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Synthesis of Some New Benzimidazole Derivatives of Pharmaceutical Interest

FAWZIA ZAKARIA EL-ABLACK

Chemistry Department, Damietta Faculty of Science
Mansoura University, Egypt
fawzia@mans.edu.eg

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Abstract: Reaction of 2-(aminomethyl)benzimidazole dihydrochloride (**1**) with ethyl acetoacetate was studied to give diazepinone-benzimidazole derivative (**2**), while, treatment of **1** with phenylhydrazono ethylacetoacetate afforded phenylhydrazino diazepinone derivative (**3**). On the other hand, reaction of **1** with acetyl acetone resulted in the formation of diazepine derivative (**4**). The reaction of **1** with ethyl cyanoacetate was studied to give 3-aminodiazepinone derivative (**5**). Also the reaction of **1** with acetophenone and/or benzophenone has been investigated to give the fused imidazolines **6** and **7** respectively, while the reaction of **1** with cyclopentanone gave benzimidazolyl derivative (**8**). Treatment of **1** with chloroacetyl chloride gave the fused pyrazinone (**9**). The treatment of **1** with benzoin gave the derivative (**10**). The structures of the hitherto unknown compounds have been confirmed from analytical and spectral data. The newly synthesized compounds were screened for antibacterial and antifungal activity

Keywords Diazepino-Benzimidazole, Pyrazino -benzimidazole and midazolo {1.5-a}benzimidazole, Antibacterial, Antifungal activity

Introduction

Benzimidazole derivatives have been reported to have a wide range of pharmacological and biochemical activity; It consider to be CNS depressant, anti-Parkinson, antiviral activity, anti ulcerative, antihypertensive, antifungal, antitumor, antihistaminic, anti-bacterial and anti-helminthes agents[1-4] .

Following the above findings and continuous to our previous work[5-8] directed towards the synthesis of fused heterocyclic compounds of potential biological activities the utilizing of 2-aminomethyl benzimidazole[9] as a title compound for the synthesis of some new benzimidazole derivatives was studied.

Due to the wide range of pharmacological activity and synthetic application of benzimidazoles in this study it was planned to synthesize benzimidazole derivatives using 2-aminomethyl benzimidazole[9] (**1**). Thus the reaction of 2-aminomethyl benzimidazole (**1**) with ethyl acetoacetate gave diazepinone derivative (**2**). IR spectrum revealed the disappearance of NH_2 absorption band at 3400-3550 cm^{-1} and the appearance of absorption band at 1680 cm^{-1} CO group. NMR spectra established the presence of a signals at δ 3.78(s, 2H, CH_2) and at δ 2.6 (s, 2H, CH_2) so it not present as tautomeric enaminone structure (**2**). Treatment of **1** with phenylhydrazeno ethyl acetoacetate afforded (1,4-diazepino [1,2-a] benzimidazole derivative (**3**), the structure of **3** was based on the analytical and spectral data, the ^{1}H NMR spectrum reveal the presence of a signal at δ 8.12 (s, 1H, NH) and δ 2.89 (s, 2H,CH_2). While the treatment of **1** with acetyl acetone in 1 N sodium hydroxide solution resulted in the formation of 3,5-dimethyl-[1,3]diazipene[1,2-a]benzimidazole derivative (**4**), the structure of **4** was inferred from the obtained analytical and spectral data. IR spectrum revealed the disappearance of NH_2 absorption band and the presence of absorption band at 1625 cm^{-1} for C=N.

When **1** was treated with ethyl cyanoacetate in ethanol containing a catalytic amount of piperdene gave 3-amino diazepinone derivative (**5**). The structure of **5** was based on the analytical and spectral data. IR spectrum reveal the presence of (NH_2) at 3345 cm^{-1}, the ^{1}H NMR spectrum revealed the presence of signal at δ 6.5 (s, 2H, NH_2), δ 7.2 - 7.7 (m, 4H, ArH), δ 2.73 (s, 2H, CH_2) and δ 2.85 (s, 2H, CH_2) so it not present in its tautomeric enaminone structure (**5**). .

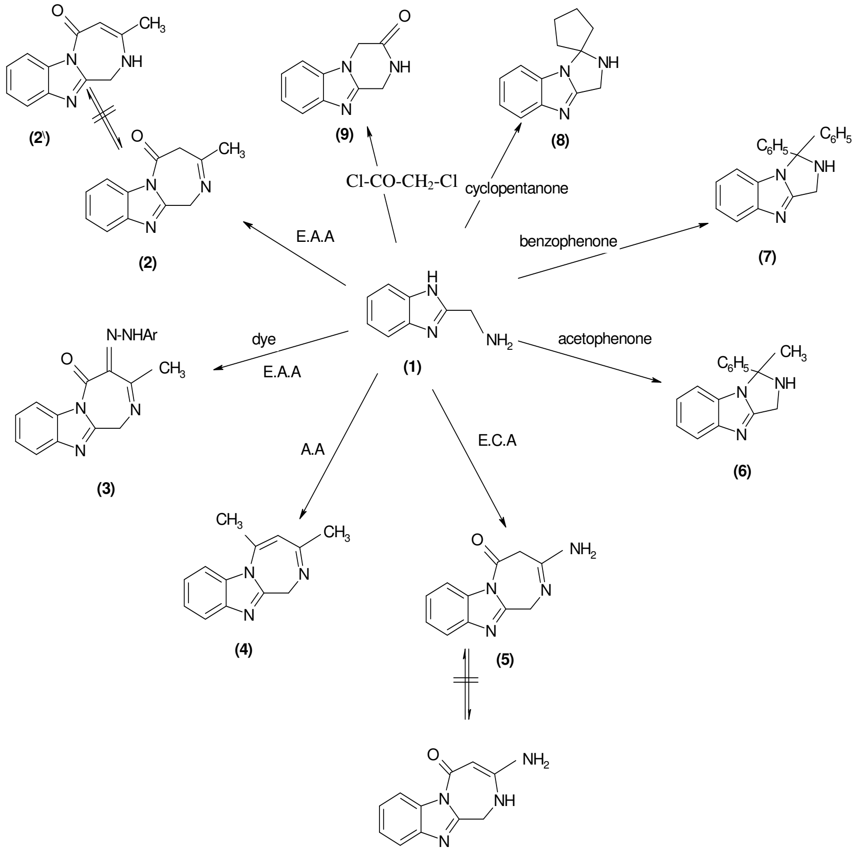
The reaction of **1** with acetophenone and benzophenone resulted in the formation of 1*H*-imidazol[1,5-a]benzimidazole derivatives (**6**,**7**) respectively. The structure of **6** was confirmed from the obtained analytical and spectral data. IR spectrum of **6** displayed absorption band at 3330 cm^{-1} (NH), ^{1}H NMR spectrum displayed signals at δ 2.1 (s, 1H, NH) (Table 3).

As a further extension of the above studies, the reaction of **1** with cyclopentanone gave benzimidazole derivative (**8**). The structure of **8** was assigned from the analytical and spectral data. ^{1}H NMR spectrum displayed signal at δ 2.3 (s, 1H, NH).

Treatment of **1** with chloroacetyl chloride gave pyrazino{1,2-a}benzimidazol-3(4*H*)-one derivative (**9**). The structure of **9** was established from the obtained analytical and spectral data. IR spectrum revealed absorption band at 3335 cm^{-1} NH. On the other hand, the reaction of **1** with benzoin in ethanol containing catalytic amount of piperdene gave 3, 4-diphenyl-1,4-dihydropyrazino[1,2-a]benzimidazole (**10**). ^{1}H NMR revealed signal at δ 5.01 (s, H, CH olefinic) and at δ 4.78 (s, 2H, CH_2) (Scheme 1& 2).

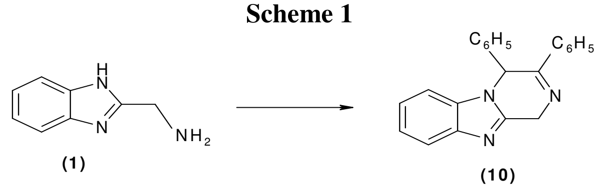
Experimental

Melting points (uncorrected) were determined on Fisher-Johns melting point apparatus. Elemental analysis was performed in the microanalysis unit, Cairo University. IR spectra were recorded by means of pressed KBr on a Perkin-Elmer 883 infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Varian 90 MHz in $CDCl_3$.



(5')

Scheme 1



Scheme 2

*Formation of 3-methyl-1,4-dihydro-5H{1,4}diazepino{1,2-a}benzimidazol-5-one (**2**)*

To a solution of **1** (0.01 mol) in NaOH solution (1 N, 25 mL) ethyl acetoacetate (0.01 mol) was added. The reaction mixture was heated on water bath for 3 h, left to cool and the solid product was separated, filtered off and recrystallized from the appropriate solvent (Table 1).

*Formation of (4E)-3-methyl-4-(2-phenylhydrazinylidene)-1,4-dihydro-5H-[1,4]diazepino [1,2-a]benzimidzol-5-one (**3**)*

To a 0.01 mol solution of **1** in NaOH solution (1 N, 25 mL), phenylhydrazino ethyl acetoacetate (0.01 mol) was added. The reaction mixture was heated on water-bath with continuous stirring and cooled. The obtained product was filtered off and recrystallized from the proper solvent (Table 1).

*Formation of 3,5-dimethyl-1H-{1,4}diazepino{1,2-a}benzimidazole (**4**)*

A mixture of **1** (0.01 mol) and acetyl acetone (0.01 mol) in 30 mL ethanol containing a catalytic amount of piperidene (1 mL) was heated under reflux for 3-4 h. The solid product was cooled, filtered off and recrystallized from ethanol (Table 1).

*Formation of 3-amino-1,4-dihydro-5H{1,4}diazepino{1,2-a}benzimidazol-5-one (**5**)*

To a solution of **1** (0.01 mole) in ethanol (30 mL) containing a catalytic amount of piperidene (0.5 mL), ethyl cyanoacetate (0.01 mole) was added. The reaction mixture was heated to reflux for 4 h, cooled, poured onto ice-cold water. The obtained products were filtered off and crystallized from ethanol (Table 1).

*Formation of 1-methyl-1-phenyl-2,3-dihydro-1H-imidazol[1,5-a]benzimidazole (**6**), and 1,1-diphenyl-2,3-dihydro-1H-imidazol[1,5-a]benzimidazole (**7**)*

A mixture of **1** (0.01 mol) and acetophenone and/or phenzophenone (0.01 mol) in ethanol (30 mL) containing a catalytic amount of piperidene (1 mL) was heated to reflux for 3-4 h, cooled and poured onto ice-cold water then acidified with dil HCl. The solid product that separated was filtered off and crystallized from the appropriate solvent (Table 1).

*Formation of 6\,7\-dihydrospiro[cyclopentane-1,5\-imidazo[**1,5a**] benzimidazole] (**8**)*

A mixture of **1** (0.005 mol) and cyclopentanone (0.005 mol) was heated under reflux for 3-4 h in ethanol (30 mL) containing piperidene (1 mL). The reaction mixture was cooled, poured onto acidified ice-cold water. The product was filtered off and recrystallized from the proper solvent (Table 1).

*Formation of 1,2-dihydro pyrazino{1,2-a}benzimidazol-3(4H)-one (**9**)*

A mixture of **1** (0.01 mol) and chloroacetyl chloride (0.03 mol) was heated in water bath for 3 h, the solid product was cooled, filtered off, washed with ethanol and recrystallized from the proper solvent (Table 1).

*Formation of 3,4-diphenyl-1,4-dihydropyrazino[1,2-a]benzimidazole (**10**)*

A mixture of **1** (0.01 mol) and benzoin (0.01 mol) in 50 mL ethanol containing a catalytic amount of piperdine (1 mL) was heated under reflux for 4 h, cooled, poured into ice-cooled water and acidified. The precipitated was filtered off and recrystallized from ethanol (Table 1).

Table 1. Characterization data of the compounds

Compound	Yield, %	M.P ^{o}C	Colour	Solvent	Formula (M.Wt).	Calc./Found %C	%H	%N
2	92	170	Dark brown	EtOH/ AcOH	$C_{12}H_{11}N_3O$ (213.23)	67.59 67.01	5.2 5.0	19.71 19.51
3	77.77	145	brown	EtOH	$C_{18}H_{15}N_5O$ (317.34)	68.12 67.99	4.76 4.52	22.07 21.96
4	60	197	Pale brown	EtOH	$C_{13}H_{13}N_3$ (211.25)	73.91 73.54	6.20 6.0	19.89 18.94
5	89.2	178	Brown	EtOH	$C_{11}H_{10}N_4O$ (214.22)	61.67 61.15	4.71 4.25	26.16 25.45
6	65.9	202	Reddish brown	EtOH	$C_{16}H_{15}N_3$ (249.3)	77.1 76.09	6.06 5.83	16.86 16.24
7	89.7	245	White	EtOH	C_{21} $H_{17}N_3$ (311.37)	81.0 80.54	5.50 5.12	13.5 12.93
8	73.9	145	Brown	EtOH	$C_{13}H_{15}N_3$ (213.27)	73.21 72.95	7.1 6.85	19.7 19.54
9	63.04	180	White	EtOH	$C_{10}H_9N_3O$ (187.192)	64.16 63.95	4.85 4.52	22.45 22.01
10	70.2	120	Yellow	EtOH	$C_{22}H_{17}N_3$ 323.390	81.73 81.01	5.26 4.96	13.00 12.80

Pharmacology

A solution of the tested compounds in acetone (1 mg/mL) was added to the nutrient agar (for bacteria) or medium (for fungi) mixed well and poured on plates, the tested organism was then streaked on the surface of agar or medium was incubated at 37 ºC for 24 h (bacteria) and 28 ºC for 48 h (fungi) and the growth was recorded the organism used were *S. Aurous*, *S. Albus, E. Coli* in addition to yeast (Table 2).

Table 2. *In vitro* biological activity of the compounds (**2, 6, 7, 8, 9**)

Compound	*S. Albus*	*S.aureus*	*E.coli*	*β.subtities*	Yeast
2	-	50	-	50	-
6	-	100	-	50	50
7	100	100	100	-	100
8	50	-	100	-	50
9	100	100	100	50	100

Table 3. Spectral data of synthesized compounds

Compd	IR. cm^{-1} (KBr)	^1H NMR. δ(ppm)
2	3095(CH aromatic), 2965 (CH_3), 2890 (CH_2), 1675 (C=O), 1620 (C=N).	1.05 (s, 3H. CH_3); 3.78 (s, 2H. CH_2); 2.6 (s, 2H. CH_2).7.24 (m, 4H, ArH).
3	3410(NH); 2995 (CH aromatic);2885(CH_2) 2930(CH_3);1680(C=O); 1620(C=N).	2.03 (s, 3H. CH_3); 2.89 (s, 2H. CH_2); 7.43-7.65 (m, 9H, ArH), 8.81 (s, H, NH)
4	3042 (CH aromatic); 2965-2980 (CH_3); 2890 (CH_2); 1625 (C=N); 1610 (C=C).	1.13(s, 6H. CH_3); 2.65(s, 2H. CH_2); 7.1-7.7 (m, 4H, ArH)); 5.1 (s, H, CH olefinic)
5	3050 (CH aromatic); 3345 (NH_2); 2895 (CH_2); 1680 (C=O); 1628 (C=N).	2.4(s, 2H. CH_2); 2.8 (s, 2H, CH_2) 7.1-7.7 (m, 4H. ArH); 6.5 (s, 2H, NH_2)
6	3330(NH); 3095(CH aromatic);2930(CH_3); 2896(CH_2); 1626(C=N);1200-1250(C-N-C).	2.03(s, 3H. CH_3); 3.8 (s, 2H. CH_2); 7.1-7.6 (m, 9H. ArH); 2.1 (s, 1H, NH).
7	3415 (NH); 3096 (CH aromatic); 2875 (CH_2); 1620 (C=N).	7.12-7.67 (m, 14H, ArH); 3.8 (s, 2H, CH_2); 2 (s, 1H, NH).
8	3445 (NH), 3095 (CH Aromatic), 2870 (CH_2), 1624 (C=N)	7.23-7.63(m, 4H, ArH); 3.43 (s, 2H, CH_2); 2.3 (s, 1H, NH);1.56-2.2 (CH_2 cyclopetane)
9	3335 (NH); 3045 (CH aromatic);2899(CH_3); 2880(CH_2); 1680(C=O);1620 (C=N).	3.4(S, 2H, 2CH_2); 4.46 (S, 2H, CH_2); 7.26-7.65 (m, 4H, ArH); 8.15 (S, 1H, NH)
10	3100 (ArH), 2910 (CH_2), 3085 (=C-H), 1628 (C=N).	7.06-7.62 (m, 14H, ArH), 5.01 (s, 1H, CH olefinic), 4.79 (s, 2H, CH_2)

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