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Synthesis of novel 2-[2-(substituted amino)phenethyl]-1*H*-benzimidazoles; 3,4-dihydro and 1,2,3,4,-tetrahydropyrimido[1,6-*a*]-benzimidazoles as potential antiulcer agents

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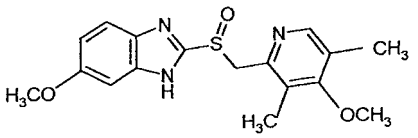
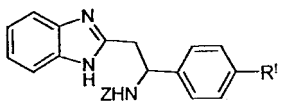
In an effort to establish new antiulcer agents a series of 2-(2-substituted amino)-1*H*-benzimidazoles **8**, **9**, **14**; 1,3-disubstituted-3,4-dihydropyrimido[1,6-*a*]benzimidazoles **4**, **7**, **11**, **12**; 3-substituted-3,4-dihydropyrimido[1,6-*a*]benzimidazol-1(2*H*)-thiones (or (2*H*)-ones) **10**, **17** and 3-substituted-1,2,3,4-tetrahydropyrimido[1,6-*a*]benzimidazoles **15** were synthesized. Representative members were selected to evaluate their gastric antisecretory activity using an *in vivo* pylorus ligated rat method. Omeprazole was used as reference. The results indicated that the test compounds exhibit gastric antisecretory activity. The percent inhibition ± SEM at the indicated dose level was demonstrated as omeprazole (59% ± 0.16 at 3 mg/kg) > **15a** (53% ± 1.39 at 3 mg/kg) > **7a** (51% ± 1.04 at 1 mg/kg) > **10a** (50% ± 1.36 at 3 mg/kg).

1. Introduction

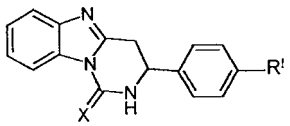
During the past decades, inhibition of gastric acid secretion has attracted considerable clinical attention as a therapeutic principle in the treatment of gastric and duodenal ulcer diseases (Fellenius et al. 1981; Lindberg et al. 1986; Olbe et al. 1979; Prous 1988; Sachs 1986). As a part of our effort to identify novel antiulcer agents, 2-(2-aminophenethyl)-1*H*-benzimidazoles (**I**) have been reported (Shafik et al. 1999, 2004) as bioisosteric relatives to omeprazole (Lindberg et al. 1986). The compounds were evaluated *in vivo* for gastric antisecretory activity using pylorus ligated rats (Doria et al. 1985; Kastura et al. 1994; Sanfilippo et al. 1988). The results indicated that **I** (Z = H) exhibited a more pronounced antisecretory activity than omeprazole. Consequently, it was assumed that the presence of the 2-amino group in **I** (Z = H) might have increased the potency to inhibit gastric acid secretion, by elevating the affinity towards the proton pump in the acidic canaliculi of the parietal cell. Hence, it was decided to study structural modifications of **I** (Z = H) in relevance to gastric antisecretory activity. Accordingly, a series of 2-(2-substituted aminophenethyl) benzimidazole (**I**) was synthesized. Compounds in which the amino function was incorporated into a cyclic ring system (**II, III**) and derivatives which include an extra amino function (**IV**) have also been prepared. Representatives of the new compounds were tested for their gastric antisecretory activity *in vivo*, using the pylorus ligated rat method (Doria et al. 1985; Kastura et al. 1994; Sanfilippo et al. 1988). Omeprazole was used as a reference.



Omeprazole



I



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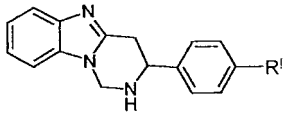

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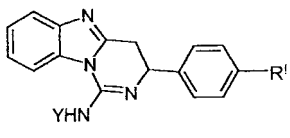


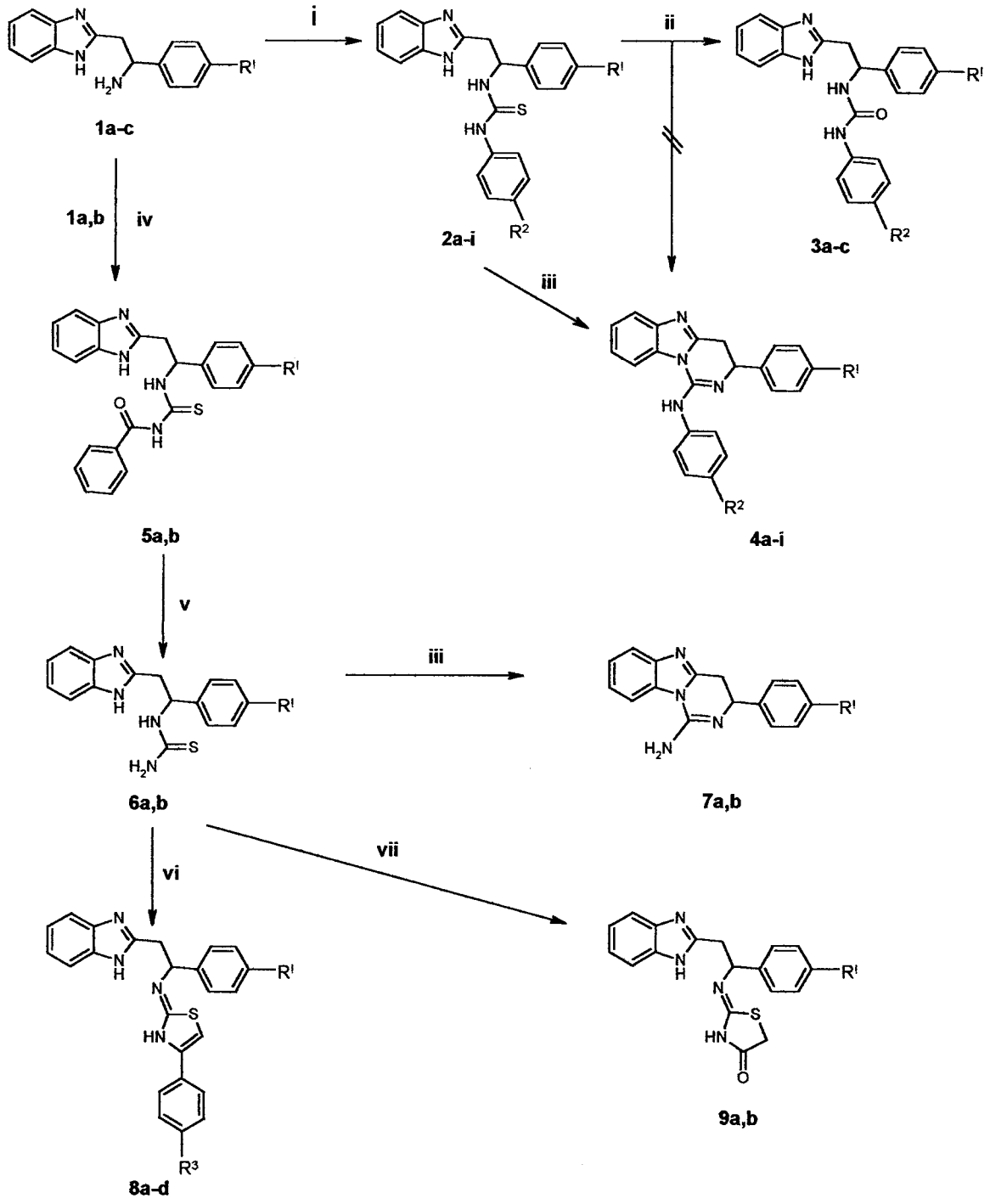
IV

2. Investigations, results and discussion

2.1. Synthesis and characterization

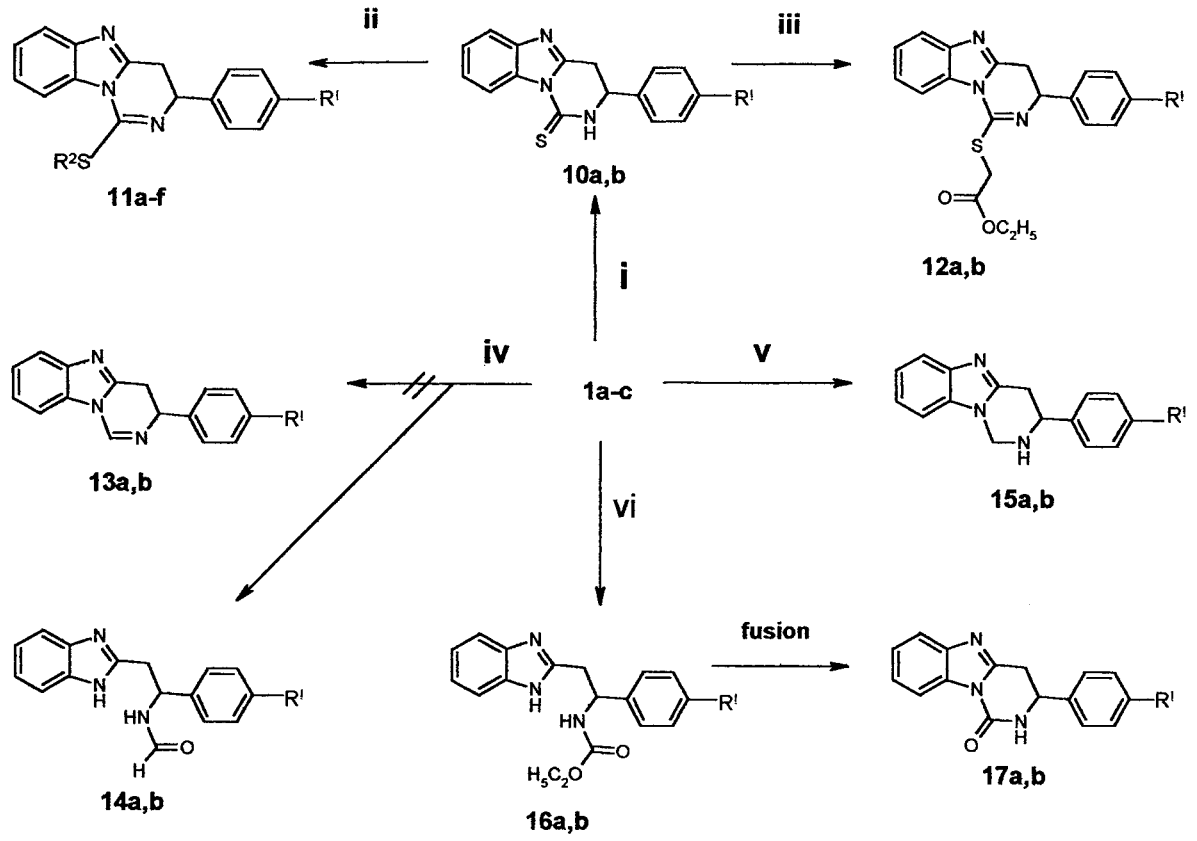
Schemes 1 and 2 outline the syntheses for the preparation of the target compounds. Reacting 2-(2-aminophenethyl)-1*H*-benzimidazoles **1a–c** with the selected aryl isothiocyanate afforded the intermediate 2-[2-(phenyl or 4-substituted phenyl)- 2-(anilino or 4-substituted anilino)thio-carbonyl-amino)ethylbenzimidazoles **2a–I** (Shafik et al. 2004). Trials for cyclocondensation of intermediates **2a–c** by DCCD as reported for the synthesis of analogous compounds (Aboul Wafa et al. 1992; Bourdais and Omar 1980; Omar et al. 1980) did not afford the desired 3,4-dihydropyrimido[1,6-*a*]benzimidazoles **4a–i**. However, the anilinocarbonylamino derivatives **3a–c** were isolated. The structure of these unexpected products were confirmed by microanalyses and spectral data. IR spectra revealed absorption bands for NH and CO groups. ^{1}H NMR spectra displayed signals for the α-CH_2 and the β-CH groups as well as two D_2O-exchangeable protons for NH groups. The ^{13}C NMR spec-

Scheme 1



Reagents; i = $R^2C_6H_4NCS$; ii = DCC; III = CH_3I; iv = C_6H_4CONCS; v = K_2CO_3; vi = $R^3C_6H_4COCH_2Br$; vii = $BrCH_2COOC_2H_5$
R^1 = H, Cl, OCH_3; R^2 = H, Cl, CH_3; R^3 = H, Cl

Scheme 2



Reagents; i = CS_2; ii = R^2X; iii = $BrCH_2COOC_2H_5$; iv = HCOOH; v = HCHO; vi = $ClCOOC_2H_5$
R^1 = H, Cl, OCH_3; R^2 = CH_3; C_2H_5, $CH_2C_6H_5$, X = Cl, I.

trum of **3a** revealed one signal for each of the aliphatic CH and CH_2; twelve Ar-CH; seven Ar-C and one C=O. MS for **3a** showed [$M^{+\cdot}$] at m/z 356 (2.5%) whereas the base peak [$M^{+\cdot} - 224$] appeared at m/z 132 (100%).

The desired 3,4-dihydropyrimido[1,6-*a*]benzimidazoles **4a–i** were prepared by cyclodesulfurization of aminothiocarbonylamino derivatives **2a–i** using methyl iodide in analogy to the synthesis of related compounds (Omar 1974; Omar et al. 1975). Treatment of **1a–c** with benzoyl isothiocyanate yielded the corresponding benzoylaminothiocarbonylamino derivatives **5a, b**. Basic hydrolysis of these derivatives produced the unsubstituted aminothiocarbonylamino derivatives **6a, b**. Cyclodesulfurization of these compounds with methyl iodide led to the formation of the target 1-amino-3,4-dihydropyrimido[1,6-*a*]benzimidazoles **7a, b**. Reacting **6a, b** with equimolar amounts of the appropriate phenacyl bromide gave the corresponding 2,3-dihydrothiazolyl derivatives **8a–d**. Treatment of **6a, b** with an equimolar amount of ethyl bromoacetate yielded the corresponding 4-oxothiazolidinyl derivatives **9a, b**.

Cyclocondensation of **1a–c** with carbon disulfide and ammonium hydroxide afforded the 3,4-dihydropyrimido[1,6-*a*]benzimidazole-1(2*H*)thiones **10a, b**. Alkylation of these thiones with alkyl or aralkyl halide gave the required alkylthio derivatives **11a–f**. Treatment of the thiones **10a, b** with ethyl bromoacetate yielded the corresponding ethoxycarbonylmethylthio derivatives **12a, b**. Experiments for cyclocondensation of 2-(aminophenethyl)-1*H*-benzimidazoles **1a, b** with formic acid in order to get 3,4-dihydropyrimido[1,6-*a*]benzimidazoles **13a, b** according to Badawey (1996) were unsuccessful. Instead, the N-formyl derivatives

Table 1: Percentage inhibition of gastric acid secretion[a] at the dose levels 0.1–3.0 mg/kg body weight of pylorus ligated rats[b,c]

Compd.	Dose, mg/kg,idu[d]					
	0. 1	0. 5	1.0	1.2	1.5	3.0
7a	15.24 ± 2.27	30.44 ± 0.36	51.3 ± 1.04	ND[e]	ND	35.1 ± 2.02
10a	30.7 ± 1.28	32.3 ± 1.87	37.5 ± 2.13	ND	ND	52.6 ± 1.39
15a	23.7 ± 2.25	48.4 ± 1.37	44.0 ± 0.44	ND	ND	50.0 ± 1.36
Omeprazole	ND	38.6 ± 2.63	43.40 ± 2.18	51.57 ± 1.84	52.25 ± 2.55	59.00 ± 0.16

[a] The values represent the mean of six replicates ± SEM. [b] DMSO was used as a solvent. [c] Data for solvent treated groups as control was 0.00%. [d] idu = intraduodenal. [e] ND = not determined

Table 2: ED_{50} values (mg/kg)[a] of the test compounds 7a, 10a and 15a in relation to omeprazole

Compd.	ED_{50}
7a	3.50
10a	2.30
15a	3.00
Omeprazole	1.40[b]

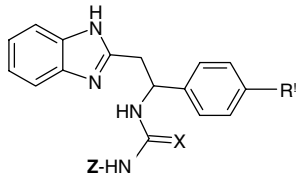
[a] Calculated on basis of semilog plot.
[b] reported ED_{50} = 1.20 (Herlig and Weidmann 1995)

14a, b were obtained as revealed from their spectral data. The 1,2,3,4-tetrahydropyrimido[1,6-*a*]benzimidazoles **15a, b** were obtained by refluxing the selected amino derivatives **1a, b** with formalin and sodium hydroxide as reported for the preparation of related derivatives (Nagarajan 1970). Treatment of a solution of **1a, b** in pyridine with ethyl chloroformate yielded the corresponding ethoxycarbonylamino derivatives (**16a, b**). Cyclocondensation of these derivatives was achieved applying a published procedure for the synthesis of analogous compounds (Davies and Dickerson 1965) by fusion in an oil-bath at the melting range.

2.2. Gastric antisecretory activity

All test compounds exhibited gastric antisecretory activity (Table 1). The sequence of percent inhibition ± SEM, at the indicated dose levels, were decreasing in the following order: omeprazole (59% ± 0.16 at 3.0 mg/kg) > **15a** (53% ± 1.39 at 3 mg/kg) > **7a** (51 ± 1.04 at 1 mg/kg) > **10a** (50.0% ± 1.36 at 3.0 mg/kg). The ED_{50} values (mg/kg, Table 2) as determined from a semilog plot were increasing in the following order: omeprazole (1.4) < **15**a (2.3) < **10a** (3.0) < **7a** (3.5). The results indicate that the test compounds might have profound affinity towards the proton pump at the acidic canaliculi of the gastric parietal cells. It also reveals that incorporation of the amino group of I (Z = H) into a cyclic ring system as in the tested tetrahydropyrimido[1,6-a]benzimidazole (**15a**) decreases the inhibitory potency. Likewise, conversion of the tetrahydropyrimido ring to the thioxo derivative **10a** or to the unsaturated analog **7a** have also decreased the inhibitory action.

Table 3: 2-[2-(Phenyl or 4-substituted phenyl)-2-[(amino or N-substituted amino)thiocarbony-amino or carbonyl-amino]ethyl}-1*H*-benzimidazoles 3a–c; 5a,b; 6a,b; 14a,b and 16a,b)



Compd.	R^1	Z	X	Yield (%)	M.p. (°C) (Cryst. solv.)[a]	Mol. formula (Mol. mass)
3a	H	C_6H_5	O	62	218–219 (AN)	$C_{22}H_{21}ClN_4O$[b] (392.88)
3b	H	p-ClC_6H_4	O	64	215–216 (E/EA)	$C_{22}H_{20}Cl_2N_4O$[b] (427.33)
3c	H	p-$CH_3C_6H_4$	O	62	199–200 (AN/EA)	$CH_{23}H_{23}ClN_4O$[b] (406.91)
5a	H	C_6H_5CO	S	77	184–185 (E)	$C_{23}H_{20}N_4OS$ (400.50)
5b	Cl	C_6H_5CO	S	75	180–181 (E)	$C_{23}HH_{19}ClN_4OS$ (434.94)
6a	H	H	S	82	204–205 (M)	$C_{16}H_{16}N_4S$ (296.40)
6b	Cl	H	S	80	200–201 (AN)	$C_{16}H_{15}N_4S$ (330.84)
14a	H	HCO	S	80	242–243 (AN)	$C_{16}H_{15}N_3O$ (265.31)
14b	Cl	HCO	S	84	235–236 (AN)	$C_{16}H_{14}ClN_3O$ (299.76)
16a	H	C_2H_5OCO	S	93	208–209 (EA)	$C_{18}H_{19}N_3O_2$ (309.36)
16b	Cl	C_2H_2OCO	S	90	216–217 (EA)	$C_{18}H_{18}ClN_3O_2$ (343.81)

[a] M = methanol; E = ethanol; AN = acetonitrile; E/EA = ethanol/ethyl acetate; AN/EA = acetonitrile/ethyl acetate;. [b]Hydrochloride salt

3. Experimental

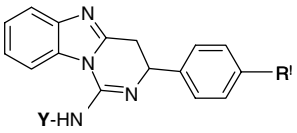
3.1. Synthesis

All melting points were determined in open-glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded using KBr discs on a Perkin-Elmer 1430 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini 200 at 200 MHz in DMSO-d_6 using TMS as internal standard. MS were run on a Finnigan mass spectrometer model SQ/7000 (70 eV). The microanalyses were performed at the microanalytical laboratory, National Research Center, Cairo, and the data were within ± 0.4% of the theoretical values.

3.1.1. 2-[2-(Phenyl or 4-substituted phenyl)-2-(anilino or 4-substituted anilinocarbonylamino)-ethyl]-1H-benzimidazols (**3a–c**)

A solution of the proper anilinothiocarbonylamino derivative **2a–c** (0.006 mol) and dicyclohexylcarbodiimide (DCCD) (1.75 g, 0.009 mol) in abs. EtOH (50 ml) was refluxed for 10 h. The solvent was removed under reduced pressure and ether was added after cooling. The mixture was placed in a freezer for 12 h. The separated dicyclohexylthiourea was filtered off and dry HCl gas was passed into the etherial filtrate. The product was filtered, dried and crystallized from the proper solvent (Table 3). IR for **3a–c**; ν (cm^{-1}): 3426–3400; 3237–3233 (NH); 1659–1655 (amide C=O). ^{1}H NMR for **3a**: 3.63 (d, J = 7.5 Hz, 2 H, CH_2); 5.45 (t, J = 7.5 Hz, 1H,CH); 6.85-7.80 (m, 15H, Ar–H & NH, exchangeable); 9.10 (s, 1 H, NH, exchangeable). ^{13}C NMR for **3a:** 34.63 (CH); 52.31 (CH_2); 114.18, 117.89, 121.60, 126.02, 126.68, 128.05, 129.07 (C_2–C_6 of the two phenyl groups and C_4–C_7 of benzimidazole); 128.98 and 131.03 (C_1 of the two phenyl groups); 140.45, 141.74 (C_{7a} and C_{3a} of benzimidazole); 151.55 (C_2 of benzimidazole); 154.98 (–CO–). MS for **3a**, m/z (relative abundance%): 357 (1.8), 356 (2.5), 265 (2.5), 264 (15.5), 263 (25.4), 221 910.3), 220 (13.2), 219 (36.4), 132 (100), 131 (18.7), 119 (22.5), 106 (35.6), 93 (20.6), 91 (14.5), 79 (12.6), 77 (18.3), 66 (10.1), 65 (12), 64 (14), 63 (10), 52 (7), 51 (13).

Table 4: 1-Amino or N-substituted amino-3-phenyl or substituted phenyl-3,4-dihydro[1,6-*a*]benzimidazoles 4a–i; 7a,b; 13a,b



Compd.	R^1	Z	Yield (%)	M.p. (°C) (Cryst. solv.)[a]	Mol. formula (Mol. mass)
4a	H	C_6H_5	57	134–136 (E/ER)	$C_{22}H_{18}N_4$ (328.41)
4b	H	4-Cl–C_6H_4	68	166–167 (E)	$C_{22}H_{17}ClN_4$ (372.85)
4c	H	4-CH_3–C_6H_4	65	149–150 (E/W)	$C_{23}H_{20}N_4$ (352.43)
4d	Cl	C_6H_5	48	226–228 (E/ER)	$C_{22}H_{19}Cl_3N_4$[b] (445.77)
4e	Cl	4-Cl–C_6H_4	48	244–245 (E/ER)	$C_{22}H_{18}Cl_4N_4$[b] (480.22)
4f	Cl	4-CH_3–C_6H_4	45	225–227 (E/ER)	$C_{23}H_{21}Cl_3N_4$[b] (459.80)
4g	OCH_3	C_6H_5	61	148–150 (E/W)	$C_{23}H_{20}N_4O$ (368.43)
4h	OCH_3	4-Cl–C_6H_4	63	166–168 (E/W)	$C_{23}H_{19}ClN_4O$ (402.88)
4i	OCH_3	4-CH_3–C_6H_4	65	149–150 (E/W)	$C_{24}H_{22}N_4O$ (382.46)
7a	H	H	51	191–192 (AN)	$C_{16}H_{14}N_4$ (262.31)
7b	Cl	H	54	196–197 (AN)	$C_{16}H_{13}ClN_4$ (296.75)

[a] E/ER = ethanol/ether, E = ethanol; E/W = ethanol/water; AN = acetonitrile. [b] Dihydrobromide salt

3.1.2. 1-Anilino (or 4-substituted anilino)-3-phenyl (or 4-substituted phenyl)-3,4-dihydropyrimido[1,6-a]benzimidazoles (**4a–i**)

A mixture of the selected anilinothiocarbonylamino derivative **2a–i** (0.002 mol) and CH_3I (0.43 g, 0.003 mol) in abs. EtOH (20 ml) was heated under reflux for 1 h. The solvent was evaporated under reduced pressure and crushed ice was added. The product was filtered, dried and crystallized from the proper solvent (Table 4). For compounds **4a–f**, dry HCl gas was passed into the ethanolic solution of the compounds which then crystallized from ethanol/ether. IR for **4a–i**; ν (cm^{-1}): 3390–3379 (NH); 1675-1667 (C=N). ^{1}H NMR for **4a**: 3.41, 3.62 (two dd, J = 7, 15 Hz, 2 H, CH_2); 4.88 (t, J = 7 Hz, 1 H,CH); 7.05-7.40 (m, 12 H, Ar–H); 7.59, 8.37 (two d, J = 7.4 Hz, 2 H, C_9-H and C_6-H of pyrimidobenzimidazole). ^{1}H NMR for **4b**: 3.40, 3.70 (two dd, J = 6.5, 15 Hz, 2 H,CH_2); 4.90 (dd, J = 6.5 Hz, 1 H, CH); 7.07–7.50 (m, 11 H, Ar–H); 7.61, 8.41 (two d, J = 7 Hz, 2 H, C_9-H and C_6-H of pyrimidobenzimidazole).
^{13}CNMR for **4b**: 30.64 (CH_2); 50.45 (CH); 115.87, 119.12, 123.75, 123.85, 124.51, 125.92, 127.78, 128.96, 129.59 ($C_{2,3,5,6}$ and C_{2-6} of the anilino and phenyl groups respectively + C_{6-9} of pyrimidobenzimidazole); 126.92 (C_1 of the phenyl group); 132.00 (C_4 of the anilino moiety); 142.07 (C_1 of the anilino moiety) 143.05, 143.70, 146.93 (C_{9a}, C_{5a} and C_{4a} of pyrimidobenzimidazole respectively); 150.11 (C_1 of pyrimidobenzimidazole). MS for **4b**: m/z (relative abundance%): 374 (24); 372[(79); 243 (15); 241 (44); 222 (20); 221 (100); 220 (12); 219 (47); 218 (13); 77 (12).

Table 5: 2-[2-(Phenyl)-2,3- or 4-substituted phenyl)-2-(phenyl or 4-substituted phenyl)-2,3-dihydrothiazol-2-ylidenamino)-ethyl]-1*H*-benzimidazoles (8a–d)

Compd.	R^1	R^2	Yield(%)	M.p. (°C) (Cryst. solv)[a]	Mol. formula (Mol. mass)
8a	H	H	60	98–100	$C_{24}H_{20}N_4S$ (396.51)
8b	H	Cl	62	116–118	$C_{24}H_{19}ClN_4S$ (430.95)
8c	Cl	H	62	119–121	$C_{24}H_{19}ClN_4S$ (430.95)
8d	Cl	Cl	64	128–129	$C_{24}H_{18}Cl_2N_4S$ (465.40)

[a] All compounds were purified by preparative tlc using chloroform/ethanol (45 : 2) as eluent and crystallized from ethanol/ether

3.1.3. 2-[2-(Phenyl or 4-substituted phenyl)-2-(benzoylaminothiocarbonylamino)ethyl]-1H-benzimidazoles (**5a, b**)

To a stirred solution of NH_4SCN (3.80 g; 0.050 mol) in dry acetone (50 ml) was added, dropwise, benzoyl chloride (5.60 g; 0.040 mol) over a period of 1 h. The suspension was then heated under reflux for 5 min. The reaction mixture was allowed to cool then filtered rapidly into a solution of the appropriate amino analog (**1a, b**) (0.025 mol) in abs. EtOH (10 ml). The reaction mixture was then stirred at RT for 2 h. The product was filtered, washed with acetone, dried and crystallized from EtOH (Table 3). IR for **5a, b**; ν (cm^{-1}): 3210–3208 (NH); 1661–1658 (amide C=O); 1325–1321, 1263–1260, 1161–1159 (N–C=S). ^{1}HNMR for **5a**: 3.53 (d, J = 7 Hz, 2 H,CH_2); 6.13 (t, J = 7 Hz, 1 H, CH); 7.00–8.00 (m, 14 H, Ar–H); 11.35 (s, 1 H, NH–CO, exchangeable); 11.75 (d, J = 7 Hz, 1 H, CS–NH, exchangeable); 12.25 (bs, 1 H, benzimidazole NH, exchangeable).

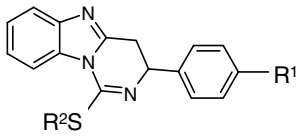
3.1.4. 2-[2-(Phenyl or 4-substituted phenyl)-2-(aminothiocarbonylamino) ethyl]-1H-benzimidazoles (**6a, b**)

To a stirred solution of the appropriate benzoylaminothiocarbonyl derivative **5a, b** (0.005 mol) in EtOH (80 ml) was added a solution of K_2CO_3 (0.42 g, 0.003 mol) in H_2O (10 ml). The reaction mixture was heated at 50 °C for 6 h, concentrated under reduced pressure and then diluted with H_2O. The product was filtered, dried and crystallized from the proper solvent (Table 3). IR for **6a, b;** ν (cm^{-1}): 3321–3316 and 3117–3114 (NH); 1269–1265, 1137–1135, 1050–1045 (N–C=S). ^{1}H NMR for **6a**: 3.27 (d, J = 6.5, 2 H, CH_2); 5.90 (t, J = 6.5 Hz, 1 H, CH); 7.00–7.45 (m, 9 H, Ar–H); 7.55 (s, 2 H, NH_2, exchangeable); 8.30 (d, J = 7 Hz, 1H, NH, exchangeable); 12.20 (bs, 1 H, benzimidazole NH, exchangeable). MS for **6a**; m/z (relative abundance%): 296 (9.3); 279 (31); 262 (4); 236 (7); 222 (12); 221 (33); 220 (45); 219 (100); 218 (16); 148 (15); 133 (7); 132 (44); 131 (21); 106 (11); 104 (10); 91 (5); 78 (4); 77 (13).

3.1.5. 1-Amino-3-(phenyl or 4-substituted phenyl)-3,4-dihydropyrimido[1,6-a]benzimidazoles (**7a, b**)

A mixture of the selected aminothiocarbonylamino derivative **6a, b** (0.002 mol) and CH_3I (0.43 g; 0.003 mol) in abs.EtOH (20 ml) was heated under reflux for 1 h. The solvent was removed under reduced pressure and the residue was crystallized from acetonitrile (Table 4). IR for **7a, b;** ν (cm^{-1}): 3423–3421 (NH); 1694–1693 (C=N). ^{1}H NMR for **7a**: 3.25, 3.45 (2dd, J = 15, 7.2 Hz, 2 H, CH_2); 4.84 (dd, J = 7.2 Hz, 1 H, CH); 6.75 (bs, 2H, NH_2, exchangeable); 7.27–7.45 (m, 7 H, Ar–H); 7.62, 8.27 (2d, J = 7.4 Hz, 2 H, C_9-H and C_6-H of pyrimidobenzimidazole). MS for **7a**; m/z (relative abundance%): 262 (47); 261 (20); 220 (15); 219 (53); 132 (100); 131 (66); 104 (83); 103 (32); 90(46.28); 89 (22); 78 (27); 77 (86); 76 (24); 64 (23); 63(32); 51 (37). MS for **7b**; m/z (relative abundance%): 298 (17); 296 (54); 295 (21); 255 (9); 254 (7); 253 (21); 220 (8); 219 (54); 218 (19); 217 (6); 185 (7); 165 (19); 133 (9); 132 (100); 131 (19); 77 (15); 75 (12); 64 (11); 63 (16).

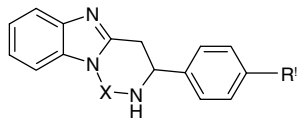
Table 6: 1-Alkylthio or ethoxycarbonylmethylthio-3-(phenyl or 4-substituted phenyl)-3,4-dihydropyrimido[1,6-*a*]benzimidazoles 11a–f and 12a, b



Compd.	R^1	R^2	Yield(%)	M.p. (°C) (Cryst. Solv.)[a]	Mol. formula (Mol. mass)
11a	H	CH_3	85	105–106 (E/W)	$C_{17}H_{15}N_3S$ (293.39)
11b	Cl	CH_3	91	156–157 (E)	$C_{17}H_{14}ClN_3S$ (327.83)
11c	H	$-CH_2CH_3$	82	100–102 (AN)	$C_{18}H_{17}N_3S$ (307.41)
11d	Cl	$-CH_2CH_3$	89	134–135 (AN)	$C_{18}H_{16}ClN_3S$ (341.86)
11e	H	$-CH_2C_6H_5$	90	129–130 (E)	$C_{23}H_{19}N_3S$ (369.48)
11f	Cl	$-CH_2C_6H_5$	92	141–142 (E)	$C_{23}H_{18}ClN_3S$ (403.93)
12a	H	$-CH_2COOCH_2CH_3$	85	140–141 (AN)	$C_{20}H_{19}N_3O_2S$ (365.46)
12b	Cl	$-CH_2COOCH_2CH_3$	90	173–174 (AN)	$C_{20}H_{18}ClN_3O_2S$ (399.90)

[a] E = ethanol; E/W = ethanol/water and AN = acetonitrile

Table 7: 3-(Phenyl or substituted phenyl)-3,4-dihydropyrimido[1,6-*a*]benzimidazole-1(2*H*)thione or 1(2*H*)one and 1,2,3,4-tetrahydropyrimido[1,6-*a*]benzimidazoles 10a,b; 15a,b; 17a,b



Compd.	R^1	X	Yield(%)	M.p. (°C) (Cryst. Solv.)[a]	Mol. Formula (Mol. mass)
10a	H	C=S	85	214–215	$C_{16}H_{13}N_3S$ (279.36)
10b	Cl	C=S	84	206–207	$C_{16}H_{12}ClN_3S$ (313.81)
15a	H	CH_2	92	236–237	$C_{16}H_{15}N_3$ (249.31)
15b	Cl	CH_2	90	238–239	$C_{16}H_{14}ClN_3$ (283.760)
17a	H	C=O	86	235–236	$C_{16}H_{13}N_3O$ (263.30)
17b	Cl	C=O	88	242–243	$C_{16}H_{12}ClN_3O$ (297.74)

[a] Ethanol

3.1.6. 2-[2-(Phenyl or 4-substituted phenyl)-2-(4-phenyl or 4-substituted phenyl-2,3-dihydrothiazol-2-ylidenamino) ethyl]-1H-benzimidazoles (**8a–d**)

A solution of the appropriate aminothiocarbonylamino derivative **6a, b** (0.007 mol) and the proper phenacyl bromide (0.007 mol) in EtOH l(40 ml) was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was triturated with ether and then purified by prep. TLC (Table 5). IR for **8a–d;** ν (cm^{-1}): 3389–3386 (NH). ^{1}H NMR for **8d**: 3.38 (d, J = 8 Hz, 2 H, CH_2); 5.36 (t, J = 8 Hz, 1 H, CH); 7.00 (s, 1 H, C_5-H of 2,3-dihydrothiazole moiety); 7.10–7.80 (m, 12 H,Ar–H); 8.52 (d, 1 H, NH, exchangeable); 12.25 (s, 1 H, benzimidazole NH, exchangeable).

3.1.7. 2-[2-(Phenyl or 4-substituted phenyl)-2-(4-oxothiazolidin-2-ylidenamino) ethyl]-1H-benzimidazoles (**9a, b**)

A solution of the selected aminothiocarbonylamino derivative (**6a, b**) (0.007 mol) and ethyl bromoacetate (1.20 g; 0.007 mol) in abs. EtOH (20 ml) was heated under reflux for 6 h. The mixture was concentrated under reduced pressure, cooled and neutralized with a saturated solution of sodium acetate. The product was filtered, washed with H_2O, dried and crystallized from a mixture of EtOH/EOAc.
Compound **9a**: R^1 = H: m.p. 211–212 °C; yield 70%; $C_{18}H_{16}N_4OS$. IR ν (cm^{-1}): 3301 (NH); 1694 ((C=O). ^{1}H NMR: 3.40 (d, J = 7.5 Hz, 2 H, CH_2); 3.85 (s, 2 H, SCH_2); 3.73 (t, J = 7.5 Hz, 1 H, CH); 7.00–7.60 (m, 9 H, Ar–H); 9.90 (s, 1 H, NH, exchangeable); 12.40 (s, 1 H, benzimidazole NH, exchangeable).
Compound **9b**: R^1 = Cl: m.p. 205–206 °C; yield 69%. IR ν (cm^{-1}): 3298 (NH); 1690 (C=O).
$C_{18}H_{15}ClN_4OS$

3.1.8. 3-Phenyl or 4-substituted phenyl-3,4-dihydropyrimido[1,6-a]benzimidazole-1(2H)-thiones (**10a, b**)

A mixture of the amino derivative **1a, b** (0.007 mol), carbon disulfide (1.60 g, 0.021 mol, 1 ml) and NH_4OH (0.25 g, 0.007 mol, 1 ml) in EtOH (20 ml) was stirred at RT for 12 h. The mixture was concentrated under reduced pressure and cooled. The product was filtered, dried and crystallized from EtOH (Table 7). IR for **10a, b;** ν (cm^{-1}): 3171–3165 (NH); 1449–1445, 1333–1311, 1261–1253(N–C=S). ^{1}H NMR for **10a**: 3.55, 3.70 (2dd, J = 8, 15 Hz, 2 H, CH_2); 5.05 (dd, J = 8 Hz, 1 H, CH), 7.20–7.40 (m, 7 H, Ar–H); 7.55, 8.85 (2d, J = 7.5 Hz, 2 H, C_9-H and C_6-H of pyrimidobenzimidazole); 10.80 (s, 1 H, NH, exchangeable).
^{13}C NMR for **10a**: 30.50 (CH); 53.23 (CH_2); 115.94, 119.19, 124.10, 124.37, 125.95, 127.98, 128.77 (C_2–C_6 of phenyl group and C_6–C_9 of pyrimidobenzimidazole); 132.83 (C_1 of phenyl group); 139.25, 142.89, 148.27(C_{5a}, C_{9a} and C_{4a} of pyrimidobenzimidazole respectively); 174.88 (C=S).). MS for **10b**; m/z (relative abundance%): 315 (39.5); 313 (100); 256 (11); 255 (45.70); 254 (31): 253 (94); 219 (54); 218 (36); 217 (13); 184 (20); 183 (6); 182 (50); 174 (13); 138 (7); 132 (5); 131 (27); 102 (10); 90 (12); 77(11); 63 (13).

3.1.9. 1-Alkylthio-3-(phenyl or 4-substituted phenyl)-3,4-dihydropyrimido-[1,6-a]benzimidazoles (**11a–f**)

A mixture of the proper thione **10a, b** (0.007 mol), the selected alkyl halide (0.01 mol) and NaOH 10% (0.28 g, 2.8 ml, 0.007 mol) in EtOH (20 ml) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure and ice-H_2O was added. The product was filtered, washed with H_2O, dried and crystallized from the proper solvent (Table 6). IR for **11a–f:** ν (cm^{-1}): 1289–1285 and 1086–1084 (C–S–C). ^{1}H NMR for **11a**: 2.70 (s, 3 H, CH_3); 3.05, 3.50 (2dd, J = 15, 7.5, 2 H, CH_2); 4.90 (dd, J = 7.5 Hz, 1 H, CH); 7.15–7.60 (m, 7 H, Ar–H); 7.70, 8.10 (2d, J = 7.3 Hz, 2 H, C_9-H and C_6-H of pyrimidobenzimidazole respectively). ^{1}H NMR for **11f**: 3.06 (2dd, J = 15, 7.8, 2 H, CH_2); 4.53 (s, 2 H, SCH_2); 5.06 (dd, J = 7.8 Hz, 1 H, CH); 7.27–7.55 (m, 12 H, Ar–H); 7.67, 8.01 (2d, J = 7.4 Hz, 2 H, C_9-H and C_6-H of pyrimidobenzimidazole respectively).

3.1.10. 1-Ethoxycarbonylmethylthio-3-(phenyl or 4-substituted phenyl)-3,4-dihydropyrimido[1,6-a]benzimidazoles (**12a, b**)

A mixture of the selected thione **10a, b** (0.004 mol), anhyd. K_2CO_3 (0.55 g, 0.004 mol) and ethyl bromoacetate (0.67 g, 0.004 mol) in dry acetone (20 ml) and dry DMF (5 ml) was heated under reflux for 2 h. The solvent was removed under reduced pressure and ice-H_2O was added. The product was filtered, washed with H_2O, dried and crystallized from acetonitrile (Table 6). IR for **12a, b;** ν (cm^{-1}): 1741–1739 (C=O). ^{1}H NMR for **12b**: 1.05 (t, 3 H, CH_3); 2.85, 3.30 (2dd, J = 7 Hz, 2 H, CH_2 at C_4-pyrimidobenzimidazole); 3.85 (q, J = 6.5 Hz, 2 H, OCH_2); 4.10 (s, 2 H, SCH_2); 4.75 (dd, J = 7 Hz, 1 H, CH); 7.10–7.30 (m, 6 H, Ar–H); 7.55, 7.90 (2d, 2 H, C_9-H and C_6-H of pyrimidobenzimidazole respectively). ^{13}C NMR for **12b**: 14.06 (CH_3); 31.93 (CH_2); 33.34 (CH); 58.76 (OCH_2); 61.94 (SCH_2); 112.88, 120.09, 124.12, 124.71, 127.82, 128.68 ($C_{2,3,5,6}$ of phenyl group and C_{6-9} ofpyrimidobenzimidazole); 129.92, 133.23 (C_1 and C_4 of phenyl group); 140.43, 142.68, 148.50 (C_{9a}, C_{5a} and C_{4a} of pyrimidobenzimidazole respectively); 150.62 (C=O); 168.16 (C_1 of pyrimidobenzimidazole). MS for **12b**; m/z (relative abundance%): 401(6); 399 (18); 354 (5); 326 (9.60); 314 (8); 312 (16); 255 (10.); 253 (22); 220 (18); 219 (100); 218 (28); 182 (14); 155 (16); 138 (12); 111 (11); 103 (17); 102 (24); 91 (12); 90 (31); 89 (16); 77 (20); 76 (14); 75 (15); 64 (18); 63 (21).

3.1.11. 2-[(2-Formylamino-2-(phenyl or 4-substituted phenyl)ethyl]-1H-benzimidazoles (**14a, b**)

A solution of the appropriate amino analog **1a, b** (0.004 mol) in HCOOH (5 ml) was heated under reflux for 4 h. The mixture was poured onto ice-H_2O and alkalinized with dilute NH_4OH. The product was filtered, washed with H_2O, dried and crystallized from acetonitrile (Table 3). IR for **14a, b;** ν (cm^{-1}): 3275–3270 (NH); 1657–1655 (amide C=O). ^{1}H NMR for **14b**: 3.34 (d, J = 7.8 Hz, 2 H, CH_2); 5.57 (q, J = 7.8 Hz, 1 H, CH); 7.08–7.56 (m, 8 H, Ar–H); 8.00 (s, 1 H, H–C=O); 8.81 (d, 1 H, NH, exchangeable); 12.30 (s, 1 H, benzimidazole NH, exchangeable)

3.1.12. 3-(Phenyl or 4-substituted phenyl)-1,2,3,4-tetrahydropyrimido[1,6-a]benzimidazoles (**15a, b**)

A mixture of the selected amino derivative **1a, b** (0.004 mol), formalin (0.12 g; 0.004 mol) and NaOH solution 4% (4ml) in EtOH (20 ml) was heated under reflux for 15 min. The mixture was filtered, washed with H_2O, dried and crystallized from EtOH (Table 7). IR for **15a, b;** ν_x (cm^{-1}): 3228–3225 (NH). ^{1}H NMR for **15a**: 3.05, 3.35 (2dd, J = 15, 7.4 Hz, 2 H, CH_2 at C_4 of pyrimidobenzimidazole); 3.60–3.80 (m, 1 H, NH, D2O-exchangeable); 4.20–4.40 (m, 1 H, CH at C_3 of pyrimidobenzimidazole); 5.05, 5.30 (2dd, J = 12, 6.5 Hz, 2 H, CH_2 at C_1 of pyrimidobenzimidazole); 7.10–7.70 (m, 9 H, Ar–H). ^{1}H NMR for **15b**: 2.90, 3.35 (2dd, J = 15, 7.3 Hz, 2 H at C_4 ofpyrimidobenzimidazole); 3.70–3.85 (m, 1 H, NH exchangeable); 4.20–4.35 (m, 1 H at C_3 of pyrimidobenzimidazole); 5.00, 5.35 (2dd, J = 12, 6.5 Hz, 2 H at C_1 of pyrimidobenzimidazole); 7.10–7.60 (m, 8 H, Ar–H). MS for **15b**; m/z (relative abundance%): 285 (37); 283 (100); 258 (27); 257 (24); 256 (76); 255 (36); 219 (19); 218 (18); 154 (29); 152 (94); 146 (17); 145 (28); 144 (56); 143 (14); 132 (14); 125 (88); 117 (21); 110 (14); 102 (11); 90 (14); 89 (19); 77 (23); 76 (12); 75 (11); 65 (10); 64 (10); 63 (17).

3.1.13. 2-[(2-N-Ethoxycarbonylamino-2-(phenyl or 4-substituted phenyl)ethyl]-1H-benzimidazoles (**16a, b**)

To a well-stirred ice-cooled solution of the appropriate amino derivative **1a, b** (0.008 mol) in dry pyridine (10 ml) was added, dropwise, ethyl chloroformate (1.10 g, 0.01 mol). Stirring was maintained at RT for 2 h, then the mixture was poured onto ice-H_2O. The obtained product was filtered, washed, dried and crystallized from EtOAC (Table 3). IR for **16a,b;** ν (cm^{-1}): 3303–3300 (NH); 1688–1685 (amide C=O). ^{1}H NMR for **16a**: 1.10 (t, J = 6.5 Hz, 3 H CH_3); 3.15 (d, J = 7 Hz, 2 H, CH_2); 3.80 (q, J = 6.5, 2 H, OCH_2); 5.20 (t, J = 7 Hz, 1 H, CH); 7.00–7.60 (m, 9 H, Ar–H); 7.90 (d, 1 H, NH, exchangeable); 12.20 (s, 1 H, benzimidazole NH,

exchangeable). MS for **16a**; m/z (relative abundance%): 310 (2); 309 (4); 263 (3); 220 (11); 219 (22); 178 (13); 133 (11); 132 (100); 131 (18); 106 (18); 104 (10); 79 (13); 77 (19).

3.1.14. 3-(Phenyl or 4-substituted phenyl)-3,4-dihydropyrimido[1,6-a]benzimidazol-1(2H)-ones (**17a, b**)

The title compounds were prepared by fusion of the selected ethoxycarbonylamino derivative **16a, b** in an oil-bath at 210–220 °C for 1 h. The mixture was allowed to cool to RT and the product was crystallized from EtOH (Table 7). IR for **17a, b;** ν (cm^{-1}): 3221–3219 (NH); 1723–1720 (C=O). ^{1}H NMR for **17a**: 3.35, 3.60 (2dd, J = 15, 8 Hz, 2 H, CH_2); 5.00 (t, J = 8 Hz, 1 H, CH); 7.20–7.45 (m, 7 H, Ar–H); 7.60, 8.05 (2d, J = 7.4 Hz, 2 H, C_9-H and C_6-H of pyrimidobenzimidazole respectively); 8.75 (s, 1 H, NH, exchangeable). MS for **17b**; m/z (relative abundance%): 299 (33); 297 (95); 253 (35); 242 (15); 220 (16); 219 (87); 218 (28); 168 (34); 166 (100); 158 (15); 132 (21); 131 (44); 130 (27); 90 (39); 77 (24).

3.2. Gastric antisecretory activity

Laboratory male albino rats (*Rattus norvegicus*, variety *albus*) weighing 90–110 g were used throughout the study. Gastric antisecretory activity was evaluated by determining the inhibition of gastric acid secretion using pylorus ligated rats by a modification of the process described by Shay et al. 1954. Six rats were grouped for each applied dose. The rats were deprived of food for 24 h. The pylorus of the stomach was ligated under ether anesthesia. The test compound was administered intraduodenally just after pyloric ligation, using the assigned dose levels (0.01, 0.05, 0.07, 0.10, 0.25, 0.50, 1.00, 1.20, 1.50, 3.00, 10.00, or 20.00 mg/kg body weight) in 0.20 ml DMSO. For control experiments, the solvent (DMSO, 0.20 ml) was injected. Four hours later, rats were sacrificed and the stomachs were isolated, suspended in 2 ml distilled H_2O, homogenized and centrifuged at 4000 rpm for 30 min. Aliquots of 1 ml from the supernatant layer containing the gastric juice were pipetted for acid determination by manual titration with 0.01 N NaOH and phenolphthalein as indicator. The recovered acidity, in the treated rats was compared with that in the control group and the percent inhibition for each dose was calculated (Tables 1 and 2). The ED_{50} values (Table 2), taken, as the dose required for 50% inhibition of the gastric secretion, were determined from the dose response curve plotted as semilog graph.

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