CYCLIZATION OF 4-(2-AMINOANILINO)-2-BENZYLTHIOPYRIMIDINE TO NOVEL 1-(2-BENZYLTHIOPYRIMIDIN-4-YI)-2-SUBSTITUTED BENZIMIDAZOLES

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Abstract: 1-(2-Benzylthiopyrimiden-4-yl)-2-substituted benzimidazoles **6a-d** were prepared efficiently in four steps. Reaction of 2-thiouracil with benzyl chloride in presence of base, furnishes 2-benzylthiouracil **2**. This on chlorination with excess $POCl_3$ furnishes 4-chloro-2-benzylthiopyrimidine **3**. Compound **3** on reaction with *ortho*-phenylenediamine *via* aromatic nucleophilic displacement reaction yielded 4-(2-aminoanilino)-2-benzylthiopyrimidine **4**. This on cyclization with CS_2 in presence of base furnishes 1-(2-benzylthiopyrimidin-4-yl)-2-thiobenzimidazole **5**. Compound **5** on reaction with alkyl, aryl halides and hydrazine hydrate yielded target compounds **6a-d** in 52-62% yield.

Introduction Benzimidazole analogs with N-1 substitution showed antiviral activity[1] against human cytomegalovirus and herpes simplex virus type-1. The biological activities of these compounds depend upon the substitution on the benzimidazole at the N-1 or C-2 position. In continuation of earlier research in the field of synthesis and biological activities of N_1-substituted benzimidazoles[2] and substituted pyrimidines[3-6], herein we report the synthesis of some hitherto unknown 1-(2-benzylthiopyrimiden-4-yl)-2-substituted benzimidazoles.

Experimental Melting points were determined by using a Thomas-Hoover melting point apparatus and were uncorrected. IR spectra in KBr disc were recorded on Perkin-Elmer-Spectrum-one FT IR spectrophotometer (ν_{max} in cm^{-1}) and ^1H NMR spectra in DMSO-d_6 and/or $CDCl_3$ on amx 400, 400 MHz spectrophotometer using TMS as internal standard (chemical shift in δ or ppm). Mass spectra were recorded on a JEOL SX 102 Mass spectrometer using Argon/Xenon (6kv, 10 mA) as the FAB gas. Purity of the compounds was checked by TLC using silica gel 'G' plates obtained from Whatman Inc, and a fluorescent indicator. 2-Benzylthiouracil **2** and 4-chloro-2-benzylthiopyrimidine **3** were prepared by following the literature methods[7,8].

Procedure for the preparation of 4-(2-aminoanilino)-2-benzylthiopyrimidine (4)
To a solution of 4-chloro-2-benzylthiopyrimidine **3** (0.001 mole) in MeOH (10 ml), *ortho*-phenylenediamine (0.001 mole) was added. The reaction mixture was refluxed for 20 hrs on water-bath. Concentrated the solvent under reduced pressure and the residue triturated with a little crushed ice and extracted with ether (3 x 25 ml) and then dried over anhydrous $MgSO_4$ and after solvent evaporation yielded the title compound **4**. Yield: 0.2 g (65%). m.p. 80-81^{0}C. IR: 3356 NH_2, 3200 NH and 1573 C=N cm^{-1}. ^1H NMR: δ 8.1 (d, 1H, C_6H), 7.5-6.7 (m, 9H, ArH), 6.4 (s, 2H, NH_2), 6 (d, 1H, C_5H), 4.38 (s, 2H, SCH_2Ph). Mass: m/z=309 (M^+, 100%), 200 (6%) and 185 (25%).Elemental analysis: Calcd for $C_{17}H_{16}N_4S$: C, 66.21: H, 5.23; N, 18.17. Found: C, 66.20; H, 5.20; N, 18.15.

Procedure for the preparation of 1-(2-benzylthiopyrimidin-4-yl)-2-thiobenzimidazoie (5)

To a mixture of 4-(2-aminoanilino)-2-benzylthiopyrimidine **4** (0.001 mol) and CS_2 (0.001 mol) in EtOH (10 ml), aq KOH solution (0.005 mol in 2 ml of water) was added and stirred for six hrs at room temperature. Solid separated was filtrated, dried and recrystallized from ethanol. Yield: 0.245 g (70%). m.p. 200-201^{0}C. IR: 3140 NH and 1565 C=N cm^{-1}. ^{1}H NMR: δ 12.7 (s, 1H, SH), 8.5 (d, 1H, C_6H), 7.5-6.9 (m, 9H, ArH), 4.34 (s, 2H, SCH_2Ph). Mass: m/z=350 (M^+, 100%), 318 (5%) and 201 (1%).Elemental analysis: Calcd for $C_{18}H_{14}N_4S_2$: C, 61.69: H, 4.03; N, 15.99. Found: C, 61.67; H, 4.02; N, 15.97.

Procedure for the preparation of 1-(2-benzylthiopyrimidin-4-yl)-2-alkyl/arylthiobenzimidazoles (6a-c)

To a Mixture of 1-(2-benzylthiopyrimidin-4-yl)-2-thiobenzimidazole **5** (0.001 mol) and appropriate alkyl/aryl halide (0.001 mol) in 10 ml of EtOH, aq NaOH (0.001 mol dissolved in 2 ml of water) was added and refluxed for 4 hrs. Reaction mixture was cooled and poured in to ice cold water (25 ml), extracted with ethylacetate (3 x 20 ml). Ethylacetate layer was dried over anhydrous sodium sulfate and after solvent evaporation yielded the title compounds **6a-c**.

1-(2-benzylthiopyrimidine-4-yl)-2-methylthiobenzimidazole (6a): Yield: 0.189 g (52%). ^{1}H NMR: δ 8.69 (d, 1H, C_6H), 7.73-7.2 (m, 9H, ArH), 4.5 (s, 2H, SCH_2Ph), 2.77 (s, 3H, SCH_3). Elemental analysis: Calcd for $C_{19}H_{16}N_4S_2$: C, 62.61: H, 4.42; N, 15.37. Found: C, 62.60; H, 4.40; N, 15.35.

1-(2-benzylthiopyrimidine-4-yl)-2-ethylthiobenzimidazole (6b): Yield: 0.226 g (60%). ^{1}H NMR: δ 8.63 (d, 1H, C_6H), 7.64-7.15 (m, 9H, ArH), 4.47 (s, 2H, SCH_2Ph), 3.34 (q, 3H, SCH_2CH_3), 1.41 (t, 2H, SCH_2CH_3). Elemental analysis: Calcd for $C_{20}H_{18}N_4S_2$: C, 63.46: H, 4.79; N, 14.80. Found: C, 63.45; H, 4.78; N, 14.79

1-(2-benzylthiopyrimidine-4-yl)-2-benzylthiobenzimidazole (6c): Yield: 0.242 g (55%). ^{1}H NMR signals are at δ 8.6 (d, 1H, C_6H), 7.7-7.2 (m, 14H, ArH), 4.68 (s, 2H, SCH_2Ph), 4.4 (s, 2H, SCH_2Ph). Mass: m/z=441 (M^+, 100%), 365 (20%), 319 (5%) and 242 (5%). Elemental analysis: Calcd for $C_{25}H_{20}N_4S_2$: C, 68.15: H, 4.58; N, 12.72. Found: C, 68.13; H, 4.55; N, 12.70.

Procedure for the preparation of 1-(2-benzylthiopyrimidin-4-yl)-2-hydrazinobenzimidazoles (6d)

To a Mixture of 1-(2-benzylthiopyrimidin-4-yl)-2-thiobenzimidazole **5** (0.001 mol) and hydrazine hydrate (0.005 mol, 99%) in 20 ml of ethanol was refluxed for 12 hrs. Reaction mixture was cooled and poured in to ice cold water (25 ml), solid separated was filterated, washed with little water, dried and recrystallized from alcohol. Yield: 0.215 g (62). IR: 3137 NH_2, 3057 NH and 1559 C=N. ^{1}H NMR: δ 8.57 (d, 1H, C_6H), 8.21 (s, 1H, NH), 7.48-6.9 (m, 9H, ArH), 4.17 (s, 2H, SCH_2Ph), 3.25 (s, 2H, NH_2). Mass: m/z=351 (M^+, 100%), 334 (15%) and 319 (20%). Elemental analysis: Calcd for $C_{18}H_{16}N_6S$: C, 62.05: H, 4.63; N, 24.12. Found: C, 62.03; H, 4.60; N, 24.10.

Results and Discussion

2-Thiouracil **1** was reacted with benzyl chloride in presence of aq NaOH solution furnished 2-benzylthiouracil **2** in 86% yield, having m.p.186-187^{0}C as a white crystalline solid. Compound **2** on subjected to chlorination with $POCl_3$ yielded 4-chloro-2-benzylthiopyrimidine **3** as a yellow crystalline solid in 75% yield, having

m.p. 60-63^{0}C. 4-(2-Aminoanilino)-2-benzylthiopyrimidine 4 was obtained by the reaction of **3** with nitrogen nucleophile such as *ortho*-phenylenediamine in MeOH for 20 hrs at refluxing temperature, *via* the aromatic nucleophilic substitution reaction. Compound **4** was obtained in 65% yield, having m.p. 80-82^{0}C as a brown solid. Compound **4** was characterized based on various spectral data, IR absorptions are at 3356 NH_2, 3200 NH and 1573 C=N cm^{-1} and ^{1}H NMR signals are at δ 8.1 (d, 1H, C_6H), 7.5-6.7 (m, 9H, ArH), 6.4 (s, 2H, NH_2), 6 (d, 1H, C_5H), 4.38 (s, 2H, SCH_2Ph). Further the structure of compound **4** was confirmed by mass spectral data, m/z=309 (M^+, 100%) and fragmented ion peaks at 200 (6%) and 185 (25%).

Compound **4** on cyclization with CS_2 in presence of aq KOH solution, EtOH as solvent medium under stirring at room temperature for six hrs yielded 1-(2-benzylthiopyrimidin-4-yl)-2-thiobenzimidazole **5** in 70% yield, having m.p. 199-201^{0}C. Structural establishment of compound **5** is based on the following spectral data, IR absorptions are at 3140 NH and 1565 C=N cm^{-1} and ^{1}H NMR signals are at δ 12.7 (s, 1H, SH), 8.5 (d, 1H, C_6H), 7.5-6.9 (m, 9H, ArH), 4.34 (s, 2H, SCH_2Ph). Further the structure of compound **5** was confirmed by mass spectral data, m/z=350 (M^+, 100%) and fragmented ion peaks at 318 (5%) and 201 (1%). Thiol group of compound **5** was reacted with various alkyl, aryl halides in presence of aq NaOH solution in ethanol refluxed for 4 hrs furnishes 1-(2-benzylthiopyrimidin-4-yl)-2-alkyl/arylthiobenzimidazoles **6a-c**. Compound **6c** was obtained in 55% yield as a semi-solid. ^{1}H NMR signals are at δ 8.6 (d, 1H, C_6H), 7.7-7.2 (m, 14H, ArH), 4.68 (s, 2H, SCH_2Ph), 4.4 (s, 2H, SCH_2Ph). Further the structure of compound **6c** was confirmed by mass spectral data, m/z=441 (M^+, 100%) and fragmented ion peaks at 365 (20%), 319 (5%) and 242 (5%).

Thiol group of compound **5** was also replaced with hydrazine hydrate in EtOH refluxed for 12 hrs furnished 1-(2-benzylthiopyrimidin-4-yl)-2-hydrazinobenzimidazole **6d**. Compound **6d** was obtained in 62% yield, having m.p. 120-124^{0}C. Spectral data of compound **6d** as follows, IR absorptions are at 3137 NH_2, 3057 NH and 1559 C=N and ^{1}H NMR signals are at δ 8.57 (d, 1H, C_6H), 8.21 (s, 1H, NH), 7.48-6.9 (m, 9H, ArH), 4.17 (s, 2H, SCH_2Ph), 3.25 (s, 2H, NH_2). Further the structure of compound **6d** was confirmed by mass spectral data, m/z=348 (M^+, 100%) and fragmented ion peaks at 334 (15%) and 319 (20%).

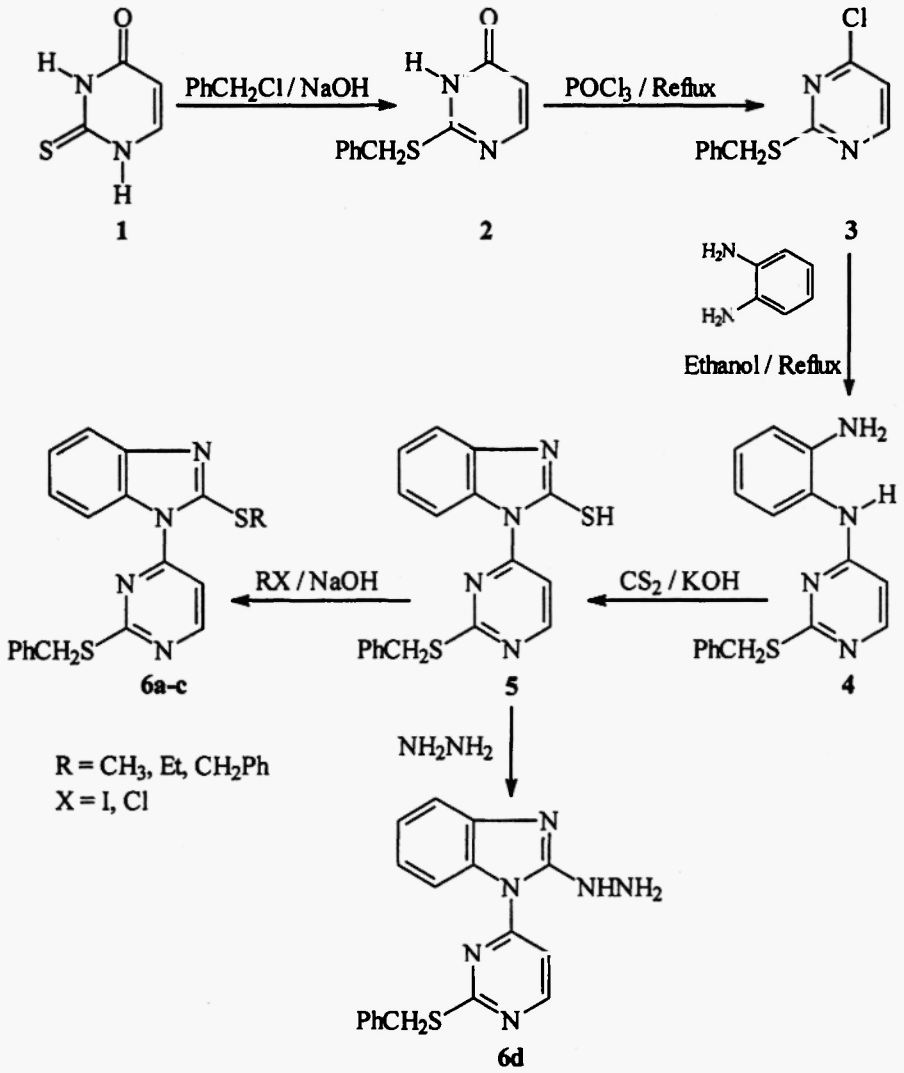
References

1. R. Zou, E. Kawashima, G.A. Freeman, G.W. Koszalka, J.C. Drach and L.B. Townsend, Nucleosides Nucleotides and Nucleic acids. **19**, 125 (2000).
2. N.M. Goudgaon, V. Dhondiba and A. Vijayalaxmi, Indian. J. Heterocyclic. Chem. **13**, 271 (2004).
3. N.M. Goudgaon and R.F. Schinazi, J. Med. Chem. **34**, 3305 (1991).
4. N.M. Goudgaon, A. McMillan and R.F. Schinazi, Antiviral Chem. Chemother. **3**, 263 (1992).
5. N.M. Goudgaon, M.H. el Kouni, F.N.M. Naguib and R.F. Schinazi, J. Med, Chem. **36**, 4250 (1993).
6. N.M. Goudgaon and A. Vijayalaxmi, Indian. J. Pharm. Sci. **65**, 545 (2003).
7 H.W. Barrett, I. Goodman and K. Dittmer, J. Amer. Chem. Soc. **70**, 1753 (1948).
8. Nakagawa and Aono, Chem. Pharm. Bull. **24**, 778 (1976).

Table-1 Physical Data of Synthesized Compounds (2-6a-d)

Compound	R	mp[a] (°C)	Yield[b] (%)
2	-	186-187	86
3	-	60-63	75
4	-	80-82	65
5	-	199-201	70
6a	CH_3	semi-solid	52
6b	Et	70-73	60
6c	CH_2Ph	semi-solid	55
6d	-	120-124	62

[a]Melting points are uncorrected, [b]Yield refers to purified product.



SCHEME-1

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