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Synthesis of A New Series of Bioactive Benzimidazoloylthiazoles

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The presence of thiazole ring in a compound is found to exhibit a wide variety of biological activity. In this synthetic method two versatile [4+1] synthetic strategies are demonstrated. 14 Densely functionalized ketothiazoles synthesized and the structure of these new compounds established spectroscopically using spectroscopic techniques. All the *keto*-thiazoles screened for antibacterial activity, out of which ten are found to be active against *Bacillus subtilis*.

Key Words: Ketothiazoles, Bioactivity, Benzimidazoles, Antitumour activity.

INTRODUCTION

The presence of thiazole ring in a compound is found to exhibit a wide variety of biological activity, for example 2-[1-(benzyloxycarbonylamino)-2-methylpropyl]-thiazole-4-carboxylic acid show potent biological activity[1,2]. Compounds containing benzimidazole moiety exhibits anticonvulsant, immuno suppressant, antitumour and antihistaminic[3] activity *e.g.*, thiabendazole was among the first member of a series of second generation anthelminitics. Lissoclinolide[4], a compound that exhibited mild antibacterial activity against the gram-negative bacteria, *Escherichia coli* was obtained from an ascidian lissoclinium patella. Thiazofurin[5] with an amide group as the 4-substituent, is a thiazole derivative with antitumour activity against general uterine tumours. When benzimidazole is attached to thiazoles, it could impart improved biological activities *e.g.*, mebendazole, oxfendazole, binomyl[2,6] and other benzimidazoles are anticonvulsants, sedatives, immune suppressants, antitumour agents and antihistaminics[7,8]. Thiabendazole[9] or 2-(4-thiazolyl)benzimidazole is widely used as an anthelminitic. Due to the biological activities of this class of compounds, it is decided to explore the possibility of a new series of compounds with a substituted amino group at C2, phenyl at C4 and a benzimidazoloyl group at C5 of 1, 3-thiazole to explore the biological activity offered by them.

EXPERIMENTAL

All chemicals used were of commercial grade. Melting points were uncorrected and were determined by open capillary method using an immersion bath of silicon oil or sulphuric acid. Thin layer chromatography was performed using silica gel- G (E. Merck, India) coated on glass plates. The spots were visualized in iodine vapour or under UV- light. The spectra were recorded on, Bruker spectrospin-100 (100 MHz), Brucker WM-400 (400 MHz) for ^{1}H and 100 MHz for ^{13}C), Jeol GSX (400 MHz) or EM-390 NMR spectrometers and Jeol D-300, Jeol SX-102, Shimadzu QP-2000.

In a novel method, we have synthesized a new series of bioactive compounds, *viz.*, 2-(N,N-dialkylamino/azacycloalkyl)-4-phenyl-5-(N-methyl-bezimidazol-2-oyl)thiazoles (**I**) by the action of N,N-dialkyl/cycloalkyl-N'-benzoylthiourea (**II**) with 2-bromoacetyl-N-methyl benzimidazole (**III**) in dry acetone. **II** was prepared by the action of benzoyl chloride and potassium thiocyanate in benzene in presence of a phase transfer catalyst tetrabutylammonium bromide (TBAB) and *in situ* reaction with dialkyl/cycloalkylamine. Compound **III** was prepared by the halogenation of 2-acetyl-N-methylbenzimidazole using a free radical catalyst azoizobutyronitrile (AIBN) in a protic solvent[10]. In order to study the effect of an aryl group instead of an alkyl/cycloalkyl group attached to amino group at C2 position of thiazoles, we have synthesized 2-arylamino-5-(N-methylbenzi-midazol-2-oyl)-4-phenylthiazoles (**IV**). Compound **IV** was prepared by using a strategy of reacting 1-aryl-3-(N-phenylbenzimidoyl)thiourea[11] (**V**) with **III** in a highly polar solvent in presence of a catalyst. Compounds **II** and **V** used as [C-N-C-S] precursor was obtained by methods developed in this laboratory and C5 of thiazole ring was provided by **III**.

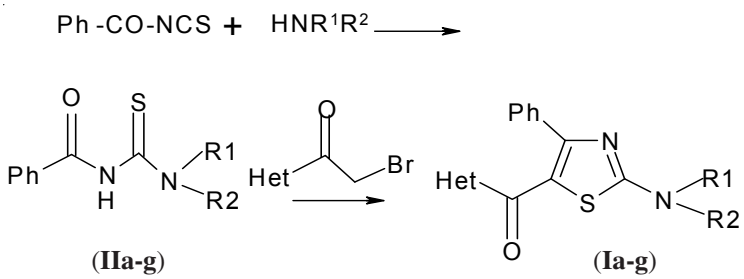
Synthesis of 2-(N, N-dialkylamino/azacycloalkyl)-4-phenyl-5-(N-methyl benzimidazol-2-oyl)thiazoles: A mixture of **III** (1 mmol) dissolved in dry acetone and **II** (1 mmol) was refluxed for 3 h. The mixture was worked up and the compound **I** obtained as a yellow crude material was purified by crystallization from ethanol-water and dried as microcrystalline powder.

Synthesis of 2-arylamino-5-(N-methylbenzimidazol-2-oyl)-4-phenyl thiazoles: To a solution of **III** (0.5 mmol) in warm DMF (0.7 mmol) and triethylamine (1 mmol) was added and the mixture was warmed. The reaction mixture was then poured to a slurry of ice and water containing a little conc. HCl with good stirring. A yellow solid precipitated was filtered, washed with water and dried. The crude material on crystallization from ethanol-water (1:1) afforded the thiazoles.

RESULTS AND DISCUSSION

Synthesis of 2-(N-alkylamino)-5-(benzimidazol-2-oyl)-4-phenyl thiazoles

The preliminary studies on the attempt to prepare the 2-substituted amino-4-phenyl-5-heteroylthiazoles were conducted using **II**. For example **III** or its hydrobromide salt was reacted with N,N-dimethyl-N'-benzoylthiourea (**IIa**) in dry acetone, a brownish yellow solid was formed under reflux which on purification by crystallization gave yellow crystals with molecular composition $C_{20}H_{18}N_4OS$ (**Ia**). The TLC analysis showed a single spot with bright yellow fluorescence under UV light. The IR spectrum showed ν(C=O) absorption at 1620 cm^{-1}. The ^1H NMR spectrum showed a singlet at δ 3.25 that was assigned to six hydrogens of dimethyl-amino group and another singlet at δ 3.95 due to a N-Me group. The signals due to nine aromatic hydrogens appeared as a multiplet at δ 7.24-7.35 (4*H*), a triplet at δ 7.40 (1*H*), a multiplet at δ 7.50-7.58 (2*H*) and two doublets at δ 7.65 and δ 7.72 for one hydrogen each. This data was in support for a structure assignment to the compound as **Ia**. The ^{13}C NMR spectrum showed fifteen peaks attributed to the eighteen carbon atoms in the compound. Six other compounds **I**(**b-g**) were also prepared with varying R1 and R2 as listed below. The reaction mechanism of the above reaction is as shown in **Scheme-I**.



(**IIa-g**) (**Ia-g**)

Het = N-methylbenzimidazol-2-oyl, R^1 & R^2 = **a**) methyl; **b**) ethyl; **c**) pyrrollidin-1-yl; **d**) pyperidin-1-yl; **e**) morpholin-4-yl; **f**) N-methylpiperazin-1-yl; **g**) 1,2,3,4-tetrahydroquinolin-1-yl

Scheme-I

Physical and spectral data of **I** was as given below:

Ia: Yield, 58 %; m.p. 165 ºC; IR (KBr, ν_{max}, cm^{-1}): 2935, 1620, 1566, 1490, 1458, 1410, 963, 865, 811, 764, 717, 575; ^1H NMR (400 MHz, DMSO-d_6), δ: 2.21 (s, 6H), 3.97 (S, 3H), 7.2-7.35 (m, 4H, Ar-H), 7.36-7.45 (t, *J* = 7.5Hz, 1H), 7.47-7.59 (m, 2H), 7.60-7.68 (d, *J* = 8Hz, 1H), 7.76 (d, *J* = 8Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 32.0 (3), 111.0, 117.2 120.5, 123.0, 124.7, 127.3 (2), 128.4, 129.3 (2), 136.0, 137.0, 140.6, 147.4, 163.6, 173.5.

Ib: Yield, 52 %; m.p. 165 ºC; IR (KBr, ν_{max}, cm^{-1}): 3056, 2982, 2955, 1627, 1539, 1465, 960, 858, 781, 750, 718, 686, 575, 543; ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.11 -1.35 (t, J = 7H_2, 6H), 3.5- 3.8 (q, J = 7Hz, 4H), 3.97 (s, 3H, N-CH_3), 7.15-7.36 (m, 4H), 7.36-7. 46 (t, J = 7Hz, 1H), 7.46-7.59 (m, 2H), 7.51-7.75 (dd, J = 8Hz, 2H); ^{13}C NMR (125 MHZ, DMSO-d_6) δ: 12.3 (2) 31.6 45.0 (2), 111, 117.0, 120.5, 122.9, 124.7, 127.3, 128.5, 129.3, 136, 136.2, 140.6, 147.6, 163.6, 171.9, 175.3.

Ic: Yield, 60 %, m.p. 227 ºC; IR (KBr, ν_{max}, cm^{-1}): 3049, 2982, 2861, 1640, 1546, 1472,, 946, 865, 811, 771, 716, 609, 669; ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.9-2.1 (S, 4H), 3.4-3.6 (S, 4H), 4.0 (S, 3H, N-CH_3), 7.2-7.36 (m, 4H), 7.36-7.45 (m, 1H), 7.6-7.6 (m, 2H), 7.6-7.7 (d, J = 8Hz, 1H), 7.7-7.77 (d, J = 8Hz, 1H).

Id: Yield, 45 %; m.p. 221 ºC; IR (KBr, ν_{max}, cm^{-1}): 3043, 2929, 2861, 1627, 1546, 1465, 953, 890, 804, 764, 710, 669.

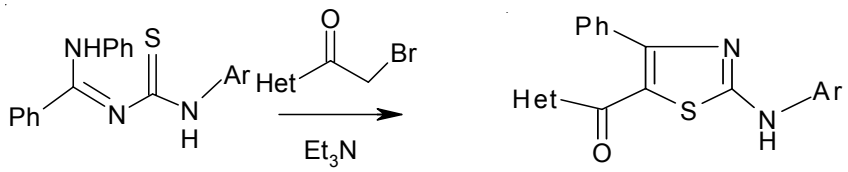
Ie: R^1 & R^2 = Morpholin-4-yl: Yield, 30 %, m.p. 175 ºC; IR (KBr, ν_{max}, cm^{-1}): 3070, 2975, 2921, 2867, 1688, 1634, 1512, 1465, 1357, 966, 949, 931, 870, 811, 744; ^{1}H NMR (400 MHz, DMSO-d_6), δ: 3.55-3.66 (t, J = 5Hz, 4H), 4H), 3.66-3.80 (t, J = 5 Hz, 4H), 3.90-4.02 (S, 3H, N-CH_3), 7.10-7.80 (m, 9H, Ar-H).

If: R^1 & R^2 = N-Methylpiperazin-1-yl: Yield, 60 %; m.p. 155 ºC; IR (KBr, ν_{max}, cm^{-1}): 3063, 2942, 2793, 1627, 1526, 1465, 1155, 1014, 959, 865, 804, 757, 724.

Ig: R^1 & R^2 = 1,2,3,4-Tetrahydroquinolin-1-yl: Yield, 62 %; m.p. 246 ºC; IR (KBr, ν_{max}, cm^{-1}): 3070, 2935, 1627, 1499, 1499, 1445, 1344, 960, 885, 757, 717.

Synthesis of 2-arylamino-5-(N-methylbenzimidazol-2-oyl)-4-phenyl thiazoles

After synthesizing the **I**, we next attempted the synthesis of the hitherto unreported **IV** by the reaction of **III** in DMF with **V** using triethylamine as catalyst as shown in the following **Scheme-II**.



Va-g **IVa-g**

Het = N-methylbenzimidazol-2-oyl ; Ar = **a**) phenyl, **b**) *o*-tolyl, **c**) *m*-tolyl, d) *p*-tolyl, e) *o*,*p*-dimethylphenyl, f) *p*-phenetyl, g) *p*-chlorophenyl

Scheme-II

Physical and spectral data of the compounds **IV** was as given below:

IVa: Yield, 98 %; m.p. 241 ºC; IR (KBr, ν_{max}, cm^{-1}): 3057, 2282, 1734, 1718, 1685, 1654, 1600, 1558, 1498, 1485, 1450, 1397, 1332, 1306, 948, 901, 852, 794, 745, 692; ^{1}H NMR (300 MHz, $CDCl_3$), δ: 406 (S, 3H), 7.0-09 (d, *J* = 12Hz, 2H) 7.19-7.22 (d, *J* = 12 H_2, 2H), 7.25-7.40 (m, 4H), 7.41-7.50 (m, 2H), 7.60-7.70 (m, 2H), 7.80-7.90 (d, *J* = 12Hz, 1H), 9.2-9.45 (br, S, 1N-H).

IVb: Yield, 89 %; m.p. 211 ºC; IR (KBr, ν_{max}, cm^{-1}): 3157, 3043, 2928, 1634, 1560, 1519, 1465, 1344, 953, 906, 865, 818, 751, 720, 575, 447; ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.08 (s, 3H, CH_3), 7.22-7.42 (m, 11H, Ar-H), 7.62-7.70 (m, 2H, Ar- H) 7.80-7.86 (d, 1H), 8.61 (br, S, 1N-H).

IVc: Yield, 94 %; m.p. 203 ºC; ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.33(s, 3H) 4.02 (d, 3H), 7.1-7.2 (t, 1H), 7.2-7.5(m, 7H, Ar-H), 7.51-7.80 (m, 5H, Ar-H), 10.32 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 18.0, 31.9, 111.0, 18.0, 121.0, 124.0, 125.0, 126.0, 127.0, 128.0, 128.5, 129.0, 129.5, 129.8, 131.0, 136.0, 137.0, 140.5, 147.0, 162.0, 163.0, 169.0, 172.0, 176.0.

IVd: Yield, 98 %; m.p. 217 ºC; IR (KBr, ν_{max}, cm^{-1}): 2363, 2343, 1752, 1734, 1718, 1701, 1690, 1654, 1625, 1601, 1556, 1508, 1484, 1859, 1332, 1305, 947, 901, 863, 818, 802, 776, 743, 701, 690, 562; ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.30 (s, 3H), 4.08 (s, 3H), 7.18-7.28 (m, 9H, Ar- H) 7.60-7.70 (m, 2H, Ar-H), 7.18-7.28 (m, 9H, Ar-H), 7.60-7.70 (m, 2H, Ar-H), 7.80-7.90 (m, 2H, Ar-H), 8.00 (br, s, 1NH).

IVe: Yield, 91 %; m.p. 227 ºC; IR (KBr, ν_{max}, cm^{-1}): 3150, 3033, 2922, 1774, 1734, 1718, 1700, 1684, 1654, 1626, 1554, 1508, 1484, 1307, 948, 900, 882, 857, 820, 799, 764, 743, 705, 690.

IVf: Yield, 90 %; m.p. 222 ºC; IR (KBr, ν_{max}, cm^{-1}): 3161, 2925, 2346, 2282, 1870, 1846, 1830, 1802, 1774, 1751, 1734, 1718, 1700, 1685, 1676, 1663, 1654, 1647, 1636, 1624, 1610, 1560, 1534, 902, 862, 832, 801, 742, 703, 690, 567; ^{1}H NMR (300 MHz, DMSO-d_6), δ: 2.32 (s, 3H) 4.06 (S, 3H), 6.93-6.94 (m, 1H), 7.08-7.15(m, 1H), 7.2-7.45 (m, 8H, Ar-H), 7.60-7.70 (m, 2H), 7.70-7.80 (m, 1H), 8.70-8.80 (S, 1NH).

IVg: Yield, 90 %; m.p. 226 ºC; IR (KBr, ν_{max}, cm^{-1}): 3161, 3118, 3056, 2923, 2346, 2282,. 1734, 1718, 1686, 1654, 1626, 1595, 901, 858, 828, 800, 735, 707, 690, 628; ^{1}H NMR (500 MHz, DMSO-d_6), δ: 1.30-1.35 (t, *J* = 5Hz, 3H), 3.97-4.05 (q, *J* = 6H_2, 5H, O-CH_2, N-CH_3), 6.93-7.01 (d, *J* = 6Hz, 2H), 7.29-7.40 (m, 4H), 7.40-7.46 (t, *J* = 6Hz, 1H), 7.53-7.60 (m, 2H), 7.66-7.65 (m, 2H) 7.66-7.75 (q, *J* = 3.6Hz, 2H), 10.78-10.84 (S, 1NH); ^{13}C NMR (125 MHz, DMSO-d_6), δ: 15.0, 32.0, 63.0, 111.0, 115.0, 118.0, 121.0, 122.0, 123.0, 124.0, 125.0, 125.2, 127.4, 128.6, 129.0, 129.4, 133.0, 135.9, 136.4, 140.5, 147.2, 154.7, 162.3, 169.3, 175.5.

Antibacterial activity: The bioactivity study shows that the 2-substituted amino-5-heteroyl-4-phenylthiazoles have potent biological activity. Out of the 14 thiazoles that have now been screened for antibacterial activity against two Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* and one Gram-negative bacteria *Escherachia coli*, ten compounds were found to be active against *Bacillus subtilis* but all were inactive towards *Staphylococcus aureus* and *Escherachia coli*. The activities of the syntheized thiazole derivatives were shown in the Table-1. It is observed that among the C2 N-substitutent pattern, a disubstituted nitrogen attached to C2 is preferable to a monosubstituted one. It is also further seen that both the dialkylamino (NR^1R^2) and the 1-azacycloalkyl type nitrogen substitution on the C2 ring position confer activity. The reported bioactivity study has been confined to antibacterical testing as the *in vitro* cytotoxicity analysis is under way.

TABLE-1
ANTIBACTERIAL ACTIVITY OF SUBSTITUTED BENZIMIDAZOLOYLTHIAZOLES

Compd.	Substitutions	Amount loaded (μg/mL)	Organism/Zone (mm)		
			SA	BS	EC
Ia	Dimethyl	0.1	Resistant	Resistant	Resistant
Ib	Diethyl	0.1	Resistant	6	Resistant
Ic	Pyrrolodinyl	0.1	Resistant	6	Resistant
Id	Piperidinyl	0.1	Resistant	6	Resistant
Ie	Morpholinyl	0.1	Resistant	6	Resistant
If	N-Methyl piperazinyl	0.1	Resistant	6	Resistant
Ig	1,2,3,4 THQ	0.1	Resistant	Resistant	Resistant
IVa	Phenyl	0.1	Resistant	7	Resistant
IVb	*o*-Tolyl	0.1	Resistant	Resistant	Resistant
IVc	*m*-Tolyl	0.1	Resistant	6	Resistant
IVd	*p*-Tolyl	0.1	Resistant	6	Resistant
IVe	*o*,*p*-Dimethyl phenyl	0.1	Resistant	Resistant	Resistant
IVf	*p*-Phenetyl	0.1	Resistant	6	Resistant
1Vg	*p*-Chloro phenyl	0.1	Resistant	6	Resistant
Penicillin G	Standard	0.1	5	6	Resistant

SA = *Staphylococcus aureus*; BS = *Bacillus subtilis*; EC = *Escherachia coli*

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