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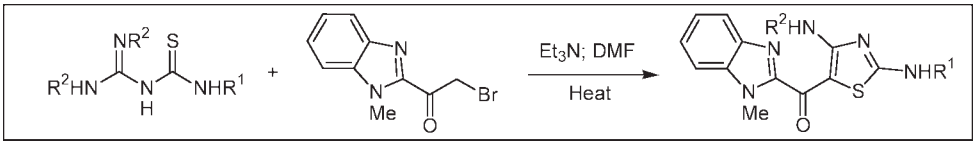

[2,4-Bis(arylamino)thiazol-5-yl]-(1-methyl-1*H*-benzimidazol-2-yl)methanones, as the analogs of the cytotoxic marine alkaloid dendrodoine, are synthesized and characterized by elemental analysis, IR, NMR, and Mass spectral data. The thiourea derivatives provide four ring atoms for the thiazole ring construction and thus act as [C—N—C—S] synthons. The remaining carbon of the thiazole is sourced from 2-(2-bromoacetyl)-1-methyl-1*H*-benzimidazole. This [4+1] heterocyclization reaction is adopted for the synthesis of novel 1-methyl-1*H*-benzimidazole derivatives.

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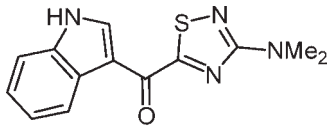
INTRODUCTION

For a natural product, either from terrestrial or from marine sources, dendrodoine **1**, [3-(*N,N*-dimethylamino-1,2,4-thiadiazol-5-yl]-indol-3-yl-methanone, isolated [1] from the ''baked bean ascidian'' or *Dendrodoa grossularia*, is unusual in that it incorporates a 1,2,4-thiadiazole ring. It has been shown to be cytotoxic *in vitro* [1,2] and has been synthesized [3] by a 1,3-dipolar cycloaddition of indoloyl cyanide to a nitrile sulfide obtained by the thermolysis of a 1,3,4-oxathiazol-2-one



1
Dendrodoine

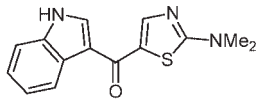
prepared from *N,N*-dimethylurea and chlorocarbonylsulphenyl chloride. This route is rather inflexible as it is confined solely to the preparation of 3-*N,N*-dialkylamino derivatives. In addition, the hetaroyl cyanides are difficult to access, thereby making the preparation of dendrodoine analogs with a variety of substituents not easy. Moreover, the scope of the substituent manipulation in **1** is restricted due to the availability of only two carbons for substitution or functionalization in the 1,2,4-thiadiazole ring. Therefore, the exchange of a 2-aminothiazole unit for the 3-amino-1,2,4-thiadiazole unit in dendrodoine seemed attractive. Thus, the synthesis of several (2-*N,N*-dimethylaminothiazol-5-yl)-(hetaryl)-methanones as thiazole analogs of dendrodoine and the cancer cell cytotoxicity of the indolyl derivative **2** at submicromolar concentration were reported by us recently [4].

In this context, the 2-amino-5-ketothiazole synthesis developed by us [5–7] appeared promising. A variety of amino substituents could be placed on C-2 and C-4 carbons of the thiazole ring by choosing the appropriate thiourea synthon and the 5-keto substituent could be accessed through a variety of α-haloketones. As typical examples, [4-amino-2-(4-methoxyphenylamino)-thiazol-5-yl)]-phenylmethanone **3** [8], [4-(4-chlorophenylamino)-2-(4-methoxyphenylamino)thiazol-5-yl)]-*1H*-indol-3-yl-methanone **4**, and 5-[4-amino-2-(4-methoxyphenylamino)-thiazol-5-yl)]-(1-methyl-1*H*-benzimidazol-2-yl)-methan-one **5** [9] were found to be cancer cell cytotoxic at submicromolar levels. To broaden the scope of this study further, we now report the synthesis of [2,4-bis(arylamino)thiazol-5-yl](1-methyl-1*H*-benzoimidazol-2-yl)methanones as further analogs of dendrodoine. Literature survey shows several examples of compounds having a 1*H*-benzimidazole ring which exhibit remarkable bioactivity including anticancer activity [10–14].

RESULTS AND DISCUSSION

The route adopted for the synthesis of these novel analogs of dendrodoine was based on a retro synthetic analysis as outlined in Scheme 1. The thiourea derivatives [5–7] (**6a–k**) provide four ring atoms for the thiazole ring construction and thus act as [C—N—C—S]

synthons. The remaining carbon of the thiazole is sourced from 2-(2-bromoacetyl)-1-methyl-1*H*-benzimidazole. This [4+1]



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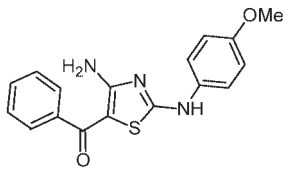
(2-*N*,*N*-dimethylaminothiazol-5-yl)-(1*H*-indol-3-yl)methanone



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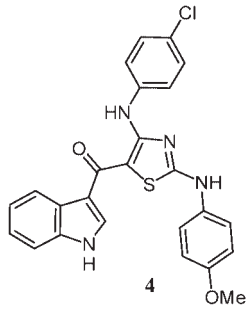

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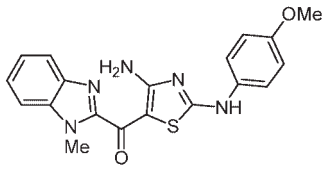

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heterocyclization reaction is now selected for the synthesis of novel 1-methyl-1*H*-benzimidazole derivatives (Scheme 2). Thus, the reaction of 1-(*N*,*N*'-diphenylamidino)-3-phenylthiourea (**6a**) in *N*,*N*-dimethylformamide (DMF) with 2-(2-bromoacetyl)-1-methyl-1*H*-benzimidazole (**7**) which was prepared from 2-(1-hydroxyethyl)-1*H*-benzimidazole [15,16], in DMF in the presence of triethylamine afforded an orange, crystalline compound which showed up in the thin layer chromatogram (TLC) as a single fluorescent yellow spot, indicating the formation of only one major product.

The molecular composition of the compound (**8a**) was found to be $C_{24}H_{19}N_5OS$. The IR (KBr) spectrum shows peaks at 3387, 3267, 3200, and 3117 cm^{-1}, which are attributed to the ν_{N-H} vibration. The aromatic ν_{C-H} band appears at 3050 cm^{-1}. The aliphatic ν_{C-H} band is observed at 2928 $cm^{-1}$and 2861 cm^{-1}. The highly conjugated carbonyl group shows $\nu_{C=O}$ vibration at 1607 cm^{-1}.

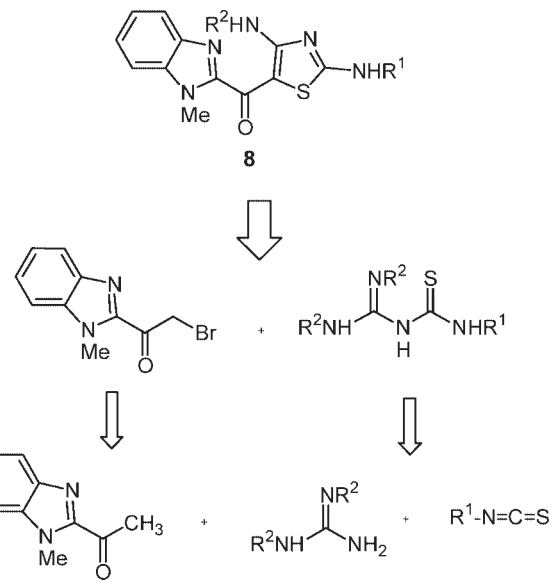
The ^{1}HNMR (300 MHz, DMSO-d_6) spectrum shows a three-hydrogen singlet at δ 4.22, which has been ascribed to the methyl group of 1-methyl-1*H*-benzimidazole ring. The spectrum consists of three multiplets in the aromatic region. The first multiplet at δ 7.06–7.18 is due to two aromatic hydrogens. The H-5 and H-6 of the 1-methyl-1*H*-benzimidazole ring and the four other aromatic hydrogens give rise to the second multiplet at δ 7.25–7.46. The third multiplet at δ 7.64–7.78 arises from H-4 and H-7 of the 1-methyl-1*H*-benzimidazole ring and the remaining four aromatic hydrogens. The two one-hydrogen singlets in the downfield region at δ 11.19 and 11.85 are assignable to NH hydrogen of the two NHAr groups.

The FAB MS confirms the molecular mass of the compound as 425 in accordance with the elemental analysis data. The presence of 24 carbons in the compound is confirmed from the 20 peaks observed in the ^{13}CNMR spectrum. Based on these data, the structure of the compound now obtained was assigned as [2,4-bis(phenylamino)thiazol-5-yl](1-methyl-1*H*-benzim-idazol-2-yl)methanone (**8a**). By following the similar procedure 10 additional [2,4-bis(arylamino)thia-zol-5-yl](1-methyl-1*H*-benzimidazol-2-yl)methanones (**8b–k**) were prepared and characterized.

EXPERIMENTAL

Melting points are uncorrected and were determined by open capillary method using an immersion bath of silicon oil. TLC was performed using silica gel-G (E. Merck, India) coated on glass plates. The spots were visualized in iodine vapor or under UV light. The spectra were recorded on: JEOL

Scheme 1



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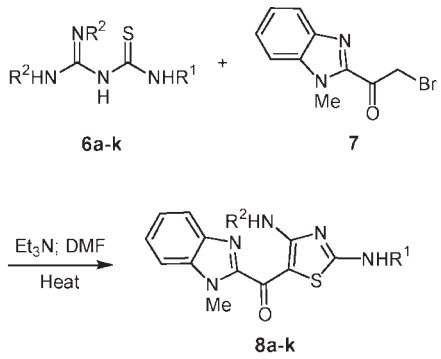
Scheme 2



Physical data of [2,4-bis(arylamino)thiazol-5-yl](1-methyl-*1H*-benzoimidazol-2-yl)methanones **(8a-k)**

	R^1	R^2	Yield % [a]	Yield % [b]
8a	phenyl	phenyl	97	65
8b	4-chlorophenyl	4-chlorophenyl	95	63
8c	4-methylphenyl	4-methylphenyl	96	65
8d	4-chlorophenyl	phenyl	93	63
8e	4-methylphenyl	phenyl	98	65
8f	4-ethoxyphenyl	phenyl	96	61
8g	phenyl	4-chlorophenyl	95	59
8h	4-methoxyphenyl	4-chlorophenyl	97	57
8i	4-methylphenyl	4-chlorophenyl	96	60
8j	4-ethoxyphenyl	4-chlorophenyl	97	58
8k	phenyl	4-methylphenyl	92	62

[a] Crude product [b] Recrystallised product

DRX 300 or DPX 300 NMR spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}CNMR spectra), JEOL SX 102/DA-6000 mass spectrometer (using Argon/Xenon, 6 KV, 10 mA as the FAB gas, and *m*-nitrobenzyl alcohol as the matrix) for FAB mass spectra and Nicolet 400D FTIR spectrometer. All new compounds gave satisfactory C, H, and N analysis (CDRI, Lucknow).

General procedure for the synthesis of [2,4-bis(arylamino)thiazol-5-yl](1-methyl-1*H*-benzoimidazol-2-yl)methanones (8a–k). A solution of 2-(2-bromoacetyl)-1-methyl-1*H*-benzimidazole (**7**) (0.254 g, 1 mmol) which was prepared from 2-(1-hydroxyethyl)-1*H*-benzimidazole [15,16], in DMF (2 mL) was added to a solution of 1-aryl-3-(*N*,*N*'-diarylamidino)thiourea (1 mmol) (**6a–k**) [5] in DMF (2 mL). Triethylamine (0.15 mL, 1 mmol) was added under stirring and the mixture was heated at 80–85°C for 5 min. It was then cooled and poured into ice-cold water with constant stirring. The yellow precipitate thus obtained was filtered, washed with water, and dried. The crude product was purified by crystallization.

[2,4-Bis(phenylamino)thiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8a). Starting from 1-(*N*,*N*'-diphenylamidino)-3-phenylthiourea (**6a**), 2-(2-bromoacetyl)-1-methyl-1*H*-benzimidazole (**7**), and following the general procedure above, **8a** was obtained as a deep orange solid. It was crystallized from ethanol-water (3:1), m.p. 180–181°C; IR (KBr) ν: 3387, 3267, 3200, 3117, 3050, 2928, 2861, 1607, 1573, 1517, 1483, 1445, 1350, 1217, 950, 900, 733, 690 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 4.22(s, 3H, *N*—CH_3), 7.06–7.18(m, 2H, 2ArH), 7.25–7.46(m, 6H, H-5, H-6, 4ArH), 7.64–7.78(m, 6H, H-4, H-7, 4ArH), 11.19(s, 1H, NH), 11.85(s, 1H, NH); ^{13}CNMR (75 MHz, DMSO-d_6): δ 32.4, 96.4, 111.2, 119.4, 120.0, 120.2, 123.2, 123.4, 124.0, 124.6, 129.2, 129.3, 136.8, 139.1, 139.3, 140.8, 147.2, 162.7, 171.7, 171.8; FABMS: *m*/*z* 426 (MH^+), 425 (M^+). *Anal.* Calcd for $C_{24}H_{19}N_5OS$: C, 67.74; H, 4.50; N, 16.46%. Found: C, 67.61; H, 4.58; 16.61%.

[2,4-Bis(4-chlorophenylamino)thiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8b). The reaction of 1-(*N*,*N*'-di(4-chlorophenyl)amidino)-3-(4-chlorophenyl)thiourea (**6b**) with **7** afforded **8b** as a deep orange solid. It was crystallized from ethanol-water (3:1), m.p. 238–239°C; IR (KBr) ν: 3449, 3238, 3189, 3111, 3032, 2933, 2867, 1627, 1576, 1493, 1455, 1411, 1356, 1210, 1093, 1023, 960, 822, 740, 674 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 4.20(s, 3H, *N*—CH_3), 7.27–7.53(m, 6H, H-5, H-6, 4ArH), 7.60–7.78(m, 6H, H-4, H-7, 4ArH), 11.26(s, 1H, NH), 11.79(s, 1H, NH); FABMS: *m*/*z* 494 (MH^+), 493 (M^+). *Anal.* Calcd for $C_{24}H_{17}Cl_2N_5OS$: C, 58.30; H, 3.47; N, 14.17%. Found: C, 58.53; H, 3.58; N, 14.02%.

[2,4-Bis(4-methylphenylamino)thiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8c). 1-(*N*,*N*'-di(4-methylphenyl)amidino)-3-(4-methylphenyl)thiourea (**6c**) and **7** on reaction as above gave **8c** a as a deep orange solid. It was crystallized from ethanol-water (3:1), m.p. 208–209°C; IR (KBr) ν: 3312, 3200, 3117, 3050, 2928, 2850, 1607, 1597, 1550, 1519, 1450, 1350, 1216, 1167, 1117, 1017, 879, 825, 733, 683 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 2.29(s, 6H, $2CH_3$), 4.23(s, 3H, *N*—CH_3), 7.16–7.26(m, 4H, 4ArH), 7.28–7.43(m, 2H, H-5, H-6), 7.54(d, J = 8.1 Hz, 2H, 2ArH), 7.63(d, J = 8.4 Hz, 2H, 2ArH), 7.69(d, J = 8.1 Hz, 1H, H-7), 7.74(d, J = 7.8 Hz, 1H, H-4), 11.08(s, 1H, NH), 11.87(s, 1H, NH); ^{13}CNMR (75 MHz, DMSO-d_6): δ 20.86, 20.94, 32.27, 95.46, 97.76, 102.35, 110.09, 120.78, 120.92, 121.03, 123.00, 124.47, 129.47, 130.14, 133.20, 135.22, 135.62, 136.82, 141.48, 148.38, 163.25, 172.28; FABMS: *m*/*z* 454 (MH^+), 453 (M^+). *Anal.* Calcd for $C_{26}H_{23}N_5OS$: C, 68.85; H, 5.11; N, 15.44%. Found: C, 68.58; H, 5.01; N, 15.58%.

[2-(4-Chlorophenylamino)-4-phenylaminothiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8d). Using 1-(*N*,*N*'-diphenylamidino)-3-(4-chlorophenyl)thiourea (**6d**), and **7**, **8d** was obtained as a deep orange solid. It was crystallized from ethanol-water (3:1), m.p. 171–173°C; IR (KBr) ν: 3367, 3282, 3184, 3117, 2929, 2864, 1621, 1582, 1522, 1494, 1456, 1406, 1355, 1222, 1097, 963, 830, 752, 686 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 4.22(s, 3H, *N*—CH_3), 7.11(t, J = 9 Hz, 1H, 1ArH), 7.26–7.51(m, 6H, H-5, H-6, 4ArH), 7.59–7.79(m, 6H, H-4, H-7, 4ArH), 11.27(s, 1H, NH), 11.80(s, 1H, NH). FABMS: *m*/*z* 460 (MH^+). *Anal.* Calcd for $C_{24}H_{18}ClN_5OS$: C, 62.67; H, 3.94; N, 15.23%. Found: C, 62.57; H, 3.81; N, 15.48%.

[2-(4-Methylphenylamino)-4-phenylaminothiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8e). The reaction of 1-(*N*,*N*'-diphenylamidino)-3-(4-methylphenyl)thiourea (**6e**) with **7** afforded **8e** as a deep orange solid. It was crystallized from ethanol-water (3:1), m.p. 161–164°C; IR (KBr) ν: 3384, 3272, 3200, 3117, 3059, 2931, 2850, 1619, 1580, 1506, 1448, 1418, 1357, 1205, 966, 825, 751 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 2.31(s, 3H, CH_3), 4.25(s, 3H, *N*—CH_3), 7.12(t, J = 6.9 Hz, 1H, 1ArH), 7.24(d, J = 7.8 Hz, 2H, 2ArH), 7.28–7.49(m, 4H, H-5, H-6, 2ArH), 7.56(d, J = 7.5 Hz, 2H, 2ArH), 7.64–7.86(m, 4H, H-4, H-7, 2ArH), 11.10(s, 1H, NH), 11.91(s, 1H, NH); FABMS: *m*/*z* 440 (MH^+), 439 (M^+). *Anal.* Calcd for $C_{25}H_{21}N_5OS$: C, 68.31; H, 4.82; N, 15.94%. Found: C, 68.53; H, 4.95; N, 16.07%.

[2-(4-Ethoxyphenylamino)-4-phenylaminothiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8f). 1-(*N*,*N*'-diphenylamidino)-3-(4-ethoxyphenyl)thiourea (**6f**) was reacted with **7** to obtain **8f** as a deep orange solid, which was crystallized from ethanol-water (3:1), m.p. 121–124°C; IR (KBr) ν: 3301, 3207, 3124, 3097, 2975, 2925, 2841, 1615, 1600, 1578, 1523, 1457, 1424, 1350, 1237, 1176, 1130, 1059, 949, 834, 747, 690 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 1.32(t, J = 6 Hz, 3H, CH_3), 4.03(quartet, J = 7 Hz, 2H, CH_2), 4.22(s, 3H, *N*—CH_3), 6.99(d, J = 8.7 Hz, 2H, 2ArH), 7.10(t, J = 7.35 Hz, 1H, 1ArH), 7.28–7.46(m, 4H, H-5, H-6, 2ArH), 7.53(d, J = 8.1 Hz, 2H, 2ArH), 7.68(d, J = 8.1 Hz, 1H, H-7), 7.74(d, J = 7.8 Hz, 3H, H-4, 2ArH), 11.04(s, 1H, NH), 11.92(s, 1H, NH); FABMS: 470 (MH^+), 469 (M^+). *Anal.* Calcd for $C_{26}H_{23}N_5O_2S$: C, 66.50; H, 4.94; N, 14.92%. Found: C, 66.32; H, 4.85, N, 14.81%.

[4-(4-Chlorophenylamino)-2-phenylaminothiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8g). Upon reaction of 1-(*N*,*N*'-di(4-chlorophenyl)amidino)-3-phenylthiourea (**6g**) with **7**, **8g** was obtained as a deep orange solid, which was crystallized from ethanol-water (3:1), m.p. 193–198°C; IR (KBr) ν: 3448, 3233, 3187, 3117, 3050, 2925, 2850, 1613, 1575, 1550, 1492, 1445, 1367, 1258, 1217, 1100, 1020, 958, 825, 767, 690 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 4.21(s, 3H, *N*—CH_3), 7.15(t, J = 7.2 Hz, 1H, 1ArH), 7.29–7.52(m, 6H, H-5, H-6, 4ArH), 7.59–7.80(m, 6H, H-4, H-7, 4ArH), 11.20(s, 1H, NH), 11.83(s, 1H, NH). *Anal.* Calcd for $C_{24}H_{18}ClN_5OS$: C, 62.67; H, 3.94; N, 15.23%. Found: C, 62.81; H, 4.00; N, 15.39.

[4-(4-Chlorophenylamino)-2-(4-methoxyphenylamino)thiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8h). Starting from 1-(*N*,*N*'-di(4-chlorophenyl)amidino)-3-(4-methoxyphenyl) thiourea (**6h**), and **7**, **8h** was obtained as a deep orange solid, which was crystallized from ethanol-water (3:1), m.p. 136–138°C; IR (KBr) ν: 3461, 3237, 3190, 3116, 3035, 2931, 2854, 1613, 1580, 1491, 1452, 1402, 1351, 1216, 1094, 1020, 965, 830, 749, 604 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 3.77(s, 3H, OCH_3), 4.22(s, 3H, *N*—CH_3), 7.02(d, J = 9 Hz, 2H, 2ArH), 7.23–7.57(m, 6H, H-5, H-6, 4ArH), 7.60–7.83(m, 4H, H-4, H-7, 2ArH), 11.07(s, 1H, NH), 11.91(s, 1H, NH). *Anal.* Calcd for $C_{25}H_{20}ClN_5O_2S$: C, 61.28; H, 4.11; N, 14.29%. Found: C, 61.40; H, 4.25; N, 14.45%.

[4-(4-Chlorophenylamino)-2-(4-methylphenylamino)thiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8i). The reaction of 1-(*N*,*N*'-di(4-chlorophenyl)amidino)-3-(4-methylphenyl)thiourea (**6i**) with **7** afforded **8i** as a deep orange solid which was crystallized from ethanol-water (3:1), m.p. 218–219°C; IR (KBr) ν: 3464, 3247, 3100, 3034, 2917, 2854, 1617, 1571, 1550, 1514, 1445, 1359, 1217, 1097, 958, 826, 752, 673 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 2.32(s, 3H, CH_3), 4.24(s, 3H, *N*—CH_3), 7.14–7.60(m, 8H, H-5, H-6, 6ArH), 7.61–7.88(m, 4H, H-4, H-7, 2ArH), 11.13(s, 1H, NH), 11.88(s, 1H, NH); FABMS: *m*/*z* 474 (MH^+), 473 (M^+). *Anal.* Calcd for $C_{25}H_{20}ClN_5OS$: C, 63.35; H, 4.25; N, 14.78%. Found: C, 63.50; H, 4.35; N, 14.95%.

[4-(4-Chlorophenylamino)-2-(4-ethoxyphenylamino)thiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8j). Upon reacting with **7**, 1-(*N*,*N*'-di(4-chlorophenyl)amidino)-3-(4-ethoxyphenyl)thiourea (**6j**) afforded **8j** as a deep orange solid, which was crystallized from ethanol-water (3:1), m.p. 172–173°C; IR (KBr) ν: 3440, 3299, 3200, 3080, 2975, 2917, 2867, 1625, 1600, 1560, 1518, 1490, 1438, 1354, 1249, 1217, 1205, 1181, 1093, 1051, 958, 821, 740, 617 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 1.33(t, J = 6.45 Hz, 3H, CH_3), 4.02(quartet, J = 6.9 Hz, 2H, CH_2), 4.19(s, 3H, *N*—CH_3), 6.98(d, J = 8.4 Hz, 2H, 2ArH), 7.21–7.82(m, 10H, H-4, H-5, H-6, H-7, 6ArH), 11.00(s, 1H, NH), 11.91(s, 1H, NH). *Anal.* Calcd for $C_{26}H_{22}ClN_5O_2S$: C, 61.96; H, 4.40; N, 13.90%. Found: C, 62.08; H, 4.51; N, 13.74%.

[4-(4-Methylphenylamino)-2-phenylaminothiazol-5-oyl](1-methyl-1H-benzoimidazol-2-yl)methanone (8k). The compound **8k** was obtained from 1-(*N*,*N*'-di-(4-methylphenyl)amidino)-3-phenylthiourea (**6k**) and **7** as a deep orange solid. It was crystallized from ethanol-water (3:1), m.p. 225–226°C; IR (KBr) ν: 3306, 3051, 2928, 2859, 1607, 1567, 1538, 1499, 1411, 1364, 1337, 1204, 958, 877, 817, 751 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 2.30(s, 3H, CH_3), 4.23(s, 3H, *N*—CH_3), 7.14(t, J = 7.35 Hz, 1H, 1ArH), 7.21(d, J = 8.4 Hz, 2H, 2ArH), 7.28–7.49(m, 4H, H-5, H-6, 2ArH), 7.58–7.82(m, 6H, H-4, H-7, 4ArH), 11.16(s, 1H, NH), 11.85(s, 1H, NH); FABMS: *m*/*z* 440 (MH^+), 439 (M^+). *Anal.* Calcd for $C_{25}H_{21}N_5OS$: C, 68.31; H, 4.82; N, 15.94%. Found: C, 68.58; H, 4.92; N, 15.75%.

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