panda received his M.Pharm. degree from Andhra University in 1995 and Ph.D. degrees from Berhampur University in 2004 respectively. Currently he is working as a Professor and Principal of Raghu College of Pharmacy, Visakhapatnam. His research interest includes synthesis of pharamacologically active heterocycles and natural products.

Dr. Gopal Krishna Padhy obtained his M.Pharm. degree in Pharmaceutical Chemistry from Poona College of Pharmacy, Bharati Vidyapeeth University, in 2007. He had carried out his Ph.D. work under joint supervision of Dr. Ajaya Kumar Behera and Dr. Jagadeesh Panda in Sambalpur University. Currently, he is working as an associate professor in Maharajah's College of Pharmacy, Phool Baugh.

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