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

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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 POCl3 to give pyrimido rings (6-9). Second part of derivatives were prepared by reaction compound (4 or 5) with benzoil 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: pyrimidines, benzimidazole.

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.

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]pyrimido[5,4-e]pyrimidin-
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-di-hydrobenzo
[4,5]imidazo[1,2-a]pyrimido[5,4-e]pyrimidin-
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]pyrimido[5,4-e]pyrimidine-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]pyrimido[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 FeCl₃ (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 Na₂SO₄. 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 | Rₚ | Yield (%) | Colour | m.p °C |
|----------|-----|-------------|--------------|-----|-----------|--------|--------|
| [4]      | C₁₂H₁₂N₃Cl | 321         | ethanol      | 0.63 | 82        | yellow | 234-236|
| [5]      | C₁₂H₁₂N₃Br | 365         | ethanol      | 0.58 | 79        | yellow | 233-235|
| [6]      | C₁₂H₁₂N₃OCl | 363        | ethanol      | 0.20 | 69        | brown  | 200-202|
| [7]      | C₂₀H₂₀N₃OCl | 377        | ethanol      | 0.27 | 65        | dark brown | 175-177|
| [8]      | C₁₀H₆N₂OBr | 407         | ethanol      | 0.25 | 60        | dark brown | 120-122|
| [9]      | C₂₆H₁₆N₄OBr | 421        | ethanol      | 0.29 | 61        | dark brown | 193-195|
| [10]     | C₂₆H₁₆N₄OCl | 425        | ethanol      | 0.26 | 71        | golden  | 110-112|
| [11]     | C₂₆H₁₆N₄OBr | 469        | ethanol      | 0.28 | 69        | yellow  | 137-139|
| [12]     | C₂₆H₁₇N₄SCl | 456        | ethanol      | 0.54 | 67        | orange  | 127-129|
| [13]     | C₂₆H₁₇N₄SBr | 500        | ethanol      | 0.60 | 62        | orange  | 142-144|
| [14]     | C₂₆H₂₀N₄Cl | 401         | ethanol      | 0.23 | 63        | brown  | 188-190|
| [15]     | C₂₆H₂₀N₄Br | 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-hydroprymido[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 \((\text{NH}_2)\) 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. | 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 |
| 5     | 3410, 3321 | 3246 | 3100       | 2906-2999  | 2185 | 1678 | 1637       | 1597 | 1089 |

The 1HNMR spectrum of compound [4,5], shows signals at \(\delta=5.25-5.26\) ppm (s, 1H, CH and NH) in pyrimidine ring, \(\delta=7.62-7.63\) ppm (s, 2H, NH\(_2\)) and signals at \(\delta=6.98-8.61\) ppm (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\(_3\) reaction. 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 \(\delta=2.45\) ppm (s, 3H, CH\(_3\)), signals at \(\delta=5.63\) ppm (s, 1H, CH and NH), signals at \(\delta=7.00-7.39\) (m, 8H, Ar-H) and \(\delta=8.14\) ppm (s, 1H, NH (pyrimidino cyclic)).

The 1HNMR spectrum of compound [7] shows signals at \(1.13\) ppm (t, 3H, CH\(_3\)), signals at \(\delta=2.03\) ppm (q, 2H, CH\(_2\)), signals at \(\delta=5.63\) ppm (s, 1H, CH and NH), signals at \(\delta=7.00-8.30\) (m, 8H, Ar-H) and \(\delta=8.48\) ppm (s, 1H, NH (pyrimidino cyclic)). The 1HNMR spectrum of compound [8] shows signals at \(\delta=2.47\) ppm (s, 3H, CH\(_3\)), signals at \(\delta=5.88\) ppm (s, 1H, CH and NH), signals at \(\delta=7.00-8.23\) (m, 8H, Ar-H) and \(\delta=8.25\) ppm (s, 1H, NH (pyrimidino cyclic)). The 1HNMR spectrum of compound [9] shows signals at 1.13 ppm (t, 3H, CH\(_3\)), signals at \(\delta=2.03\) ppm (q, 2H, CH\(_2\)), signals at \(\delta=5.69\) ppm (s, 1H, CH and NH), signals at \(\delta=7.00-8.19\) (m, 8H, Ar-H) and \(\delta=8.43\) ppm (s, 1H, NH (pyrimidino 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 of 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 | NH₂ | 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| 1591| -   |
| 14   | 3369| 3298| 3080      | 2854-2928  | -   | 1645| 1593| -   |
| 15   | 3348| 3326| 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 (pyrimidino cyclic)).

The 1HNMR spectrum of compound [11] shows signals at δ=7.00-8.19 (m, 13H, Ar-H) and δ=12.95ppm (s, 1H, NH (pyrimidino 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 (pyrimidine 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 (pyrimidine cyclic)) and δ=9.80ppm (s, 1H, N=H)

The 1HNMR spectrum of compound [15] shows signals at δ=1.22-2.98 ppm (m, 8H, CH₂(CH₂)₂CH₂), signals at δ=5.36 ppm (s, 1H, CH and NH), signals at δ=7.00-7.50 (m, 10H, Ar-H and NH₂).

CONCLUSION
All pyrimido[1,2-a] benzimidazole derivatives had been synthesised 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 pocl₃ or with benzoyl chloride in pyridine or with phenyl isothiocyanate in pyridine or with cyclohexanone in presence ferric chloride.

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