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Synthesis of fused dihydrobenzo [4,5]imidazo[1,2-a]pyrmido[5,4-e]pyrmidin-3(4H)-amine derivatives

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ABSTRACT

Some of fused dihydrobenzo [4,5]imidazo [1,2-a] pyrmido [5,4-e] pyrmidin-3(4H)-amine derivatives were synthesized, theses derivatives derived from 4-amino-2-(4-chloro or bromophenyl) -1,2-dihydropyrimido[1,2-a] benzimidazole-3-carbonitrile (4 and 5), which prepared by reaction 1H-benzimidazol-2-amine (1) and p-chlorobenzaldehyde or p-bromobenzaldehyde (2) and malononitrile (3). These derivatives prepared by reaction compound (4 and 5) with with triethylorthoformate in presence acetic anhydride to give the products (6 and 7), then the products were reacted with aliphatic amines (hydrazine, methyl amine, ethyl amine, propyl amine and isobutyl amine) to give pyrimidine rings (8-17) respectively. All these derivatives characterization by FT-IR , 1HNMR spectra and physical properties.

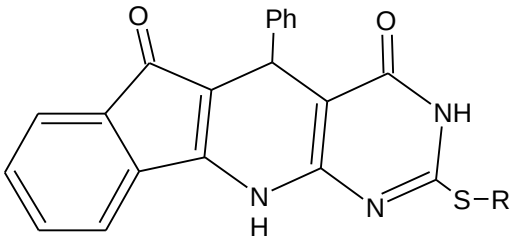
Introduction

Pyrimidine structural moiety constitutes a major class of heterocyclic compounds which have various pharmaceutical applications. For example, they are found to possess antineoplastic, antiviral [15,3], antibiotic[8], and anti-inflammatory properties. Pyrimidines also exhibit a range of pharmacological activities such as antibacterial[14,18], antifungal [12], anticancer[16], and cardioprotective effects[13]. Bicyclic and tricyclic fused pyrimidine derivatives have received much attention in connection with biologically significant systems such as pyrido[2,3-d]pyrimidines. Pyrido[2,3-d]pyrimidine structural motif is present in pirenperone (tranquilizer) and ramastine (antiallergic), as well as in some antiulcerative and antiasthmatic agents. In addition, quinolines have pharmacological properties which include wide applications in medicinal chemistry; for example, this scaffold structure is present in

anti-inflammatory agents, antimalarial drugs, and antihypertensive, antiasthmatic, antibacterial, and tyrosine kinase inhibiting agents[17].

Moreover the importance of uracil and its annulated derivatives is well recognized by synthetic as well as biological chemists. The 6-amino-uracil derivatives represent very important classes of functionalized uracils; also 6-amino-uracils find wide applications as starting materials for the synthesis of a number of fused uracils of biological significance, for example, pyrano-, pyrido-, pyrazolo-, pyrimido-, and pyridazinopyrimidines[1].

On the other hand, ultrasonic reactions have been increasingly used as clean, green, and environmentally benign routes for the preparation of organic compounds of synthetic and biological values[7,6,9,10]. A large number of organic reactions can be carried out in higher yield, shorter reaction time, and under milder conditions, by using ultrasonic irradiation [5,2,19,4].



indenopyrido[2,3-d]pyrimidine

2. Experimental

2.1. Chemical materials

All reactants and solvents used in this study were reagents grade and they are available from Sigma-Aldrich and Fluka companies Melting points are determined in open capillary tubes in a Germany, Stuarts, SMP30 Melting points apparatus and are uncorrected. Infrared (spectra (FT-IR) were recorded using a SHIMADZU FT-IR8400S spectrophotometer at the Department of Chemistry/Collage of Science/ University of Mustansiriyah.

1HNMR spectra were recorded on a Bruker, Ultra Shield 400Mhz, spectrometer (Switzerland) using DMSO-d6 as a solvent with a tetramethylsilane (TMS) as an internal standard, at the Turkey, all progress of the reactions and checking the purity were performed with thin layer chromatography (TLC) technique and revealed by mixture of n-hexane and ethyl acetate (3 : 2) as eluent in the staining jar and irradiation with UV. light chromatograms.

2.2. Synthesis of 4-amino-2-(4-chloro or bromophenyl)-1,2-dihydropyrimido[1,2-a] benzimidazole-3-carbonitrile (4 and 5)

In a typical procedure, equimolar amounts of p-chloro or p-bromo benzaldehyde (0.01mol), malononitrile (0.66g, 0.01mol) and 1H-benzimidazol-2-amine (1.33g, 0.01mol) were mixed with few drops of NaOH (20 %) in (10mL) of ethanol and refluxed with stirring for 60 min. After the completion of the reaction, the mixture was cooled to room temperature and poured into the ice to get the crude products. The crude products were purified by recrystallization from ethanol to give [**4** or **5**]. The physical properties of compound [**4** and **5**] are listed in table (1).

2.3. Synthesis of ethyl 2-(4-chloro or bromophenyl)-3-cyano-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazol-4-ylimidoformate

[6 and 7]

A mixture of compound [**4** or **5**] (0.01mol) and triethylorthoformate (1.48g, 0.01mol) and acetic anhydride (15mL) was refluxed for 7hs. The solvent was removed under reduced pressure and the resulting solid product is recrystallized from ethanol to give [**6** or **7**]. The physical properties of compound [**6** and **7**] are listed in table (1).

2.4. Synthesis of 5-chloro or bromo-4-imino-5,6-dihydrobenzo [4,5]imidazo[1,2-a]pyrmido[5,4-e]pyrmidin-3(4H)-amine. [8,9] ;

5-chloro or bromo-3-methyl-5,6-dihydrobenzo [4,5]imidazo[1,2-a]pyrmido[5,4-e]pyrmidin-3(4H)-amine. [10,11] ;

5-chloro or bromo-3-ethyl-5,6-dihydrobenzo [4,5]imidazo[1,2-a]pyrmido[5,4-e]pyrmidin-3(4H)-amine. [12,13] ;

5-chloro or bromo-3-propyl-5,6-dihydrobenzo [4,5]imidazo[1,2-a]pyrmido[5,4-e]pyrmidin-3(4H)-amine. [14,15] ;

5-chloro or bromo-3-isobutyl-5,6-dihydrobenzo [4,5]imidazo[1,2-a]pyrmido[5,4-e]pyrmidin-3(4H)-amine. [16,17]

To a solution of [**6** or 7] (0.001mol) in dioxan (5mL), a solution of hydrazine hydrate (0.5g, 0.001mol), or methyl amine (0.031g, 0.001mol) or ethyl amine (0.045g, 0.001mol) or propyl amine (0.059g, 0.001mol) or isobutyl amine (0.073g, 0.001mol) was added and the mixture stirred for 1hr. Then it is allowed to stand overnight. The precipitate formed is filtered, dried and crystallized from methanol to give compounds [**8-17**] respectively. The physical properties of compounds [**8-17**] are listed in the table (1).

Table (1) : The physical properties of compounds (4-17)

Com. No.	M.F	M.W g/mole	Rec. solvent	R_f	Yield (%)	Color	m.p °C
4	$C_{17}H_{12}N_5Cl$	321	ethanol	0.63	82	yellow	234-236
5	$C_{17}H_{12}N_5Br$	365	ethanol	0.58	79	yellow	233-235
6	$C_{20}H_{16}N_5OCl$	377	ethanol	0.42	75	grey	170-173
7	$C_{20}H_{16}N_5OBr$	421	ethanol	0.37	72	grey	167-169
8	$C_{18}H_{14}N_7Cl$	363	methanol	0.74	70	Pale yellow	235-237
9	$C_{18}H_{14}N_7Br$	407	methanol	0.51	60	yellow	229-231
10	$C_{19}H_{15}N_6Cl$	362	methanol	0.66	68	Pale yellow	215-217
11	$C_{19}H_{15}N_6Br$	406	methanol	0.49	59	pale yellow	202-204
12	$C_{20}H_{17}N_6Cl$	376	methanol	0.53	63	Pale yellow	272-274
13	$C_{20}H_{17}N_6Br$	420	methanol	0.52	56	Pale yellow	292-294
14	$C_{21}H_{19}N_6Cl$	390	methanol	0.41	60	Pale yellow	258-260
15	$C_{21}H_{19}N_6Br$	434	methanol	0.44	56	Pale yellow	272-274
16	$C_{22}H_{21}N_6Cl$	404	methanol	0.39	56	yellow	245-247
17	$C_{22}H_{21}N_6Br$	448	methanol	0.31	58	Pale yellow	269-271

3. Results and discussion

fused dihydrobenzo [**4** and **5**] imidazo[1,2-a]pyrmido[5,4-e]pyrmidin-3(4H)-amine derivatives were synthesized from 4-amino-2-(4-chlorophenyl or 4-bromophenyl)-1,2-dihydropyrimido [1,2-a] benzimidazole-3-carbonitrile [**4** and **5**], which prepared by reaction 1H-benzimidazol-2-amine [**1**] and p-chlorobenzaldehyde or p-bromobenzaldehyde [**2**] and malononitrile [**3**], the FTIR of [**4** or **5**], shows stretching bands symmetrical and unsymmetrical of (NH_2) at 3321-3410 cm^{-1} and 2185 cm^{-1} for (C≡N) , other stretching bands found in table (2).

Table (2): The Stretching bands (cm^{-1}) of compounds (4,5)

Comp.	Stretching bands (cm^{-1})								
	NH_2	NH	C-H arom.	C-H aliph.	C≡≡N	C=N	N-H bend.	C=C	C-X
4	3410, 3325	3219	3070	3009	2185	1647	1637	1597	1091 (C-Cl)
5	3410, 3321	3246	3100	2906-2999	2185	1678	1637	1597	1089 (C-Br)

The ^{1}HNMR spectrum of compound [**4** or **5**], shows signals at δ = 5.25-5.26 ppm (s, 1H, CH and NH) indicated for cyclic formation , δ = 7.62-7.63 ppm (s, 2H, NH_2) and signals at δ = 6.98-8.61 (m,8H, Ar-H)

The mass spectral data were consistent with the structures of the synthesized compounds [**4,5**]. Compounds [**4** or **5**] was selected as starting compounds to synthesize compounds [**6** or **7**]. Compounds [**4** or **5**] was reacted with triethyl orthoformate in acetic anhydride to gave imidoformate derivatives [**6** or **7**], the compounds [**6** or **7**] was reacted for one hour at room temperature with hydrazine hydrate, methylamine and ethyl amine, propyl amine and isobutyl amine to give fused pyrimidine derivatives [**8-17**].

These compounds [**6-17**] were characterized by FT-IR and ^{1}HNMR, the FTIR of compound [**6** or **7**], shows disappearance stretching bands of (NH_2) , the stretching bands of compound [**6** or **7**] found in table (3).

Table (3): The Stretching bands (cm^{-1}) of compounds [6,7]

Comp.		Stretching bands (cm^{-1})							
	NH	C-H arom.	C-H aliph.	C≡≡N	C=N	N-H bend.	C=C	C-O-C	C-X
6	3200	3032	2854-2953	2196	1695	1622	1593	1246	1091 (C-Cl)
7	3100	3050	2901-2993	2196	1695	1622	1593	1244	1091 (C-Br)

The FTIR of compounds [**8 –17**], shows disappearance stretching band

of (C≡N), this indication to successful of cyclization reaction, and the other characteristic bands shows in the table (4).

Table (4) : The Stretching bands (cm^{-1}) of compounds [8-17]

Comp.	Stretching bands (cm^{-1})					
	NH_2	NH	C-H arom.	C-H aliph.	C=N	C=C
8	3331, 3292	3180	3086	3049-3028	1658	1597
9	3223,3296	3190	3070	2951-2906	1658	1597
10	-	3323	3022	2901-2852	1660	1600
11	-	3331	3032	2916-2852	1662	1600
12	-	3431	3059	3020-2901	1658	1597
13	-	3431	3061	3016-2901	1658	1597
14	-	3362	3134	2933-2912	1668	1597
15	-	3363	3126	2962-2912	1668	1595
16	-	3363	3053	2962-2856	1666	1597
17	-	3358	3060	2962-2856	1668	1600

The ^{1}HNMR spectrum of compound [**6,7**], shows signals at δ = 1.44 ppm (t, 3H, CH_3), δ = 3.43-3.31 ppm (q, 2H, CH_2), overlapping signals at δ = 4.57ppm (s, 1H, CH and NH), at δ = 6.53-7.70 (m,8H, Ar-H) and δ = 8.72 ppm (s, 1H, N=CH).

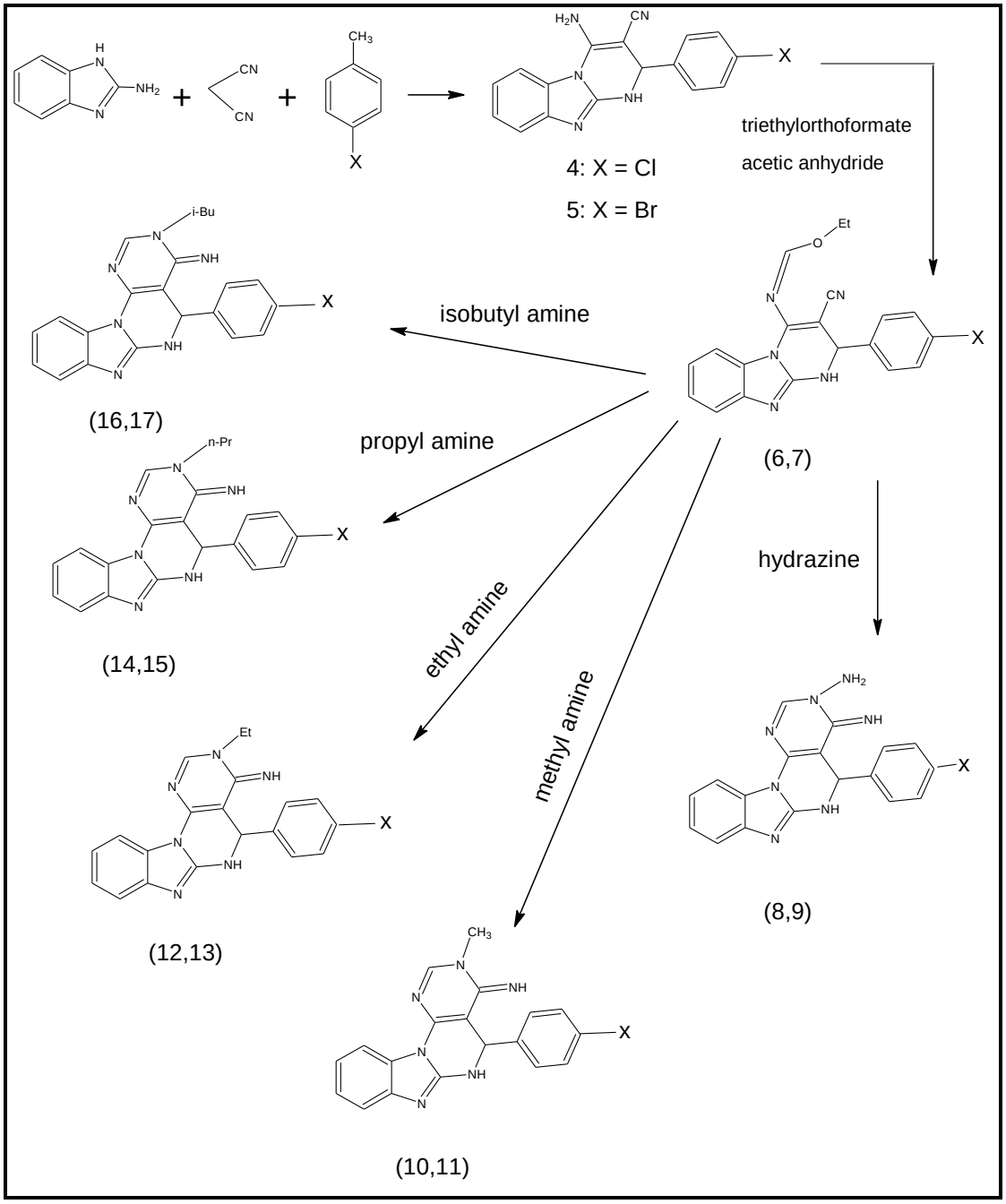
The ^{1}HNMR spectrum of compound [**8,9**], shows overlapping signals at δ = 4.51-4.40 ppm (s, 1H, CH and NH), δ = 6.97 ppm (s, 1H, C=NH), δ = 6.99 ppm (s, 2H, NH_2), δ = 7.08-8.30 (m,8H, Ar-H) and δ = 8.53 ppm (s, 1H, N=CH).

The ^{1}HNMR spectrum of compound [**10,11**], shows signals at δ = 3.57 ppm (s, 3H, CH_3), overlapping signals at δ = 5.77 ppm (s, 1H, CH and NH), δ = 6.97 ppm (s, 1H, C=NH), at δ = 7.08-8.33 (m,8H, Ar-H) and δ = 8.56 ppm (s, 1H, N=CH).

The ^{1}HNMR spectrum of compound [**12,13**], shows signals at δ = 1.20-1.22 ppm (t, 3H, CH_3), δ = 3.57 ppm (q, 2H, CH_2), overlapping signals at δ = 5.88 ppm (s, 1H, CH and NH), δ = 7.01 ppm (s, 1H, C=NH), at δ = 7.08-8.48 (m,8H, Ar-H) and δ = 8.76 ppm (s, 1H, N=CH).

The ^{1}HNMR spectrum of compound [**14,15**], shows signals at δ = 0.88 ppm (t, 3H, CH_3), δ = 1.49 ppm (m, 3H, CH_2), δ = 3.43 ppm (t, 3H, CH_2), overlapping signals at δ = 5.89 ppm (s, 1H, CH and NH), δ = 7.02 ppm (s, 1H, C=NH), at δ = 7.08-8.46 (m,8H, Ar-H) and δ = 8.75 ppm (s, 1H, N=CH).

The ^{1}HNMR spectrum of compound [**16,17**], shows signals at δ = 0.78 ppm (d, 6H, $(CH_3)_2$), δ = 1.58 ppm (m, 1H, CH), δ = 3.40 ppm (t, 3H, CH_2), overlapping signals at δ = 5.92 ppm (s, 1H, CH and NH), δ = 7.02 ppm (s, 1H, C=NH), at δ = 7.08-8.46 (m,8H, Ar-H) and δ = 8.75 ppm (s, 1H, N=CH). All these results are agreement with literatures[(11)].



Scheme (1): Synthesizes of pyrimidine- rings derivatives

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