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Synthesis and antimicrobial activity of some new benzimidazole derivatives

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ABSTRACT

*Some new substituted 5-Pyrrol-1-yl-1H-*benzimidazole *-2-thiol* derivatives *have been synthesised from different their chemical structures have been confirmed by IR, 1H NMR, and MASS and by elemental analysis. Investigation of antimicrobial activity of compound was done by the disk diffusion technique. Among the compound with Nitrogen containing heterocyclic compounds showed the most favourable antimicrobial activity.*

Keywords: Benzimidazole , antibacterial and antifungal activity.

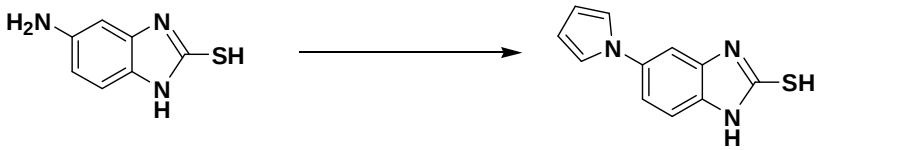
INTRODUCTION

Benzimidazole and their derivatives constitute an important class of heterocyclic compounds. It is evident from literature that benzimidazole derivatives are known to be associated with broad spectrum of biological activity like antibacterial[1,10], anti-inflammatory[2,11,12], analgesic[3], antiviral[4], antifungal[5], antitubercular[6] and anti cancer activity[7,13].

MATERIALS AND METHODS

All the melting points were determined by open capillary using V-Scientific Melting Point apparatus and are uncorrected. Purity of compound was checked by TLC on silica Gel-coated plates. IR spectra were recorded in KBr on FTIR Prestige-211 Simadzu spectrophotometer.^{1}H NMR spectra were recorded on 300 MHz Bruker using $CDCl_3$/DMSO and Mass spectra were recorded on using EI-MS mode. Elemental analysis was performed on Perkin-Elmer Series 2400.

Scheme-I



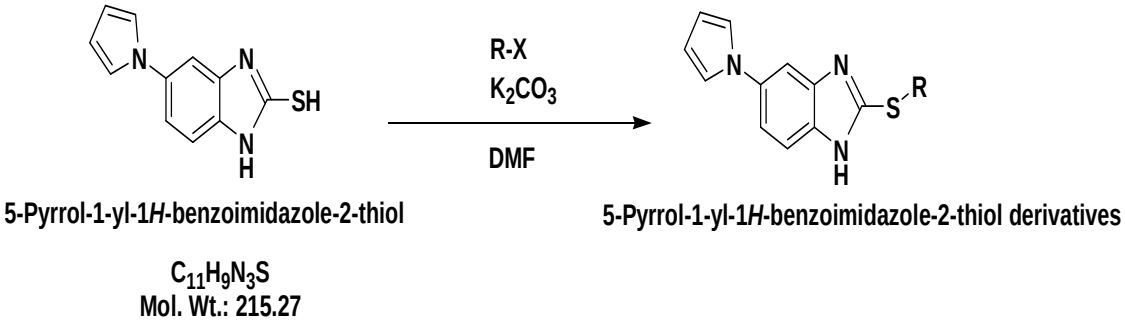
5-Amino-1*H*-benzoimidazole-2-thiol

$C_7H_7N_3S$
Mol. Wt.: 165.22

5-Pyrrol-1-yl-1*H*-benzoimidazole-2-thiol

$C_{11}H_9N_3S$
Mol. Wt.: 215.27

Scheme-II



5-Pyrrol-1-yl-1*H*-benzoimidazole-2-thiol **5-Pyrrol-1-yl-1*H*-benzoimidazole-2-thiol derivatives**

$C_{11}H_9N_3S$
Mol. Wt.: 215.27

Where X - Cl, Br ,F, I.

R-Different substituent
*Synthesis of 5-Pyrrol-1-yl-1H-b*enzimidazole *-2-thiol :(**DJP/002-010**)*
As shown in above scheme. As literature serve the synthesis 2-Chloromethyl-4-methyl-quinazoline derivatives synthesis by the process [8].

The 5-Amino-1H-benzimidazole -2-thiol was react with 2,5-Dimethoxy furan in anhydrous condition in presence of dioxane to yield corresponding *5-Pyrrol-1-yl-1H-b*enzimidazole *-2-thiol* further more reaction with different derivatives to get *5-Pyrrol-1-yl-1H-b*enzimidazole *-2-thiol* derivatives. (**DJP/D130-140**).All these 5-Pyrrol-1-yl-1H-benzimidazole -2-thiol derivatives were identified by IR, ^{1}H NMR and MASS.

Synthesis of substituted 5-Pyrrol-1-yl-1H-benzimidazole -2-thiol derivatives:

(DJP/A130-140)
General Procedure
*5-Pyrrol-1-yl-1H-b*enzimidazole *-2-thiol* derivatives (0.01 mol) **DJP/D130-140** and different halide derivatives (0.01 mol) and potassium carbonate(0.01) in 10 ml of N,N-Dimethyl formamide stir for 2-3 hours at 90-95°C temperature then charge 100 ml water in to reaction mass then stir for another 1 hour and add 50ml x 2 times of Dichloromethane for extraction then distil out solvent completely then crystallization in ether and dry material at 55-60°C.As shown in **scheme-II**.

Spectral Data
1. *5-Pyrrol-1-yl-1H-b*enzimidazole *-2-thiol* **(DJP/D130)**:
IR (KBr): 3093.65 (Aromatic –C-H stretching), 1500.75(Aromatic –C=C– stretching), 1618.55(–C=N Stretching), 1354.82(–C=C– ring skeleton vibration); 1 H NMR (DMSO) ppm: 6.245 (2H,m,ArH), 7.165-7.331(4H,s of pyrrole ring), 7.63-7.68 (1H,m,ArH), 12.668 (2H,-NH and -SH); MS m/z:215.9[M^+]

2. *4-(5-Pyrrol-1-yl-1H-benzoimidazol-2-ylsulfanyl)-butyric acid ethyl ester* **(DJP/D131)**:
IR (KBr): 2978.15 (Aromatic –C-H stretching), 1485.70 (Aromatic –C=C– stretching), 2861.72 (Aliphatic –C-H stretching), 1443.66 (Aliphatic –C-H bending), 1630.73 (–C=O stretching of carbonyl), 1596.24 (–C=N Conjugation), 1401.10 (–C=C– ring skeleton vibration); 1 H NMR ($CDCl_3$) ppm: 1.319 (3H,t,-CH_3), 2.101-2.195 (2H,m,-CH_2-), 2.520-2.564 (2H,m,-CH_2-), 3.259-3.308 (2H,m,-CH_2-), 4.174-4.246 (2H,m,-CH_2-), 6.354 (2H,m, ArH), 7.095 (1H,s,ArH), 7.095-7.675 (4H,dd,pyrrole),10.559-10.663(-NH); MS m/z: 330.1[M^+]

3. *(5-Pyrrol-1-yl-1H-benzoimidazol-2-ylsulfanyl)-acetic acid tert-butyl ester* **(DJP/D132)**:
IR (KBr): 3073.2 (Aromatic –C-H stretching), 1513.78 (Aromatic–C=C–stretching), 2981.34 (Aliphatic –C-H stretching), 1487.70 (Aliphatic –C-H bending), 2344.86 (-SH stretching), 1718.49 (–C=O stretching of carbonyl), 1524.19 (–C=N Conjugation), 1438.37 (–C=C– ring skeleton vibration); 1 H NMR ($CDCl_3$) ppm: 1.530 (9H,s,3-CH_3), 3.848 (2H,s,-CH_2-), 6.35-6.359 (2H,m,ArH), 7.080 (1H, dd,ArH), 7.252-7.656 (4H,m,Pyrrole ring), 10.743-10.806(-NH broad singlet); MS m/z: 330.2 [M^+],352 [M^{+1}+Na]

4. *2-(4-Methoxy-3-methyl-pyridin-2-ylmethylsulfanyl)-6-pyrrol-1-yl-1H-b*enzimidazole **(DJP/D133)**:
IR (KBr): 2940 (Aromatic –C-H stretching), 1584.10 (Aromatic-C=C-stretching), 1481.53 (Aliphatic –C-H bending), 2371.86(-SH stretching, 1537.88 (–C=N Conjugation), 1437.64 (–C=C– ring skeleton vibration); 1 H NMR ($CDCl_3$) ppm: 2.272 (3H, s,-CH_3), 3.914 (3H,s,-CH_3), 4.390 (2H,2,-CH_2-), 6.356 (2H,m,ArH), 6.718-6.737 (1H,s,pyridine), 6.789-6.806 (1H,s,ArH), 7.108 (1H, m, pyridine), 7.237-7.266 (1H, m, pyrrole ring), 7.466-8.396 (3H, m, pyrrole ring), 13.308(-NH broad singlet); MS m/z: 351.1[M^+],273 [M^{+1}+Na]

5. *N-(4-Fluoro-phenyl)-2-(6-pyrrol-1-yl-1H-benzoimidazol-2-ylsulfanyl)-acetamide* **(DJP/D134)**:
IR (KBr) : 3052.2 (Aromatic –C-H stretching), 1523.28 (Aromatic–C=C–stretching), 2981.34 (Aliphatic –C-H stretching), 1487.71 (Aliphatic –C-H bending), 2354.86 (-SH stretching), 1719.29 (–C=O stretching of carbonyl), 1524.54 (–C=N Conjugation), 1438.37 (–C=C– ring skeleton vibration); 1 H NMR ($CDCl_3$) ppm: 4.05 (2H,s,-CH_2-), 6.28 (1H, broad singlet of –NH), 6.40-6.42 (2H,m,Pyrrole ring), 7.023-7.12 (2H,m,ArH), 7.21-7.23 (3H,m,ArH), 7.25-7.27 (2H,m,pyrrole ring), 7.65-7.69 (2H,m,ArH) ; MS m/z: 367.4[M^+], 389.5 [M^{+1}+Na]

6. *N-(4-Fluoro-phenyl)-3-[6-(methyl-vinyl-amino)-1H-benzoimidazol-2-ylsulfanyl]-propionamide* **(DJP/D135)**:
IR (KBr): 3245.21 (-NH stretching), 3085.24 (Aromatic –C-H stretching), 1545.15 (Aromatic–C=C–stretching), 2997.34 (Aliphatic –C-H stretching), 1410.90 (Aliphatic –C-H bending), 2389.56 (-SH stretching), 1748.09 (–C=O stretching of carbonyl), 1567.35 (–C=N Conjugation), 1483.73 (–C=C– ring skeleton vibration); 1 H NMR ($CDCl_3$) ppm: 2.53-2.56 (2H,t,-2CH_2-), 3.25-3.28 (2H,t,-CH_2-), 6.5(1H,broad singlet,-NH), 6.40-6.42 (2H,m,pyrrole ring), 7.022-7.12 (2H,m,ArH), 7.22-7.23 (3H,m,ArH), 7.245-7.251(2H,m,pyrrole ring), 7.65-7.68 (2H,m,ArH), 11.245-11.249 (1H,broad singlet,-NH); MS m/z: 281.4[M^+], 397.8 [M^{+1}+NH_3]

7. *2-(4-Methoxy-3-nitro-benzylsulfanyl)-6-pyrrol-1-yl-1H-b*enzimidazole **(DJP/D136)**:
IR (KBr): 3002.31 (Aromatic –C-H stretching), 1498.78 (Aromatic–C=C–stretching), 2918.04 (Aliphatic –C-H stretching), 1487.70 (Aliphatic –C-H bending), 2381.26 (-SH stretching), 1518.29 (–N-O stretching of Nitro), 1524.19 (–C=N Conjugation), 1418.71 (–C=C– ring skeleton vibration); 1 H NMR ($CDCl_3$) ppm: 3.215 (3H,s,-CH_3), 4.230 (2H,s,-CH_2-), 6.521-6.541 (1H,m,ArH), 6.785-6.732 (1H,m,ArH), 6.750-6.784 (2H,m,ArH), 7.574-7.582 (2H,m,ArH), 7.621-7.749 (1H,m,ArH), 8.01-8.03 (1H,m,ArH),12.241(1H,broad singlet,-NH); MS m/z: 381.1[M^+], 403 [M^{+1}+Na]

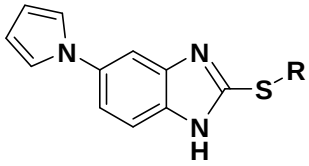
8. *2-(2-Nitro-benzylsulfanyl)-6-pyrrol-1-yl-1H-b*enzimidazole **(DJP/D137)**:
IR (KBr): 3012.23 (Aromatic –C-H stretching), 1565.08 (Aromatic–C=C–stretching), 2925.78 (Aliphatic –C-H stretching), 1578.70 (Aliphatic –C-H bending), 2384.26 (-SH stretching), 1545.34 (–C=N Conjugation), 1483.72 (–C=C– ring skeleton vibration); 1 H NMR ($CDCl_3$) ppm: 4.024 (2H,s,-CH_2-), 6.412-6.427 (2H,m,pyrrole ring), 7.156-7.159 (3H,m,ArH), 7.203-7.231(2H,m,ArH), 7.248-7.252 (2H,m.pyrrole ring), 7.421-7.436 (3H,m,ArH), 12.145 (1H,broad singlet,-NH); MS m/z: 351.4[M^+], 392.3 [M^{+1}+ACN]

9. *2-Benzylsulfanyl-6-pyrrol-1-yl-1H-b*enzimidazole *; compound with methane* **(DJP/D138)**:
IR (KBr): 3004.8 (Aromatic –C-H stretching), 1512.18 (Aromatic–C=C–stretching), 2897.81 (Aliphatic –C-H stretching), 1510.25 (Aliphatic –C-H bending), 2289.24 (-SH stretching), 1554.10 (–C=N Conjugation), 1398.57 (–C=C– ring skeleton vibration); 1 H NMR ($CDCl_3$) ppm: 3.947 (2H,s,-CH_2-), 6.394-6.416 (2H,m,pyrrole ring), 7.109-7.164 (3H,m,ArH), 7.194-7.245(2H,m,ArH), 7.248-7.252 (2H,m.pyrrole ring), 7.405-7.429 (3H,m,ArH), 12.457-12.491 (1H,broad singlet,-NH); MS m/z: 322[M^+], 363.2 [M^{+1}+ACN]

10. *4-(6-Pyrrol-1-yl-1H-benzoimidazol-2-ylsulfanylmethyl)-benzonitrile* **(DJP/D139)**:
IR (KBr): 3105.8 (Aromatic –C-H stretching), 1509.45 (Aromatic–C=C–stretching), 2929.34 (Aliphatic –C-H stretching), 2250(-CN stretching), 1487.70 (Aliphatic –C-H bending), 2344.86 (-SH stretching), 1524.19 (–C=N Conjugation), 1438.37 (–C=C– ring skeleton vibration); 1 H NMR ($CDCl_3$) ppm: 4.062 (2H,s,-CH_2-), 6.257-6.298 (2H,m,pyrrole ring), 7.086-7.164 (3H,m,ArH), 7.194-7.245(2H,m,ArH), 7.349-7.359 (2H,m.pyrrole ring), 7.409-7.424 (2H,m,ArH), 13.042 (1H,broad singlet,-NH); MS m/z: 346.45 [M^+], 369 [M^{+1}+Na]

11. *(5-Pyrrol-1-yl-1H-benzoimidazol-2-ylsulfanyl)-acetic acid ethyl ester* **(DJP/D140)**:
IR (KBr): 3035.21 (Aromatic –C-H stretching), 1578.19 (Aromatic–C=C–stretching), 2976.48 (Aliphatic –C-H stretching), 1405.19 (Aliphatic –C-H bending), 2294.51 (-SH stretching), 1769.48 (–C=O stretching of carbonyl), 1568.16 (–C=N Conjugation), 1479.24 (–C=C– ring skeleton vibration); 1 H NMR ($CDCl_3$) ppm: 1.28 (3H,s,-CH_3), 3.51 (2H,s,-CH_2-), 6.957-7.03 (1H,m,ArH), 6.489-6.487 (2H.m,pyrrolr ring) 7.135-7.214 (1H,s,ArH), 7.177-7.182 (1H,d,ArH),7.184-7.95 (2H,m,pyrrole ring), 7.201 (1H,d,ArH), 12.054-12.154 (1H,broad singlet.-NH); MS m/z: 302.3 [M^+], 320.8 [M^{+1}+NH_3]

Table: 1 Physical data and elemental analysis of synthesized 2-chloromethyl-4-methyl-quinazoline derivatives (DJP/D131-DJP/D140)



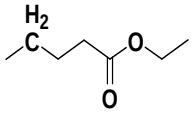
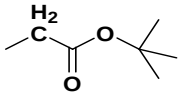
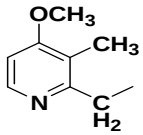
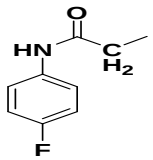
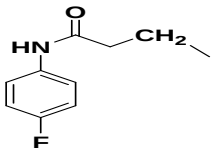
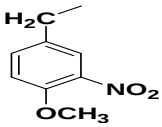
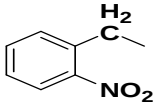
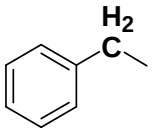
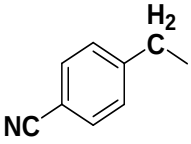
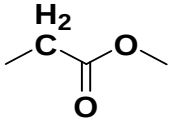
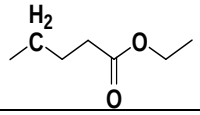
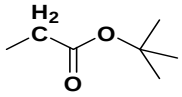
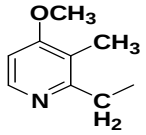
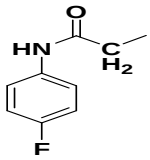
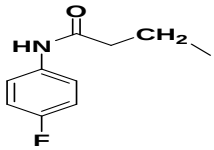
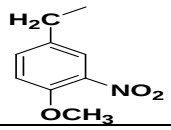
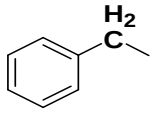
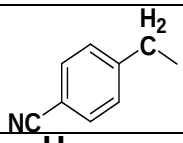
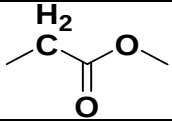
Sr. No.	R	Molecular Formula	M.P. (^{0}C)	Mol. Weight	Yield (%)	Elemental analysis Found (Calculated)		
						% C	% H	% N
DJP/D131		$C_{17}H_{19}N_3O_2S$	150-154	329.42	68	58.54 (61.98)	4.23 (5.81)	11.43 (12.76)
DJP/D132		$C_{17}H_{19}N_3O_2S$	124-126	313.42	72	60.58 (61.98)	5.24 (5.81)	12.14 (12.76)
DJP/D133		$C_{19}H_{18}N_4OS$	135-138	350.44	71	61.48 (65.12)	5.10 (5.18)	14.58 (15.99)
DJP/D134		$C_{19}H_{15}FN_4OS$	175-178	366.41	66	61.24 (62.28)	3.49 (4.13)	14.87 (15.29)
DJP/D135		$C_{20}H_{17}FN_4OS$	158-160	380.44	80	60.12 (63.14)	4.62 (4.50)	13.84 (14.73)
DJP/D136		$C_{19}H_{16}N_4O_3S$	124-128	380.42	68	58.54 (59.99)	3.98 (4.24)	13.78 (14.73)
DJP/D137		$C_{18}H_{14}N_4O_2S$	136-139	350.39	81	60.41 (61.70)	3.28 (4.03)	15.65 (15.99)
DJP/D138		$C_{19}H_{19}N_3S$	126-125	321.44	62	66.45 (70.99)	6.05 (5.96)	11.04 (13.07)
DJP/D139		$C_{20}H_{18}N_4S$	133-136	346.45	74	66.37 (69.34)	5.12 (5.24)	15.47 (16.17)
DJP/D140		$C_{15}H_{15}N_3O_2S$	88-90	301.36	77	57.45 (59.78)	4.98 (5.02)	12.47 (13.94)

Table: 2 In Vitro antimicrobial activity of 2-Chloromethyl-4-methyl-quinazoline derivatives (DJP/D131-DJP/D140)

Sr. No.	R	*E-coli*	*B-Subtillis*	*S-Aureus*	*S-Cerevisiae*	*A-niger*
DJP/D131		++	+	++	+	++
DJP/D132		+	+	++	++	+
DJP/D133		++	++	+	++	+
DJP/D134		+	++	+	++	++
DJP/D135		+	+	+	++	+
DJP/D136		+	++	+	++	+
DJP/D137		++	++	+	+	++
DJP/D138		++	+	++	+	++
DJP/D139		++	++	+	+	++
DJP/D140		+	++	++	+	++

**Effectively was classified in to three zones on the bases of the diameter of zone of inhibition*

+++ : *Most effective*
++ : *Moderate effective*
+ : *Slightly effective*
- : *Non effective*

In Vitro Antimicrobial Activity

Evaluation of antibacterial and antifungal activities was done by the disk diffusion techniqu[9]. The tested compound solution were prepared in dimethylformamide (DMF) and evaluated them for their in vitro antibacterial and

antifungal activity against *Bacillus subtillis* NCIM 2250, *Staphylococcus aureus* NCIM 2079, *Escherichia coli* NCIM 2109, *Aspergillus niger* NICM 501 and *Candida albicans* NICM 7431, respectively.

All bacteria were grown on Mueller-Hinton agar (Hi media) plates (37°C, 24 h) and fungi were grown on subouraud dextrose agar (Hi media) plates (26°C, 48-72h). The results were established by the presence of clear zone of inhibition around the activity compound.

RESULTS AND DISCUSSION

As many as new ten compounds were synthesized by adopting similar above procedure and then characterized by their physical, analytical and spectral data. The detail of some of the representative compounds are given in the experimental section. Their physical and elemental analysis data are presented in **Table 1**.

The entire synthesized compounds were tested for in vitro antimicrobial activity by the disk diffusion technique. The results are summarized in **Table 2** that includes the activity of reference compound Ampicillin.

The tested compound exhibited mild to moderate antibacterial activity against all three strains of bacteria. The compound DJP/D131, DJP/D133, DJP/D134, DJP/D137, DJP/D138, DJP/D139, and DJP/D140 shows highest activity.

The antifungal activity of the compound was studied for the two pathogenic fungi. Amphotericin B was used as reference for inhibitory activity against fungi. It was observed that compound DJP/D132, DJP/D133, DJP/D134, DJP/D13, and DJP/D136 had highest activity against *S-Cerevisiae* and DJP/D131, DJP/D133, DJP/D136, DJP/D137, DJP/D138, DJP/D139, and DJP/D120 tested against *E-coli* and showed good activity against *A-Niger*. It has also observed that compound DJP/D133, DJP/D134, DJP/D136, DJP/D137, DJP/D139, DJP/D140 *B-Subtillis* and compound DJP/D131, DJP/D132, DJP/D138, DJP/D140 against *S-Aureus.*

CONCLUSION

The antimicrobial study revealed that substitution in the 3rd position of quinazoline with methyl and Nitrogen containing heterocyclic compound produced more active compound in a series.

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