Al-Mustansiriyah Journal of Science
ISSN: 1814-635X (print), ISSN:2521-3520 (online) Volume 33, Issue 1, 2022 DOI: http://doi.org/10.23851/mjs.v33i11.1020

Research Article **Open Access**

Synthesis and Characterization of Novel Pyrimido [1,2-a] benzimidazole and its Derivatives

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Article Info

Received
14/06/2021

Accepted
31/08/2021

Published
14/03/2022

ABSTRACT

A few pyrimido[1,2-a] benzimidazole derivatives had been synthesized, derived from 4-amino-2-(4-chloro or bromophenyl) -1,2-dihydropyrimido[1,2-a] benzimidazole-3-carbonitrile (4 or 5) is made through one pot three components condensation reaction of 1H-benzimidazol-2-amine (1) with p-chloro or bromobenzaldehyde (2) and malononitrile (3). First part of these derivatives prepared by reaction compound (4 or 5) with acetic acid or propionic acid in presence $POCl_3$ to give pyrmidino rings (6-9). Second part of derivatives were prepared by reaction compound (4 or 5) with benzoyl chloride or phenylisothiocyanate or cyclohexanone to give cyclic compounds (10-15) respectively. All these derivatives characterized by FT-IR and HNMR spectroscopy analysis in addition to physical properties.

KEYWORDS: pyrmidines, benzimidazole.

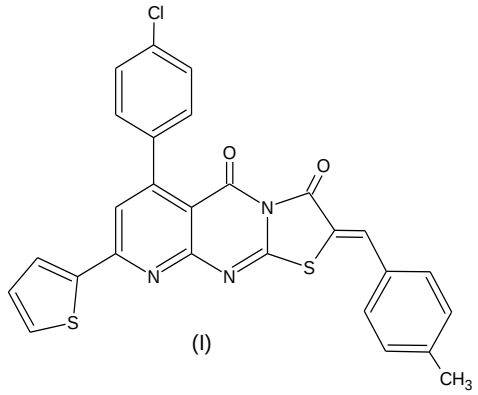
الخلاصة

تم تحضير بعض من مشتقات البيرميدينو[**1,2**-a] بنزايميدازول المشتقة من **4**-امينو-**2**-(**4**-كلورو او بوموفنيل) –**1**, **2**– ثنائي هايدروبيرميدينو [**1,2**-a] بنزايميدازول -**3**-كاربونايترايل (**4**, **5**) والذي حضر بواسطة تفاعل 1H – بنزايميدازول -**2**- امين (**1**) وبارا-كلورو او بروموبنزالديهايد (**2**) و المالونونايترايل (**3**). الجزء الاول من هذه المشتقات حضر بواسطة تفاعل المركب (**4** او **5**) مع حامض الخليك او حامض البروبيونك بوجود $POCl_3$ ليعطي حلقات البيرميدينو (**6** -**9**). الجزء الثاني من هذه المشتقات حضر بواسطة تفاعل المركب (**4** او **5**) مع البنزويل كلورايد او فنيل ايزوثايوسيانات او السايكلوهكسانون ليعطي مركبات حلقية (**10**-**15**) على التوالي. جميع هذه المشتقات شخصت بواسطة اطياف الاشعة تحت الحمراء FT-IR و الرنين النووي المغناطيسي 1HNMR.

INTRODUCTION

Pyrimidine-fused derivatives are an inextricable portion of RNA and DNA, play an important role in a variety of biological processes, and are chemically and biologically significant. As a pharmacophore, pyrimidine-condensed derivatives have many different biological actions, including anti-bacterial [1], anti-viral [2], antifungal [3], antimalarial (4), anti-inflammatory [5], anti-cancer [6], and anti-HIV [7]. For the synthesis of pyrimidine-fused analogues, many retrosynthetic techniques are available, which opens up many possibilities in the field of medicinal chemistry. Starting from their existence in biologically active resources has been recognized to elicit additive effect on molecules' bio-efficacy, scientists were interested in ring fused pyrimidine and its numerous derivatives [8]. Over the last few decades, significant development was achieved in the anticancer agents' development, with a large number of novel anticancer agents generated from both synthetic and natural sources. From heterocyclic compounds, pyrimidine-fused bicyclic heterocycles have antiviral, anti-cancer, and other biological activities [9]. Pyrido[2,3-d] pyrimidine derivatives (I), as shown in Figure 1, are one of the key components in developing new cytotoxic drugs that operate on cell cycle apoptosis induction via extrinsic or intrinsic pathways [10]. Pyrimidine derivative chemistry is significant in the fields of agriculture chemicals, drugs and a variety of biological activities. A great number of pharmacological investigations on pyrimidine and its derivatives have been conducted in recent

decades. Yet, additional research is needed to determine the biological chemicals' requirement. In medicinal chemistry, many approaches for pyrimidine synthesis, as well as their various reactions, create an enormous scope. These researches were aided by the fact that pyrimidines can be used as a core structure for a variety of biologically active compounds.



(I)

Figure 1: Pyrido[2,3-d] pyrimidine derivatives.

A wide variety of pyrimidine derivatives were found to have antitumor [11], antimycobacterial [12], anticancer [13], antiviral [14], antimicrobial [15], anti-inflammatory [16] and analgesic activities [17].

EXPERIMENTAL PART

1. Chemical materials

All solvents and reactants utilized in this research were reagent grade and were purchased from Sigma Aldrich and Fluka. In Germany, Stuarts, SMP30 Melting Points apparatus, melting points are specified in open capillary tubes and uncorrected. At the Dept. of Chemistry/Collage of Science/Univ. of Mustansiriyah, infrared spectra (FT-IR) were acquired with the use of Shimadzu FT-IR8400S spectrophotometer.

1HNMR spectra have been recorded on a Bruker, Ultra Shield 400Mhz, spectrometer (Switzerland) utilizing tetra-methylsilane (TMS) as internal standard and DMSO-d-6 as a solvent, in 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. Synthesis of 4-amino-2-(4-chlorophenyl)-1,2-dihydropyrimido [1,2-a] benzimidazole-3-carbonitrile (4,5)

In a typical procedure from [18], 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 ethanol of (10ml) and refluxed with 60 mins stirring. After the reaction is completed, the mix has been cooled to room temperature and after that poured to ice for getting crude products. In addition, the crude products were purified through recrystallization from ethanol [4,5]. The compound's physical properties [4,5] are provided in Table 1.

3. Synthesis of 5-(4-chloro or bromophenyl)-2alkyl-5,6-di-hydrobenzo [4,5]imidazo[1,2-a]pyrmido[5,4-e]pyrmidin-4(3H)-one[6-9]

A mixture of compound [4,5] (0.001mol) was dissolved in aliphatic carboxylic acid (15ml), then POCl3 (2ml) was added quickly. For 22 hours, the mix was refluxed. After the reaction mixture had cooled, ice water was added to it (50ml). The result was a large amount of white precipitate. To neutralize the acid, fused K2CO3 was added until no bubbles appeared. Compounds [6-9] were obtained by filtering the reaction mixture, washing it with a tiny amount of ethanol, drying it, and recrystallizing it from ethanol. Table 1 lists the physical characteristics of compounds [6-9].

4. Synthesis of 5-(4-chloro or bromophenyl)-2-phenyl-5,6-dihydrobenzo [4,5]imidazo[1,2-a]pyrmido[5,4-e]pyrmidin-4(3H)-one[10-11]

A mixture of compound [4,5] (0.003mol) as well as benzoyl chloride (0.42g, 0.003mol) in pyridine (15ml) has been refluxed for a period of 24 hrs. Solid product formed upon pouring into ice-water has been collected through filtration as well as re-crystallized from ethanol [10,11]. Furthermore, the compound's physical properties [10,11] are provided in Table 1.

5. Synthesis of 5-(4-chloro or bromophenyl)-4-imino-3-phenyl-3,4,5,6-tetrahydrobenzo [4,5]imidazo[1,2-a]pyrmido[5,4-e]pyrmidine-2(1H)-thione [12,13]

A mixture of compound [4,5] (0.003mol) and phenyl isothiocyanate (0.4g, 0.003mol) in pyridine (15ml) has been refluxed for a period of 18 hrs. In addition, the solid product created when pouring into ice-water has been gathered through filtration as well as washed by distilled water and after that recrystallized from ethanol for giving compounds [12], and [13] respectively. The compound's physical properties [12], and [13] are provided in Table 1.

6. Synthesis of 7-(4-chloro or bromophenyl)-6,7, 9,10,11,12-hexahydrobenzo [4/,5/]imidazo[2/,1/:2,3]pyrmido[4,5-b]quinolin-8-amine[14,15]

To a mixture of compound [4,5] (0.001mol) and cyclohexanone (10ml) placed in a round bottom flask connected to a reflux condenser, was added $FeCl_3$ (0.16g, 0.001mol). The mixture was heated for 24 hrs at a temperature of 120°C under stirring. Following cooling to r.t, the remaining solids have been treated by NaOH solution (2 mol/L, 8ml), while such mixture has been heated at reflux for a period of 24 hrs. On cooling to r.t, the reaction mixture has been extracted with the CHCl3 (3x8ml), the organic layers have been combined and dried over Na_2SO_4. The solvent has been evaporated under decreased pressure and re-crystallized from the ethanol for the purpose of giving the compound [14,15], the physical characteristics have been listed in Table 1.

Table 1. The compound's physical properties (4-15).

Com. No.	M.F	M.W *gm/mole*	Rec. solvent	R_f	Yield (%)	Colour	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]	$C_{19}H_{14}N_5OCl$	363	ethanol	0.20	69	brown	200-202
[7]	$C_{20}H_{16}N_5OCl$	377	ethanol	0.27	65	dark brown	175-177
[8]	$C_{19}H_{14}N_5OBr$	407	ethanol	0.25	60	dark brown	120-122
[9]	$C_{20}H_{16}N_5OBr$	421	ethanol	0.29	61	dark brown	193-195
[10]	$C_{24}H_{16}N_5OCl$	425	ethanol	0.26	71	golden	110-112
[11]	$C_{24}H_{16}N_5OBr$	469	ethanol	0.28	69	yellow	137-139
[12]	$C_{24}H_{17}N_6SCl$	456	ethanol	0.54	67	orange	127-129
[13]	$C_{24}H_{17}N_6SBr$	500	ethanol	0.60	62	orange	142-144
[14]	$C_{23}H_{20}N_5Cl$	401	ethanol	0.23	63	brown	188-190
[15]	$C_{23}H_{20}N_5Br$	445	ethanol	0.19	64	dark brown	200-202

RESULTS AND DISCUSSION

The derivatives of the Pyrimido [1,2-a]benzimidazole (6-15) have been synthesized from 4-amino-2-(4-chlorophenyl or 4-bromophenyl)-1,2-di-hydropyrimido[1,2-a] benzimidazole-3-carbonitrile (4,5), which prepared via one thee components condensation reaction of 1H-benzimidazol-2-amine (1) with p-chlorobenzaldehyde or p-bromobenzaldehyde (2) and malononitrile (3), the FTIR of [4,5], 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 band (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 1HNMR spectrum of compound [4,5], shows signals at δ=5.25-5.26 ppm (s, 1H, CH and NH) in pyrimidine ring, δ=7.62-7.63 ppm (s, 2H, NH_2) and signals at δ=6.98-8.61 (m,8H, Ar-H).

The synthesized compounds' structures were consistent with the mass spectral data (4,5). Compounds 4 or 5 were chosen as starting compounds for synthesizing further compounds (6 -15). The reaction of a compound [4,5] with a few aliphatic carboxylic acids (propionic acid, acetic acid) in the existence of $POCl_3$ yielded pyrimidinone derivatives, which were fused benzoimidazo – pyrmidine ring (6-9) $POCl_3$ served as a chlorinating reagent as well as an oxidant in this reaction system. As a result, this work indicated that the compound [4,5] was oxidized first and after that reacted with acyl chloride that was produced in situ from carboxylic acid with $POCl_3$ reaciton. The target products were produced after cyclization as well as condensation of the intermediate. Through controlling the amount of $POCl_3$, the reaction occurred smoothly, and products have been acquired in good yields. Our past research backs up these findings [19].

Compounds [6-9] have been characterized by FT-IR and 1HNMR, FTIR of compound [6-9], exhibits disappearance stretching band of (C≡N), and the other characteristic bands have been shown in Table 3.

Table 3. Bands (cm^{-1}) of compounds (6-9).

Comp. NO.	NH	C-H arom.	C-H aliph.	C=O pyrmi.	C=N	C=C
6	3228	3184	2939-2883	1654	1606	1589
7	3211	3080	2993	1681	1651	1591
8	3236	3115	3041-2933	1693	1653	1573
9	3362	3171	3028-2912	1668	1640 (weak)	1597

The 1HNMR spectrum of compound [6] shows signals at δ=2.45ppm (s,3H, CH_3), signals at δ=5.63 ppm (s, 1H, CH and NH), signals at δ=7.00-7.39 (m,8H, Ar-H) and δ=8.14ppm (s,1H, NH (pyrmidino cyclic)).

The 1HNMR spectrum of compound [7] shows signals at 1.13ppm (t,3H,CH_3), signals at δ=2.03ppm (q,2H, CH2), signals at δ=5.63 ppm (s, 1H, CH and NH), signals at δ=7.00-8.30 (m,8H, Ar-H) and δ=8.48ppm (s,1H, NH (pyrmidino cyclic)). The 1HNMR spectrum of compound [8] shows signals at δ=2.47ppm (s,3H, CH_3), signals at δ=5.88 ppm (s, 1H, CH and NH), signals at δ=7.00-8.23 (m,8H, Ar-H) and δ=8.25ppm (s,1H, NH (pyrmidino cyclic)). The 1HNMR spectrum of compound [9] shows signals at 1.13 ppm (t,3H,CH_3), signals at δ=2.03ppm (q,2H, CH_2), signals at δ=5.69 ppm (s, 1H, CH and NH), signals at δ=7.00-8.19 (m,8H, Ar-H) and δ=8.43ppm (s,1H, NH (pyrmidino cyclic)) Reaction [4,5] with benzoyl chloride in presence of pyridine gave compound [10,11]. Treatment of compound [4,5] with the phenyl isothiocyanate in pyridine for 16 h had resulted in the fused pyrimidino derivative [12,13] in 81% yield. Cyclization of compound [4,5] with cyclohexanone performed in presence lewis acids as catalyst and NaOH for synthesizing pyridine derivative [14,15], compounds [10-15] were characterized by FT-IR and 1HNMR, the FT-IR illustrates the disappearance stretching band of (C≡N), and the rest of the characteristic bands have been listed in Table 4.

Table 4. The bands of compounds (10- 15).

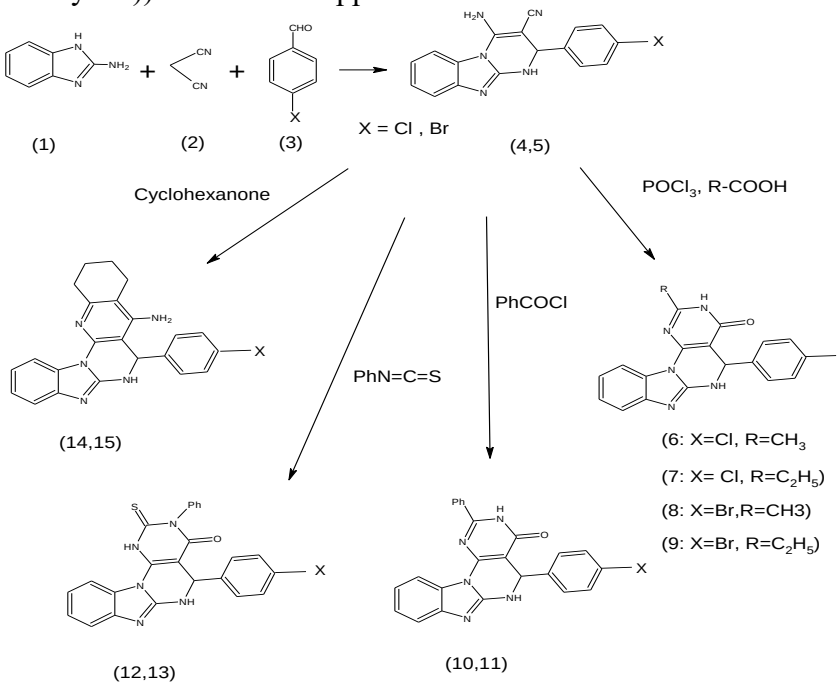
Comp.	Stretching bands (cm^{-1})							
	NH_2	NH	C-H arom.	C-H aliph.	C=O	C=N	C=C	C=S
10		3317	3198	2881-3003	1681	1645	1600	-
11		3317	3198	2816-3003	1681	1654	1600	-
12		3338	3183	2877-3007	-	1616	1593	1531
13		3338	3136	2953	-	1614	1591	1529
14	3369, 3298	3200	3080	2854-2928	-	1645	1593	-
15	3348,3326	3150	3090	2856-2928	-	1633	1591	

The 1HNMR spectrum of compound [10] shows signals at δ=7.00-8.19 (m,13H, Ar-H) and δ=12.92ppm (s,1H, NH (pyrmidino cyclic)).

The 1 HNMR spectrum of compound [11] shows signals at δ=7.00-8.19 (m,13H, Ar-H) and δ=12.95ppm (s,1H, NH (pyrmidino cyclic)).

The 1HNMR spectrum of compound [12] shows weak signals at δ=4.50 ppm (s, 1H, CH and NH), signals at δ=7.00-7.79 (m,13H, Ar-H), δ=8.50 ppm (s,1H, NH (pyrmidine cyclic)) and δ=9.70 ppm (s,1H, N=H). The 1HNMR spectrum of compound [13] shows weak signals at δ=4.50ppm (s, 1H, CH and NH), signals at δ=7.00-7.62 (m,13H, Ar-H), δ=8.60ppm (s,1H, NH (pyrmidine cyclic)) and δ=9.80ppm (s,1 H, N=H)

The 1HNMR spectrum of compound [15] shows signals at δ=1.22-2.98 ppm (m, 8H, $CH_2(CH_2)_2CH_2$), signals at δ=5.36 ppm (s, 1H, CH and NH), signals at δ=7.00-7.50 (m,10H, Ar-H and NH_2).



Scheme 1. **Synthesis pyrimido[1,2-a] benzimidazole derivatives (4-15)**

CONCLUSION

All pyrimido[1,2-a] benzimidazole derivatives had been synthesized with cyclization using different methods and reagents. Pyrimidine ring was prepared from reaction compounds containing an amine group adjacent to a cyano group with aliphatic carboxylic acids in presence $pocl_3$ or with benzoyl chloride in pyridine or with phenyl isothiocyanate in pyridine or with cyclohexanone in presence ferric chloride.

ACKNOWLEDGMENT

Very thanks for Mustansiriyah University, College of Science, department of Chemistry for the facilities in this work.

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