Received: 16 February 2021 | Revised: 28 March 2021 | Accepted: 12 April 2021
DOI: 10.22034/ecc.2021.277531.1151
Eurasian Chemical Communications
SAMI

FULL PAPER

Anti-cancer and antioxidant activities of some new synthesized 3-secondary amine derivatives bearing imidazo [1,2-A] pyrimidine

Thamer A. Rehan[a,*] |Naeemah Al-Lami[a] |Rafal Shakeeb Alanee[b]

[a]*Department of Chemistry, College of Sciences, University of Baghdad, Iraq*

[b]*College of Pharmacy, Al-Nahrain University, Iraq*

In this study, new series of 2-aryl-3-(pyrimidine-2-ylamino)imidazo[1,2-a]pyrimidine derivatives (3-secondary amine) were synthesized through one-pot reaction of aromatic ketones and 2-aminopyrimidine. These reactions were performed in the presence of I_2 and **DMSO**. Derivatives of 3-amine compound were reacted with propargyl bromid to yield 2-phenyl-N-(prop-2-yn-1-yl)-N-(pyrimidine-2-yl) derivatives of imidazo/pyrimidine rings. Then, by Mannich reaction, one of 3-secondary amine derivatives (contains NH2 group) (1d) was reacted with different aromatic amines to form Mannich bases. All synthesized compounds were characterized via FT-IR spectroscopy, some of which were characterized by ^{1}H-NMR spectroscopy. Other derivatives of imidazo(1,2-a)pyrimidine(1c,2c,2d,3a) were evaluated for anti-oxidant activity and one of these derivatives (2d) was tested for cytotoxic activity against breast cancer using MTT assay.

KEYWORDS

Imidazo[1,2-a]pyrimidine; one-pot reaction; anti-oxidant; MTT assay.

***Corresponding Author:**
Thamer A. Rehan
Email: thamerabdr1988@gmail.com
Tel.: +9647505323708

Introduction

Heterocyclic compounds that contain a bridge of nitrogen atom are of great importance in medical chemistry and industrial applications as anti-corrosion. Imidazo[1,2-a]pyrimidines are a prevalent and important fused heterocyclic system containing three nitrogen atoms and demonstrate structural similarities with purines [1]. Imidazo(1,2-a)pyrimidines are widespread structural motifs in pharmaceutically and biologically active compounds [2]. They have also been used in other applications such as azo dyes[3], fabric whiteners [4], anticonvulsant and anxiolytic activity [5]. To further explore their applications, their scaffold also acts as organic flurophore used as biomarkers and photochemical sensors [6]. Also, some imidazo[1,2-a]pyrimidine derivatives have been reported to have significant anti-inflammatory and analgesic actions in experimental animal models[7,8]. Furthermore, The structural unit of imidazo[1,2-a]pyrimidines has been also found in a number of investigational drugs, such as divaplon, taniplon and fasiplon[9](Figure 1).

One of the most important reactions in organic chemistry is one-pot reaction. This type of reaction is widely used in organic synthesis to prevent separation and purification processes and thus obtain a large reaction yield in the shortest possible time. Many steps of bond- forming and chemical transformation can be accomplished by one-

pot reaction [10]. Recently, one-pot reaction has been used for synthesis of 2,3-disubstituted imidazo[1,2-a]pyridine by the reaction of 2-aminopyridine with different substituted acetophenone in the presence of DMSO and $\mathbf{I_2}$ [11]. In this work, 2,3-disubstituted imidazo[1,2-a]pyrimidine (3-secondary amine) (DIP) was prepared using the abovementioned method. On the other hand, propargylamines were synthesized by the reaction of DIP derivatives with propargylbromide. Propargylamines are widely used in organic synthesis to form diverse heterocyclic compounds [12], natural products and bioactive compounds [13-15]. These compounds have a significant role in many pharmaceutical and biological applications, such as anti-cancer [16], anti-bacterial [17], anti-funal [18], antiproliferative [19]. Conventional methods of synthesis of propargylamines involve amination of propargylic halides, phosphates, or triflates [20-22] and reaction of lithium acetylides or Grignard reagents with imines or their derivatives [23,24].

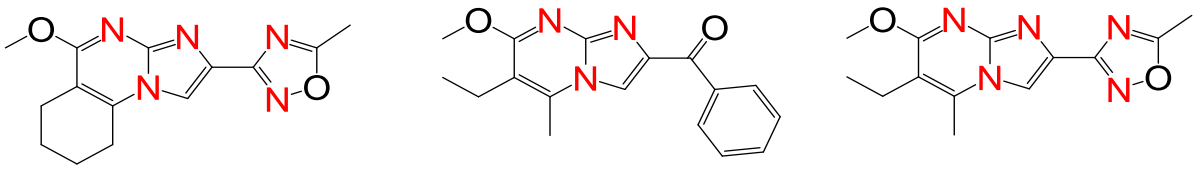


FIGURE 1 structures of some drugs that contain imidazo[1,2-a]pyrimidine core

In addition, the synthesis of Mannich bases can be performed by the reaction of one of the DIP derivatives with different amines. These compounds were synthesized by Mannich reaction that is a widely used reaction to the production of new drugs and as a key reaction for the development of biological active compounds [25]. Mannich bases show a wide variety of biological and pharmaceutical activities as the final product of the Mannich reaction such as antifammatory [26], antibacterial [27], antitumor [28], anti-oxidant [29], anti-fungal [30].

The aim of the research was to synthesize new compounds of imidazo[1,2-a]pyrimidine and study their activities as anticancer and antioxidant .

Materials and methods

Experimental instruments

A. Melting point was recorded using electro thermal melting point apparatus.
B. All the (1H and 13C NMR) spectra were recorded on bruker ultra-shield 500MHz spectrometer using DMSOd6 as solvent as an internal standard.
C. Chemical shift values are listed in δ scale The IR spectra were recorded on Schimadzu FTIR spectro photometer by using 1% potassium bromide discs.

Synthesis of 2-Aryl-3-(pyrimidine-2-ylamino)imidazo(1,2-a)pyrimidine (General procedure (1a))

A mixture of acetophenone (0.0026 mol) and $\mathbf{I_2}$ (2 mL, 0.0026 mol) in **DMSO** (5 mL) was heated under reflux at 100 C^0 for 6 hours. After that, 2-aminopyrimidine(0.0052 mol) was added and then heated for an additional 2 hours. The resulting solution was cooled and poured in crushed ice. The formed precipitate was filtered and recrystallized from ethanol to obtain compound (**1a**). Elemental analysis was as follows: $C_{16}H_{12}N_6$: IR(KBr/cm^{-1}): 3159(N-H), 3037(Ar-H), 1614(C=N)imidazo, 1575(C=N)pytimidine, 1560(C=C). ^{1}H-NMR (DMSO,°00 MH_Z) δ: 6.87-8.83(m,Ar-H, s, 1H,NH), ^{13}C-NMR (DMSO, °00 MH_Z) δ: 169.3-138.8(C=N), 138.6-115.3(C=C).

2-(4-Bromophenyl)-3-(pyrimidine-2-ylamino)imidazo(1,2-a)pyrimidine (1b)

Elemental analysis was as follows: $C_{16}H_{11}BrN_6$**:** IR(KBr/cm^{-1}):: 3110(N-H), 3078(Ar-H), 1641(C=N)imidazo, 1614(C=N)pyrimidine, 1537(C=C), 744(C-Br); ^{1}H-NMR (DMSO,°00 MH$_Z$) δ: 6.75-8.77(m, Ar-H, s,1H,NH), ^{13}C-NMR (DMSO, °00 MH$_Z$) δ: 168.5-148.3(C=N), 136.6-115.3(C=C).

2-(4-Nitrophenyl)-3-(pyrimidine-2-ylamino)imidazo(1,2-a)pyrimidine (1c)

Elemental analysis was as follows: $C_{16}H_{11}N_7O_2$**:** IR(KBr/cm^{-1}):: 3224(NH-), 3074(Ar-H), 1633(C=N)imidazo, 1593(C=N)pyrimidine,1456(C=C), 1517 and 1344(NO_2). ^{1}H-NMR (DMSO,°00 MH$_Z$) δ: 8.48-6.88 (m, Ar-H, s,1H,NH) and ,^{13}C-NMR (DMSO, °00 MH$_Z$) δ: 160(C-NO_2), 158.89, 149, 93, 146.56(C=N), 141.3- 127.64(C=C).

2-(4-Aminophenyl)-3-(pyrimidine-2-ylamino)imidazo(1,2-a)pyrimidine (1d)

Elemental analysis was as follows: $C_{16}H_{13}N_7$: IR(KBr/cm^{-1}):: 3373,3340 (NH_2), 3224(NH), 3058(Ar-H), 1656(C=N)imidazo, 1641(C=N)pyrimidine, 1596,1475(C=C); ^{1}H-NMR (DMSO,°00 MH$_Z$) δ : 7.83-6.08(m. Ar-H, s, NH), 5.37(s, 2H,NH_2). ^{13}C-NMR (DMSO, 500 MH$_Z$) δ: 165.3-147.4(C=N), 137.1-108.3(C=C).

2-(4-Hydroxyphenyl)-3-(pyrimidine-2-ylamino)imidazo(1,2-a)pyrimidine (1e)

Elemental analysis was as follows: $C_{16}H_{13}N_7$ IR(KBr/cm^{-1}):: 3415(OH), 3103(NH), 3014(Ar-H), 1650(C=N)imidazo, 1600(C=N)pyrimidine, 1583(C=C); ^{1}H-NMR (DMSO,°00 MH$_Z$) δ: 8.83-6.86 (m, Ar-H, s, 1H, NH), 9.67 (s, OH), ^{13}C-NMR (DMSO, °00 MH$_Z$) δ: 169.3-148.6 (C=N, C-OH), 138.6-109.6(C=C).

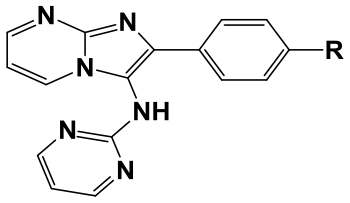


TABLE 1 Physical properties of compounds **(1a-e)**

Com.No.	R	M.F.	M.P.(C^0)	Color	Yield(%)
1a	-H	$C_{16}H_{12}N_6$	66	brown	60
1b	-Br	$C_{16}H_{11}BrN_6$	82	yellow	65
1c	-NO_2	$C_{16}H_{11}N_7O_2$	58	orange	75
1d	-NH_2	$C_{16}H_{13}N_7$	86	brown	72
1e	-OH	$C_{16}H_{12}N_6O$	74	Dark brown	68

Synthesis of propargylamines (2a-e)(General procedure)

2-Phenyl-N-(prop-2-yn-1-yl)-N-(pyrimidine-2-ylamino)imidazo(1,2-a)pyrimidine (2a):

To a mixture of compound (1a 0.02 mol) and K_2CO_3 (0.01 mol) in DMF(25 mL) solvent, the propargylbromide (1 mL) was added at room temperature. The reaction mixture was refluxed for 5 hours. After the reaction ended, the reaction mixture was poured into crushed ice and stirred for 15 minutes. The formed precipitate was filtered and recrystallized from chloroform to obtain compound **(2a).** with brown solid, yield 73% and mp 136C^0 properties . Elemental analysis was as follows: $C_{19}H_{14}N_6$: IR(KBr/cm^{-1}):: 3277(C≡C-H), 2165(C≡C), 1598(C=N)imidazo, 1583(C=N)pyrimidine, 1514(C=C), ^{1}H-NMR (DMSO,500 MH$_Z$) δ: 8.83-6.67(m, Ar-H), 4.67(s,2H,CH_2), 3.08(s,1H, C≡C-H). ^{13}C-NMR (DMSO, 500 MH$_Z$) δ: 167.3-148.4(C=N), 138.6-115.3(C=C), 78, 73(C≡C), 43.3(CH_2).

2-(4-Bromophenyl)-N-(prop-2-yn-1-yl)-N-(pyrimidine-2-ylamino)imidazo(1,2-a)pyrimidine (2b)

Elemental analysis was as follows: $C_{19}H_{13}BrN_6$: IR(KBr/cm^{-1}):: 3245(C≡C-H), 2183 (C≡C), 1616(C=N)imidazo, 1575(C=N)pyrimidine, 1556,1514(C=C). ^{1}H-NMR (DMSO,500 MH_Z) δ: 8.43-6.95(m. Ar-H), 4.47(s.2H,CH_2), 3.2(s,1H, C≡C-H), ^{13}C-NMR (DMSO, 500 MH_Z) δ: 168.2-147.3(C=N), 138.7-109.4(C=C), 78.4,73.1(C≡C), 43.3(CH_2).

2-(4-Nitrophenyl)-N-(prop-2-yn-1-yl)-N-(pyrimidine-2-ylamino)imidazo(1,2-a)pyrimidine (2c)

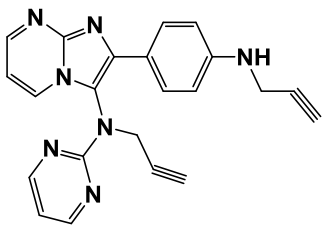
Elemental analysis was as follows: $C_{19}H_{13}N_7O$: IR(KBr/cm^{-1}):: 3224(C≡C-H), 2139(C≡C), 1656(C=N)imidazo, 1642(C=N)pyrimidine, 1566,1361(NO_2). ^{1}H-NMR (DMSO,°00 MH_Z) δ: 8.83-6.87(m. Ar-H), 4.67(s, 2H, CH_2), 2,9(s. 1H, C≡C-H), ^{13}C NMR (DMSO, 500 MH_Z) δ: 167.1-149.3(C=N), 137.3-109.7(C=C), 77.2,73.3(C≡C).

N-(prop-2-yn-1-yl)-2-(4-(prop-2-yn-1-ylamino)phenyl)-N-(pyrimidin-2-yl)imidazo[1,2-a]pyrimidin-3-amine (2d)

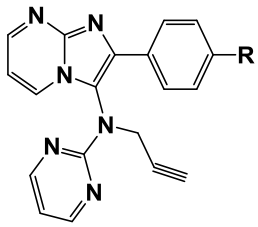
Elemental analysis was as follows: $C_{19}H_{15}N_7$: IR(KBr/cm^{-1}):: 3285,(C≡C-H),2173(C≡C), 1616(C=N)imidazo, 1583(C=N)pyrimidine, 3162(NH). ^{1}H-NMR (DMSO, °00 MH_Z) δ: 8.65-6.51(m, Ar-H, 7.2, s, NH), 4.87(s, 2H, CH_2), 3.8(s, 2H, CH_2), 3.1(s, 1H, C≡C-H). ^{13}C-NMR (DMSO, °00 MH_Z) δ: 169.3-148.7(C=N), 138.2-109.3(C=C), 78.5 ,72.3(C≡C), 43.1, 25.3(2CH_2)

2-(4-Hydroxyphenyl)-N-(prop-2-yn-1-yl)-N-(pyrimidine-2-ylamino)imidazo(1,2-a)pyrimidine (2e)

Elemental analysis was as follows: $C_{19}H_{14}N_7O$: IR(KBr/cm^{-1}):: 3255(C≡C-H), 2133(C≡C), 1631(C=N), 1598(C=N)pyrimidine, 3419(OH). ^{1}H-NMR (DMSO,°00 MH_Z) δ: 9.67(s, 1H, OH), 8.83-6.67(m, Ar-H), 4.63(s, 2H, CH_2). ^{13}C-NMR (DMSO, °00 MH_Z) δ: 169.3-148.2(C=N), 137.3-109.6(C=C), 78.03,73.2(C≡C), 43.3(CH_2).

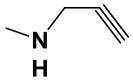


(2d)



(2a, 2b, 2c and 2e)

TABLE 2 Physical properties of compounds **(2a-e)**

Com.No.	R	M.F.	M.P. (C⁰)	Color	Yield(%)
2a	-H	$C_{19}H_{14}N_6$	136	brown	73
2b	-Br	$C_{19}H_{13}BrN_6$	240	Dark yellow	68
2c	-NO_2	$C_{19}H_{13}N_7O_2$	154	Off yellow	84
2d		$C_{22}H_{17}N_7$	218	orange	79
2e	-OH	$C_{19}H_{14}N_6O$	176	black	70

Synthesis of Mannih·s bases (3a-j)(General procedure)

A Mannich bases were synthesized by adding of **(1d)** compound, formaldehyde and differentamines in an equimolar ratio as one-pot reaction. Amixture of **(1d)** (0.001 mol), 37% formaldehyde (0.001 mol) and primary or secondary amines (0.001 mol) in absolute

ethanol was refluxed for 12 hours**.** After the reflux stopped, the reaction mixture was allowed to cool at room temperature and the solid mass obtained was filtered, dried and recrystallized from absolute ethanol. Physical properties of compounds (**3a-j**) are shown in Table 3.

N-(2-Methoxy-4-nitrophenyl)-N′-(4-(3-(pyrimidin-2-ylamino)imidazo[1,2-a]pyrimidin-2-yl)phenyl)methanediamine (3a)

Elemental analysis was as follows: $C_{24}H_{21}N_9O_3$: IR(KBr/cm^{-1}):: 3404, 3371 and 3301(NH), 2920 and 2893(CH aliphatic), 1654(C=N)imidazo, 1496 and 1452(C=C), 1521(NO_2). ^{1}H-NMR (DMSO,°00 MH_Z) δ: 8.83-6.51(m,Ar-H), 6.34, 5.8(NH), 4.83(s,2H,CH_2), 3.9(s,3H,CH_3). ^{13}C-NMR (DMSO, 500 MH_Z) δ: 167.4-149.1(C=N), 138.6-108.1(C=C), 70.4(CH_2), 55.1(CH_3).

2-(4-((Morpholinomethyl)amino)phenyl)-n-(pyrimidin-2-yl)imidazo[1,2-a]pyrimidin-3-amine (3b)

Elemental analysis was as follows: $C_{21}H_{22}N_8O$: IR(KBr/cm^{-1}): 3415 and 3386 (NH), 2970 and 2920(CH aliphatic), 1645 (C=N)imidazo, 1519(NO_2). ^{1}H-NMR (DMSO,°00 MH_Z) δ: 8.67-6.63(m, Ar-H), 8.47 and 6.34(two singlets, 1H, 2NH), 4.13(s, 2H, CH_2), 3.47(t, 4H, 2CH), 2.43(t, 4H, $2CH_2$).

^{13}C NMR (DMSO, 500 MH_Z) δ: 168.1-147.3(C=N), 139.2-111.3(C=C), 74.3(CH_2), 66.3($2CH_2$ of morpholin), 53.5($2CH_2$ of morpholin).

N-(3-nitrophenyl)-N′-(4-(3-(pyrimidin-2-ylamino)imidazo[1,2-a]pyrimidin-2-yl)phenyl)methanediamine (3c)

Elemental Analysis calculated for $C_{23}H_{19}N_9O_2$**:** IR (KBr/cm^{-1}): 3413, 3380 and 3342(NH), 2987 and 2885 (CH aliphatic), 1654(C=N) imidazo, 1495 and 1450 (C=C), 1521 (NO_2). ^{1}H-NMR (DMSO,° 00 MH_Z) δ: 8.79.1-6.52(m, Ar-H), 8.43 and 6.31 (3 singlets, 1H,3NH),4.83(s, 2H, CH_2) ^{13}C-NMR (DMSO, °00 MH_Z) δ: 169.1- 147.4(C=N), 137.2-106.4(C=C), 71.1(CH_2).

N-(4-Chlorophenyl)-N′-(4-(3-(pyrimidin-2-ylamino)imidazo[1,2-a]pyrimidin-2-yl)phenyl)methanediamine (3d)

Elemental analysis was as follows: $C_{23}H_{19}ClN_8$: IR(KBr/cm^{-1}):: 3417, 3359 and 3317 (NH), 2974 and 2887(CH aliphatic), 1656(C=N)imidazo, 1517 and 1475(C=C). ^{1}H-NMR (DMSO,°00 MH_Z) δ: 8.77-6.53(m,Ar-H), 8.47 and 6.34(3 singlets, 3NH), 4.79(s,2H,CH_2).^{13}C-NMR (DMSO, ٤00 MH_Z) δ: 165.3-146.6(C=N), 136.2-107.4(C=C), 68.5(CH_2).

N-(2-Nitrophenyl)-N′-(4-(3-(pyrimidin-2-ylamino)imidazo[1,2-a]pyrimidin-2-yl)phenyl)methanediamine (3e)

Elemental analysis was as follows: $C_{23}H_{19}N_9O_2$: IR(KBr/cm^{-1}): 3473, 3411 and 3392(NH), 2975 and 2887 (CH aliphatic), 1654(C=N)imidazo, 1494 and 1445 (C=C), 1521(NO_2). ^{1}H-NMR (DMSO,°00 MH_Z) δ: 8.83-6.51(m, Ar-H), 6.34-5.8(s, 2H, NH), 4.84(s, 2H, CH_2). ^{13}C-NMR (DMSO, °00 MH_Z) δ: 168.2-147.3(C=N), 146.7-109.5(C=C), 69.1(CH_2).

N-(4-((((4-(3-(Pyrimidin-2-ylamino)imidazo[1,2-a]pyrimidin-2-yl))phenyl)amino)methyl)amino)phenyl)acetamide(3f)

Elemental analysis was as follows: for $C_{25}H_{23}N_9O$: IR(KBr/cm^{-1}): 3267,3207,3109(NH), 1676(C=O),1645(C=N)imidazo, 1614(C=N)pyrimidine,1583,1539,1498 and 1479(C=C). ^{1}H-NMR (DMSO,500 MH_Z) δ: 9.78(HN-C=O) 8.78-6.56(m, Ar-H), 6.34 and 5.77(s, 2H, NH), 2.1(s, 3H, CH_3). ^{13}C-NMR (DMSO, 500 MH_Z) δ: 167.3-149.1(C=N, C=O), 147.6-109.1(C=C), 70.1 (CH_2), 24.01(CH_3).

N-(Benzo[d]thiazol-2-yl)-n-(4-(3-(pyrimidin-2-ylamino)imidazo[1,2-a]pyrimidin-2-yl)phenyl)methandiamine (3g)

Elemental analysis was as follows: $C_{24}H_{19}N_9S$: IR (KBr/cm^{-1}): 3456 and 3427(NH), 2947 and 2883(CH aliphatic), 1616(C=N)imidazo, 1514 and 1438(C=C), 765 (C-S-C) . ^{1}H-NMR (DMSO,°00 MHz) δ: 8.83-6.7(m, Ar-H), 6.34-5.9(s, 2H, NH), 4.83(s, 2H, CH_2). ^{13}C-NMR (DMSO, °00 MHz) δ: 169.1-148.3(C=N), 147.2-108.3(C=C), 69.3(CH_2).

N-(4-Methoxyphenyl)-N-(4-(3-(pyrimidin-2-ylamino)imidazo[1,2-a]pyrimidin-2-yl)phenyl)methanediamine (3h)

Elemental analysis was as follows: $C_{24}H_{22}N_8O$: IR (KBr/cm^{-1}): 3411, 3392 and 3238(NH), 2975 and 2887(CH aliphatic), 1654(C=N)imidazo, 1521 and 1446(C=C), 1176 (C-O-C). ^{1}H-NMR (DMSO,°00 MHz) δ: 8.73-6.51(m, Ar-H), 6.34(s, 2H, NH), 4.83(s, 2H, CH_2), 3.81(s, 3H, CH_3). ^{13}C-NMR (DMSO, °00 MHz) δ: 167.1-146.3(C=N), 138.3-111.1(C=C), 70(CH_2), 55.7(CH_3).

N-(4-(3-(Pyrimidin-2-ylamino)imidazo[1,2-a]pyrimidin-2-yl)phenyl)-N-(p-tolyl)methandiamine (3i)

Elemental analysis was as follows: $C_{24}H_{22}N_8$: IR(KBr/cm^{-1}):: 3429, 3394 and 3261(NH), 2989 and 2887(CH aliphatic), 1654(C=N)imidazo, 1523 and 1492(C=C). ^{1}H-NMR (DMSO, °00 MHz) δ: 8.76-6.45(m, Ar-H), 6.23(s, 2H, NH), 4.77(s, 2H, CH_2), 2.32(s, 3H, CH_3). ^{13}C-NMR (DMSO, °00 MHz) δ: 169.3-149.1(C=N), 138.1-108.3(C=C), 68.3(CH_2), 21.3(CH_3).

N-(4-(3-(Pyrimidin-2-ylamino)imidazo[1,2-a]pyrimidin-2-yl)phenyl)-N-(o-tolyl)methandiamine (3j)

Elemental analysis was as follows: $C_{24}H_{22}N_8$: IR (KBr/cm^{-1}): 3407, 3367 and 3315(NH), 2952 and 2891(CH aliphatic), 1650(C=N)imidazo, 1510 and 1444(C=C). ^{1}H-NMR (DMSO, 500 MHz) δ: 8.83-5.6(m, Ar-H), 6.3-5.8(s,2H, NH), 4.79(s, 2H, CH_2), 2.01(s, 3H, CH_3). ^{13}C-NMR (DMSO, 00 MHz) δ: 167.7-147.8(C=N), 189.1-109.3(C=C), 96.2(CH_2), 22.3(CH_3).

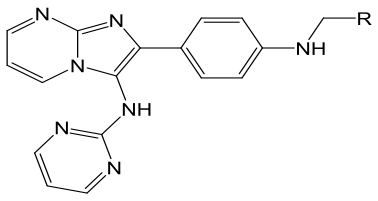
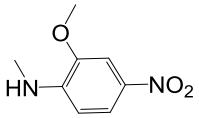
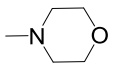
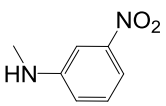
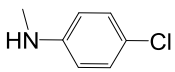
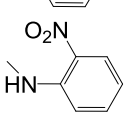
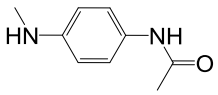
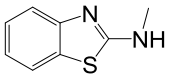
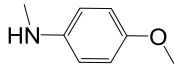
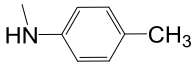
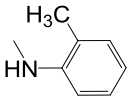


TABLE 3 Physical properties of compounds (3a-j)

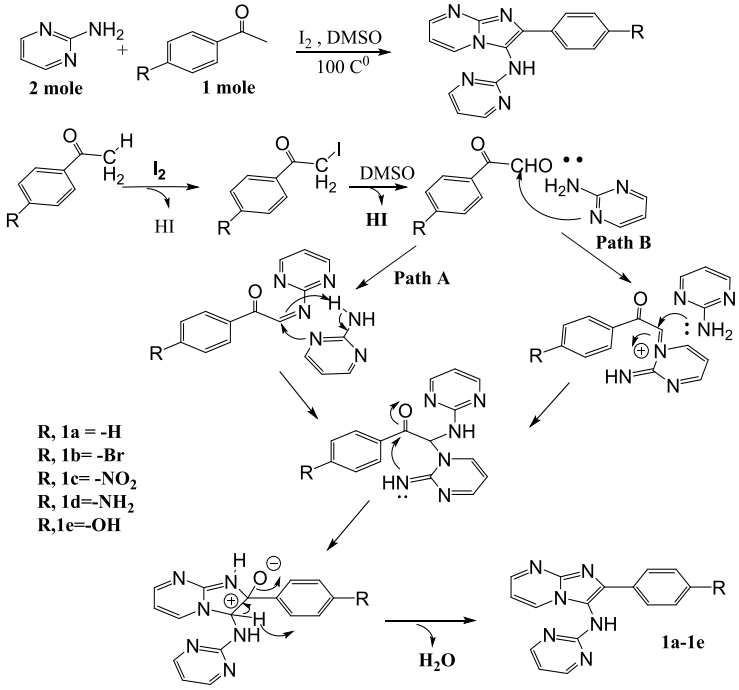
Com.No.	R	M.F	M.P.(C^0)	Color	Yield (%)
3a		$C_{24}H_{21}N_9O_3$	116	ark brown	69
3b		$C_{21}H_{22}N_8O$	135	Yellow	86
3c		$C_{23}H_{19}N_9O_2$	142	Yellow	77
3d		$C_{23}H_{19}ClN_8$	109	Dark yellow	68
3e		$C_{23}H_{19}N_9O_2$	164	Orange	69

3f		$C_{25}H_{23}N_9O$	127	White	89
3g		$C_{24}H_{19}N_9S$	132	Bright yellow	92
3h		$C_{24}H_{22}N_8O$	103	Yellow	95
3i		$C_{24}H_{22}N_8$	124	Dark yellow	88
3j		$C_{24}H_{22}N_8$	153	Yellow	81

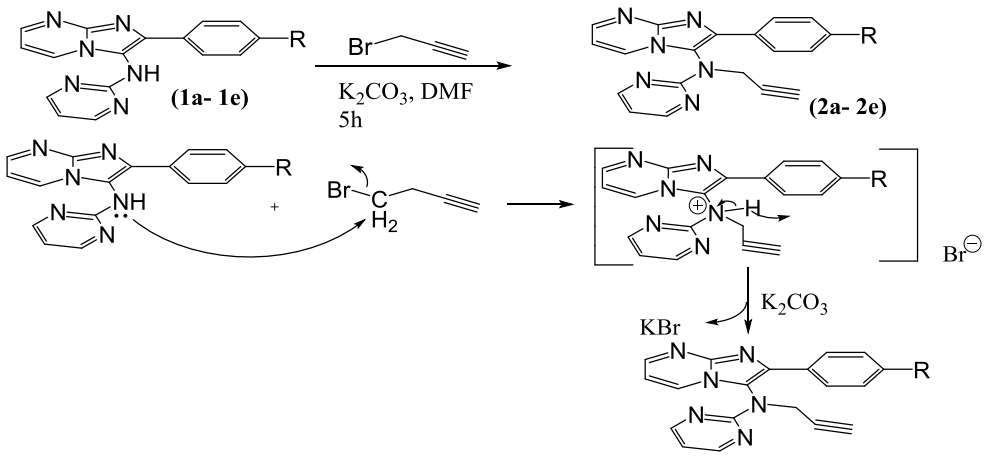
Results and discussion

One-pot reaction was performed for synthesis 2-aryl-3-(pyrimidine-2-ylamino)imidazo[1,2-a]pyrimidine derivatives (1a-1e) from the reaction of 2-aminopyrimidine with different substituted acetophenones in the prescience of I_2 and DMSO (Scheme 1). These compounds were identified by the absence of the characteristic bands in the FT-IR spectrum for one carbonyl group and one NH_2 group and the appearance of new peaks at (1600-1650 cm^{-1}) for (C=N) imidazo and at (3100-3300 cm^{-1}) for (NH) group. ^{1}HNMR spectrum showed multiple signals for (Ar-H, NH) protons at (8.83-6.5 ppm) and for(s,1H,OH) for (1e) compound 9.67 ppm. Also, the synthesis of these compounds were identified by ^{1}CNMR spectrum that showed signals at 169.3-147.1 ppm (C=N) and at 138.1-109.3 ppm(C=C).

The second step was the synthesis of propargylamines by the reaction of (1a-1e) compounds with propargylbromide as SN_2 reaction (Scheme 2). The absorption characteristic peaks of these compounds in the FT-IR spectrum were at (2183- 2133 cm^{-1}) owing to (C≡C) and at (3277- 3224 cm^{-1}) owing to (C≡C-H). ^{1}HNMR signals at 2.9-3.2 ppm (s, 1H, C≡C-H). ^{1}CNMR showed new signals at 79-71 ppm(C≡C), 43.3 ppm(CH_2).

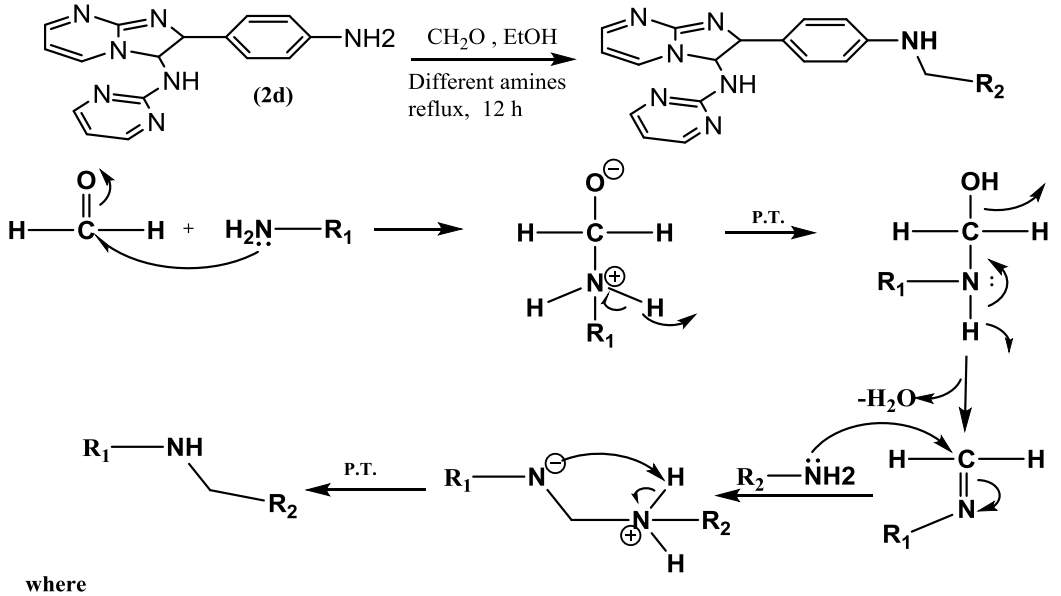


SCHEME 1 synthesis mechanism of compounds (1a-1e)



SCHEME 2 The possible mechanism of formation of compounds (2a-2e)

On the third step, Mannich's reaction was performed to form Munnich bases by the reaction of (1d) compound with different substituted aromatic amines in the prescience of formaldehyde (37%). The FT-IR spectrum of these compounds showed new peaks at (3400-3100 cm^{-1}) for (NH) groups and at (3000-2800 cm^{-1}) owing to (CH_2), also the appearance of ^{1}HNMR signals at 4.9-4.1ppm for (s, 2H, CH_2), for all synthesized Mannich bases.



where
R_2 = 3-nitro-2-aminoanisole, morpholine, 3-nitroaniline, 4-chloroaniline, 2-nitroaniline, 4-aminoacetanilide, 2-aminobenzothiazole, 4-methoxyaniline, p-toluidine, o-toluidine

R_1= 2d

SCHEME 3 synthesis mechanism of compounds (3a-3j)

Cytotoxic effect of (2d) compound on MCF-7 cancer cell line using MTT assay

The test of 3-(dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was accomplished to evaluate the cytotoxic effect of (2d) compound on breast cancer cell line (MCF-7). MTT assay was performed to calculate the cell viability and inhibition rate on the tumor cell line by using different concentrations of (2d) compound. The

percentage viability of treated cells was calculated in a comparison to normal cell line WPL-68. The cytotoxic effect of (2d) compound in concentration ranged from 6.25-400 µg/mL on MCF-7 cells (Table 4), which presented a decrease in cell viability in a dose-dependent pattern. The cell viability was reduced by increasing the concentration of (2d) compound. The decreasing in MCF-7 cell viability (%) was noticed at 400µg/mL (43.842±3.41%) while the highest MCF-7 cell viability at 6.25 µg/mL reached (94.791±1.64%). A (2d) compound exhibited cytotoxic activity with IC50 value of 96.37 µg/mL. However, an IC50 of 230.1 µg/mL was obtained from the effect of (2d) compound on WRI-68 normal cell line (Figure 2).

TABLE 4 Cytotoxicity effect of (2d) compound on MCF-7 and WRI-68 cells after 24 hours incubation at 37 ^{O}C

Concentration of(2d)compound µg/mL	Viable cell count of MCF-7 cell line Mean ± SD	Viable cell count of WRL-68 cell line Mean ± SD
400	43.842 ± 3.41	65.671 ± 7.809
200	54.977 ± 2.02	78.24 ± 1.53
100	63.773 ± 3.712	84.336 ± 2.662
50	75.27 ± 4.262	94.714± 0.984
25	82.855 ± 2.072	95.216 ± 0.8209
12.5	95.177 ± 1.28	94.83 ± 0.9638
6.25	94.791 ± 1.64	95.023 ± 0.8349

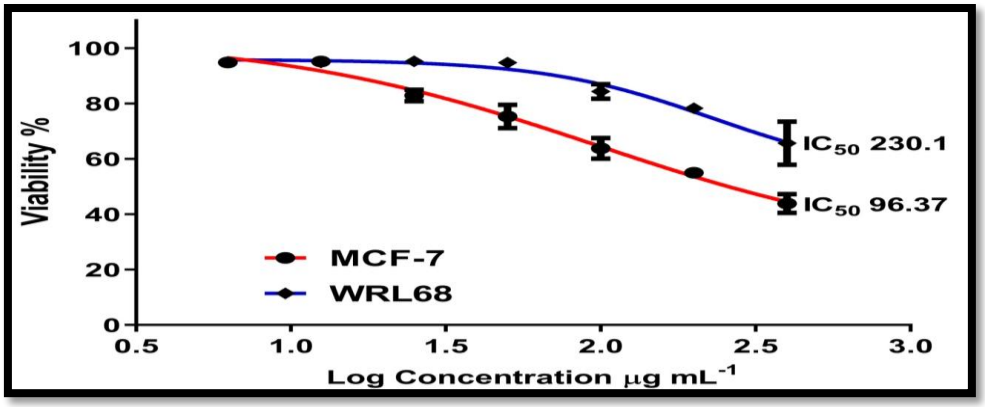


FIGURE 2 Cytotoxic effect of (2d) compound on MCF-7 and WRL-68 cells after 24 hours incubation at 37 ºC.

DPPH radical scavenging activity

All tested samples possessed DPPH scavenging activity in a dose dependent manner. For sample (**2d**), it showed DPPH scavenging activity ranging from (15.5±3.8 to 74.81±2.9 %) for (12.5 to 100 mg/mL), respectively, with IC_{50} value of (22.48 mg/mL), while sample (**2c**) possessed DPPH scavenging activity ranging from (15.51±3.74 to 68.17±0.9 %) for (12.5 to 100 mg/mL), respectively, with IC_{50} value of (127.3 mg/mL). On the other hand, DPPH scavenging activity range of sample (1c) appeared from (10.27±1.59 to 38.65±3.57 %) for (12.5 to 100 mg/mL), respectively, with IC_{50} value of (377.4 mg/mL). Finally, sample (**3a**) showed DPPH scavenging activity ranging from (13.13±5.76 to 58.29±8.63 %) for (12.5 to 100 mg/mL), respectively, with IC_{50} value of (162 mg/mL). Vitamin C shows a strongest DPPH radical scavenging activity ranging from (24.89±4.96 to 85±2.6 %) for (12.5 to 100 mg/mL), respectively, with IC_{50} value of (**34** mg/mL).

Con. (mg/mL)	DPPH Radical Scavenging Activity (Mean ± SD %) Sample(2d))	Sample (2c)	Sample (1c)	Sample (3a)	Vitamin C IC_{50}(34)
100	74.81±2.9	68.17±0.9	38.65±3.57	58.29±2.97	85±2.6
50	56.57±12.2	50.07±8.66	24.94±3.12	39.81±8.63	71.27±3.22
25	38.35±3.84	12.93±1.43	10.33±2.78	12.58±3.95	39.26±5.52
12.5	15.5±3.8	15.51±3.74	10.27±1.59	13.13±5.76	24.89±4.96

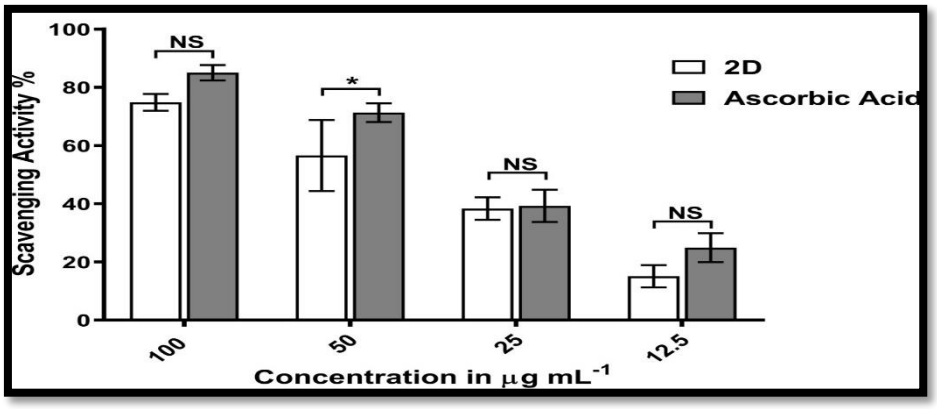


FIGURE 3 DPPH scavenging activity of compound(2D) compared with vitamin C

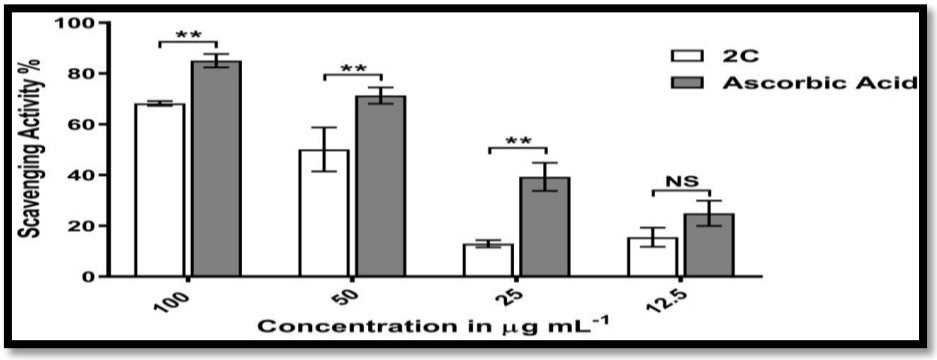


FIGURE 4 DPPH scavenging activity of compound (2C) compared with vitamin C

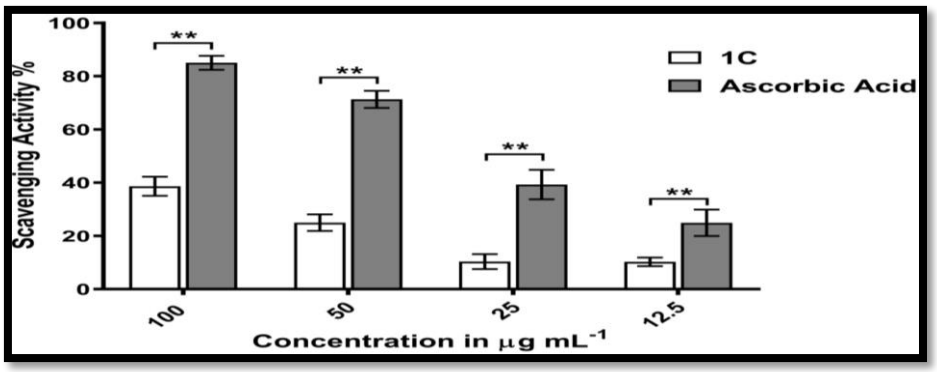


FIGURE 5 DPPH scavenging activity of compound (1C) compared with vitamin C

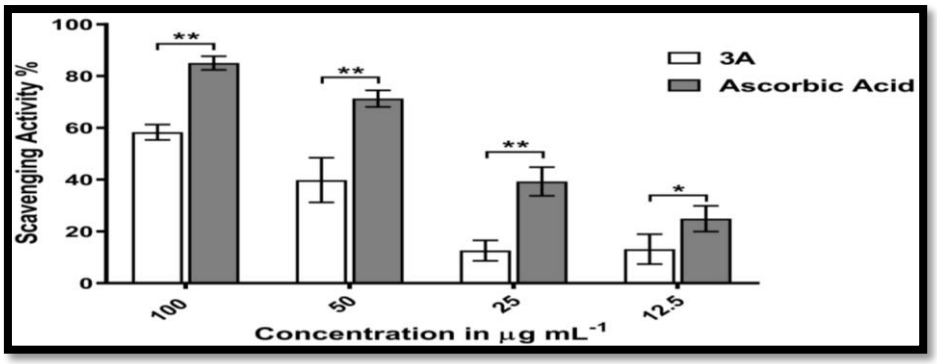


FIGURE 6 DPPH scavenging activity of compound (3A) compared with vitamin C

Conclusion

In this work, a variety of imidazo[1,2-a]pyrimidine derivatives have been synthesized from 2-aminopyrimidine and different substituted acetophenones. The newly synthesized compounds (1c, 2c, 2d and 3a) have been evaluated for in vitro and anti-oxidant activity against DPPH radical compared to vitamin C . Compound **2d** showed the best DPPH scavenging activity. Compounds **2c, 3a** also showed DPPH scavenging activity but less effective than compound **2d**. Compound **1c** showed DPPH scavenging activity, but effectiveness was very low compared with the previous compounds. Also, compound **2d** was evaluated for in vitro cytotoxic activity against human breast cancer (MCF-7) cell line. This compound exhibited the most potent cytotoxic activity at (400 mg/mL) with IC50 value of 96.37 µg/mL

Orcid:

Thamer A. Rehan: https://orcid.org/0000-0003-0111-5435

Naeemah Al-Lami: https://orcid.org/0000-0003-1022-3315

Rafal Shakeeb Alanee: https://orcid.org/0000-0002-3282-3306

References

[1] R. Goel, V. Luxami, K. Paul, *RSC Adv.*, **2015**, *5*, 81608-81637. [crossref], [Google Scholar], [Publisher]

[2] a) A. Marwaha, J. White, F. El_Mazouni, S.A. Creason, S. Kokkonda, F.S. Buckner, P.K. Rathod, *J. Med. Chem.*, **2012**, *55*, 7425-7436. [crossref], [Google Scholar], [Publisher] b) A. Linton, P. Kang, M. Ornelas, S. Kephart, Q. Hu, M. Pairish, C. Guo, *J. Med. Chem.*, **2011**, *54*, 7705-7712. [crossref], [Google Scholar], [Publisher] c) W. Meng, R.P. Brigance, H.J. Chao, A. Fura, T. Harrity, J. Marcinkeviciene, L.G. Hamann, *J. Med. Chem.*, **2010**, *53*, 5620-5628. [crossref], [Google Scholar], [Publisher] d) S.P. O'Connor, Y. Wang, L.M. Simpkins, R.P. Brigance, W. Meng, A. Wang, L.G. Hamann, *Bioorg. Med. Chem. let.*, **2010**, *20*, 6273-6276. [crossref], [Google Scholar], [Publisher] e) K.C. Rupert, J.R. Henry, J.H. Dodd, S.A. Wadsworth, D.E. Cavender, G.C. Olini, J.J. Siekierka, *Bioorg. Med. Chem. lett.*, **2003**, *13*, 347-350. [crossref], [Google Scholar], [Publisher] f) K. Terashima, , O. Muraoka, M. Ono. *Chem. Pharm. Bull.*, **1995**, *43*, 1985-1991. [crossref], [Google Scholar], [Publisher] g) W.R. Tully, C.R. Gardner, R.J. Gillespie, R. Westwood, *J. Med. Chem.*, **1991**, *34*, 2060–2067. [crossref], [Google Scholar], [Publisher] h) M. Adib, E. Sheibani, H.R. Bijanzadeh, L.G. Zhu. *Tetrahedron*, **2008**, *64*, 10681-10686. [crossref], [Google Scholar], [Publisher]

[3] Y.Y. Xie, *Synth. Commun.*, **2005**, *35*, 1741-1746. [crossref], [Google Scholar], [Publisher]

[4] L.E. Craig (Mar.12.1975) U.S Patent 2, 785, 133.

[5] A.S. Oganisyan, A.S. Noravyan, I.A. Dzhagatspanyan, I.M. Nazaryan, A.G. Akopyan.

Pharm. Chem. J., **2007**, *41*, 588-590. [crossref], [Google Scholar], [Publisher]
[6] S. Velázquez-Olvera, H. Salgado-Zamora, M. Velázquez-Ponce, E. Campos-Aldrete, A. Reyes-Arellano, C. Pérez-González, *Chem. Central J.*, **2012**, *6*, 1-9. [crossref], [Google Scholar], [Publisher]
[7] S. Laneri, A. Sacchia, M. Gallitelli, F. Arena, E. Luraschi, E. Abignente, F. Rossi, *European J. Med. Chem.*, **1998**, *33*, 163-170. [crossref], [Google Scholar], [Publisher]
[8] J.P. Zhou, Y.W. Ding, H.B. Zhang, L. Xu, Y. Dai, *Chin. Chem. Lett.*, **2008**, *19*, 669-672. [crossref], [Google Scholar], [Publisher]
[9] B. Jismy, M. Akssira, D. Knez, G. Guillaumet, S. Gobec, M. Abarbri, *New J. Chem.*, **2019**, *43*, 9961-9968. [crossref], [Google Scholar], [Publisher]
[10] Y. Hayashi, *Chem. Sci.*, **2016**, *7*, 866-880. [crossref], [Google Scholar], [Publisher]
[11] Z. Fei, Y.P. Zhu, M.C. Liu, F.C. Jia, A.X. Wu, *Tetrahedron Lett.*, **2013**, *54*, 1222-1226. [crossref], [Google Scholar], [Publisher]
[12] K. Lauder, A. Toscani, N. Scalacci, D. Castagnolo, *Chem. Rev.*, **2017**, *117*, 14091-14200. [crossref], [Google Scholar], [Publisher]
[13] B.M. Nilsson, H.M. Vargas, B. Ringdahl, U. Hacksell, *J. Med. Chem.*, **1992**, *35*, 285-294. [crossref], [Google Scholar], [Publisher]
[14] K. Hattori, M. Miyata, H. Yamamoto, *J. Am. Chem. Soc.*, **1993**, *115*, 1151-1152. [crossref], [Google Scholar], [Publisher]
[15] M.A. Huffman, N. Yasuda, A.E. DeCamp, E.J. Grabowski, *J. Org. Chem.*, **1995**, *60*, 1590-1594. [crossref], [Google Scholar], [Publisher]
[16] D. Ma, T. Han, M. Karimian, N. Abbasi, H. Ghaneialvar, A. Zangeneh, International Journal of Biological Macromolecules, **2020**, *165*, 767-775. [crossref], [Google Scholar], [Publisher]
[17] N.S. Vatmurge, B.G. Hazra, V.S. Pore, F. Shirazi, P.S. Chavan, M.V. Deshpande, *Bioorg. Med. Chem. lett.*, **2008**, *18*, 2043-2047. [crossref], [Google Scholar], [Publisher]
[18] M.R. Aouad, *Molecules*, **2014**, *19*, 18897-18910. [crossref], [Google Scholar], [Publisher]
[19] M. Jeleń, K. Pluta, M. Zimecki, B. Morak-Młodawska, J. Artym, M. Kocięba, I. Kochanowska, *J. Enzy. Inhib. Med. Chem.*, **2016**, *31*, 83-88. [crossref], [Google Scholar], [Publisher]
[20] I.E. Kopka, Z.A. Fataftah, M.W. Rathke, *The Journal of Organic Chemistry*, **1980**, *45*, 4616-4622. [crossref], [Google Scholar], [Publisher]
[21] S. Czernecki, J.M. Valéry, A, *J. Carbohyd. Chem.*, **1990**, 9, 767-770. [crossref], [Google Scholar], [Publisher]
[22] Y. Imada, M. Yuasa, I. Nakamura, S.I. Murahashi, *J. Org. Chem.*, **1994**, *59*, 2282-2284. [crossref], [Google Scholar], [Publisher]
[23] a) D. Enders, U. Reinhold, *Tetrahedron: Asym.*, **1997**, *8*, 1895-1946. [crossref], [Google Scholar], [Publisher] b) R. Bloch, *Chem. Rev.*, **1998**, *98*, 1407-1438. [crossref], [Google Scholar], [Publisher]
[24] a) T. Murai, Y. Mutoh, Y. Ohta, M. Murakami. *J. Am. Chem. Soc.*, **2004**, *126*, 5968-5969. [crossref], [Google Scholar], [Publisher] b) C.W. Ryan, C. Ainsworth, *J. Org. Chem.*, **1961**, *26*(5), 1547-1550. [crossref], [Google Scholar], [Publisher] c) M.E. Jung, A. Huang, *Org. lett.*, **2000**, *2*, 2659-2661. [crossref], [Google Scholar], [Publisher]
[25] Y. Liu, Y. Dang, D. Yin, L. Yang, Q. Zou, *Res. Chem. Intermed.*, **2019**, *45*, 4907-4926. [crossref], [Google Scholar], [Publisher]
[26] S.A. Pishawikar, H.N. More, *Arabian J. Chem.*, **2017**, *10*, S2714-S2722. [crossref], [Google Scholar], [Publisher]
[27] Y. Liu, Q. WU, D. Yin, D.Y. Li, *Chin. J. Org. Chem.*, **2016**, *36*, 927-938. [crossref], [Google Scholar], [Publisher]
[28] A. Idhayadhulla, R.S. Kumar, A.J.A. Nasser, J. Selvin, A. Manilal, *Arabian J. Chem.*, **2014**, *7*, 994-999. [crossref], [Google Scholar], [Publisher]

[29] D.H. Park, J. Venkatesan, S.K. Kim, V. Ramkumar, P. Parthiban, *Bioorg. Med. Chem. Lett.*, **2012**, *22*, 6362-6367. [crossref], [Google Scholar], [Publisher]
[30] A.N. Vereshchagin, K.A. Karpenko, M.N. Elinson, A.S. Goloveshkin, I.E. Ushakov, M. P. Egorov, *Res. Chem. Intermed.*, **2018**, *44*, 5623-5634. [crossref], [Google Scholar], [Publisher]

How to cite this article: Thamer A. Rehan*, Naeemah Al-Lami, Rafal shakeeb Alanee. Anti-Cancer and antioxidant activities of some new synthesized 3-secondary amine derivatives bearing imidazo [1,2-A] pyrimidine**.** *Eurasian Chemical Communications*, 2021, 3(5), 339-351. **Link:** http://www.echemcom.com/article_130112.html