

**How to Cite:**

Sami, M. H., & Younis, S. K. (2022). Selective approaches to synthesize a new series of fused 4-amino pyrimidine derivatives by using of 4- amino nicotino nitrile as an effective precursor. *International Journal of Health Sciences*, 6(S9), 2832–2843. <https://doi.org/10.53730/ijhs.v6nS9.13134>

# Selective approaches to synthesize a new series of fused 4-amino pyrimidine derivatives by using of 4- amino nicotino nitrile as an effective precursor

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**Abstract**--Pyrimidines and its derivatives are one of the most fascinating type of six membered heterocyclic compounds which received a great deals of attention due to its diverse importance and activity in many different field such as biological, medicinal, pharmaceutical and also in industrial and agricultural field. In this presentation, fused 4-amino pyrimidine derivatives were achieved using green chemistry technique represented by solid phase one-pot multicomponent reaction, microwave irradiation and grinding and also by traditional methods. Firstly, equimolar of aromatic(heterolytic) amines, piperonal and malononitriles were grinding for few minutes then accelerated by microwave irradiation (MWI) at (270 watt) for 3 minutes to afford fused 4-amino nicotino nitrile (1a-e) which then underwent cycloaddition reaction with formamide, urea and thiourea via traditional methods using acidic or basic conditions to afford a new series of fused 4-amino pyrimidines represented by compounds (2a-e), (3a-e) and (4a-e) respectively. All prepared compounds were illustrated by the available physical and spectral methods.

**Keywords**--Fused pyrimidine, Green chemistry, One-pot multicomponent reaction, 4-amino nicotino nitrile, Microwave irradiation.

## 1 Introduction

Fused heterocyclic compounds containing pyrimidine moiety consist of high activity in many different field especially in medical field as anti cancer (Boger et

al., 1989; Fathalla et al., 2009; Prachayasittikul et al., 2017), anti hypertensive (Darwish, Abdelrahman, & Salaheldin, 2011; Farghaly et al., 2019), anti HIV (Farouk Elsadek, Mohamed Ahmed, & Fawzi Farahat, 2021; Kumar, Deep, & Narasimhan, 2019), anti inflammatory (Amer, El-Eraky, & Mahgoub, 2018; Thakur, 2011), antibacterial (Mahfoudh, Abderrahim, Leclerc, & Campagne, 2017; Raghavendra, Bhojya Naik, & Sherigara, 2006), antimicrobial (Mallikarjunaswamy, Mallesha, Bhadregowda, & Pinto, 2017), and antifungal activity (Maddila, Gorle, Seshadri, Lavanya, & Jonnalagadda, 2016; Naik & Chikhalia, 2007). Thus considering the importance of fused pyrimidine, this research focuses on the synthesis a unique poly fused heterocyclic system starting from solid phase one-pot multi component reaction among piperonal, aromatic (heterolytic) amines and malononitrile which grinding for few minutes then accelerated via microwave irradiation (MWI) in power (270 watt) for few minutes (3 min.) to achieve 6-piperonyl-4-amino fused nicotine nitriles (1a-e). These compounds then used as active precursor to prepare a new series of fused 4-amino pyrimidine via cycloaddition reaction in acidic or basic conditions with formic acid, urea and thiourea and also represented by the compounds (2a-e), (3a-e) and (4a-e) respectively. In fact, solid phase one-pot multicomponent reaction was used in the first step of preparation due to its supreme properties as rapid, environmentally safe, inexpensive and yield enhancement (Bariwal, Trivedi, & Eycken, 2010).

## 2 Materials and Methods

### Synthesis of 4-amino nicotinonitrile (1a-e) (Shi, Tu, Fang, & Li, 2005):

A mixture of equimolar (0.003mol) of piperonal, malononitrile and aromatic amine where well grinding for few minutes followed by irradiated via microwave oven at power (270 watt/3min.). The reaction mixture allowed to cool, the formed sticky mass was solidified by washing thoroughly with cold water with stirring. Followed by filtration, dried then recrystallization with appropriate solvent to produce (1a-e) in good yields, Table (1).

#### (1a) 5-amino-2-( piperonyl -5-yl)-5H-thiazolo[3,2-a]pyrimidine-6-carbonitrile :

Yellow powder, yield %(70%), m.p °C (194-197), T.L.C(R<sub>f</sub>) (0.47) ; <sup>1</sup>H-NMR (δ ppm) : (s, 3.54, CH<sub>2</sub>-piperonal), (m, 6.23-6.24, piperonal), (d-d, 7.20-7.22, thiazole), (m, 7.35-7.56, aromatic), (s, 8.38, NH<sub>2</sub>). FT-IR (cm<sup>-1</sup>): 3372, 3429 (NH<sub>2</sub>), 3030 (=C-H), 2224 (CN), 1612 (C=C), 1568 (C=N), 1289 asym. and 1032 sym. (C-O-C), 1111 (C-S). U.V λ<sub>max</sub> (nm): (375, 340).

#### (1b) 4-amino-2-( piperonyl -5-yl)-4H-pyrimido[1,2-a]pyrimidine-3-carbonitrile:

Deep yellow powder, yield %(75%), m.p °C (194-196), T.L.C(R<sub>f</sub>) (0.744) ; FT-IR (cm<sup>-1</sup>): 3371, 3402 (NH<sub>2</sub>), 3030 (=C-H), 2224 (CN), 1612 (C=C), 1568 (C=N), 1295 asym. and 1032 sym. (C-O-C). U.V λ<sub>max</sub> (nm): (371, 327).

#### (1c) 4-amino-2-( piperonyl -5-yl)-6-nitro-1,8-naphthyridine-3-carbonitrile:

Yellow powder, yield %(65%), m.p °C (125-128), T.L.C(R<sub>f</sub>) (0.626); <sup>1</sup>H-NMR (δ ppm) : (s, 6.18, CH<sub>2</sub>-piperonal), (m, 6.49-6.51, piperonal), (m, 7.14-8.85, aromatic), (s, 9.81, NH<sub>2</sub>). FT-IR (cm<sup>-1</sup>): 3322, 3400 (NH<sub>2</sub>), 3030 (=C-H), 2194 (CN), 1668 (C=C), 1588 (C=N), 1281 asym. and 1091 sym. (C-O-C), 1490 asym. and 1330 sym. (NO<sub>2</sub>). U.V λ<sub>max</sub> (nm): (302, 371).

**(1d) 4-amino-2-(piperonyl -5-yl)-7,12-dioxo-7,12-dihydronaphtho[2,3-h]quinoline-3-carbonitrile:**

Brown powder, yield %(80%), m.p °C (144-146), T.L.C( $R_f$ ) (0.581) ; FT-IR ( $\text{cm}^{-1}$ ): 3320,3415 ( $\text{NH}_2$ ) , 3037 (=C-H) , 2377 (CN) , 1676 (C=O), 1600 (C=C) , 1588 (C=N) , 1232 asym. and 1095 sym. (C-O-C). U.V  $\lambda_{\text{max}}$  (nm):(375,340).

**(1e) 4-amino-2-(piperonyl -5-yl)-6,11-dioxo-6,11-dihydronaphtho[2,3-g]quinoline-3-carbonitrile:**

Brown powder, yield %(96%), m.p °C (167-170), T.L.C( $R_f$ ) (0.36) ;  $^1\text{H-NMR}$  ( $\delta$  ppm): (s,6.18, $\text{CH}_2$ -piperonal), (m,6.94-6.96,piperonal), (m,7.14-8.16, aromatic), (s,9.81,  $\text{NH}_2$ ). FT-IR ( $\text{cm}^{-1}$ ): 3341,3435 ( $\text{NH}_2$ ) , 3064 (=C-H) , 2687 (CN) , 1672 (C=O) , 1624 (C=C) , 1587 (C=N) , 1281 asym. and 1090 sym. (C-O-C). U.V  $\lambda_{\text{max}}$  (nm): (444,323).

**Synthesis of 2-amino pyrimidines (2a-e)(Mohamed, Rashad, Zaki, & Fatahala, 2005; Orlov, 2018) :**

In round bottomed flask (100 ml) equipt with magnetic stirrer dissolve (0.00025 mol) of compound (1a-e) in (5ml) ethanol in acid media of glacial acetic acid (2-3 drops) as acidic catalyst followed by adding an ethanolic solution of formamide (0.00025 mol) dropwise with stirring until the mixture become homogenous followed by reflux for (4-5 hrs.) (under T.L.C control). The reaction mixture allow to cool, poured into ice-water (20ml) with shaking. The precipitate was collected by filtration then washed thoroughly with cold water, dried and recrystallized from appropriate solvent to produce compounds(2a-e) Tabel (2).

**(2a) 5-( piperonyl -5-yl)-6aH-pyrimido[5,4-e]thiazolo[3,2-a]pyrimidin-4-amine:**

Yellow powder, yield %(81%), m.p °C (96-99), T.L.C( $R_f$ ) (0.633) ; FT-IR ( $\text{cm}^{-1}$ ): 3320, 3384

( $\text{NH}_2$ ) , 3091 (=C-H) , 1590 (C=C) , 1546 (C=N) , 1248 (C-O-C asym.) , 1103 (C-O-C sym.), 1033(C-S). U.V  $\lambda_{\text{max}}$  (nm):(376-366).

**(2b) 5-( piperonyl -5-yl)-6aH-dipyrimido[1,2-a:5',4'-e]pyrimidin-4-amine:**

Yellow powder, yield %(88%), m.p °C (186-189), T.L.C( $R_f$ ) (0.621) ; FT-IR ( $\text{cm}^{-1}$ ): 3320-3368 ( $\text{NH}_2$ ) , 3082 (=C-H), 1560 (C=C) , 1493 (C=N) , 1257 asym. , 1104 sym. (C-O-C). U.V  $\lambda_{\text{max}}$  (nm): (370,317).

**(2c) 5-( piperonyl -5-yl)-9-nitropyrimido[5,4-c][1,8]naphthyridin-4-amine:**

Light brown powder, yield %(84%), m.p °C (194-196), T.L.C( $R_f$ ) (0.61) ; FT-IR ( $\text{cm}^{-1}$ ): 3314-3368 ( $\text{NH}_2$ ) , 3015 (=C-H) , 1687 (C=C) , 1594 (C=N) , 1238 asym. and 1104 sym. (C-O-C), 1488 asym. and 1290 sym. ( $\text{NO}_2$ ). U.V  $\lambda_{\text{max}}$  (nm): (302,271).

**(2d) 1-amino-14-( piperonyl -5-yl)naphtho[2,3-h]pyrimido[5,4-c]quinoline-7,12-dione:**

Reddish brown powder, yield %(81%), m.p °C (205-207), T.L.C( $R_f$ ) (0.55) ; FT-IR ( $\text{cm}^{-1}$ ): 3427,3498 ( $\text{NH}_2$ ) , 3066 (=C-H) , 1672(C=O),1604 (C=C), 1544 (C=N) , 1280 asym. and 1167 sym. (C-O-C),. U.V  $\lambda_{\text{max}}$  (nm):(378,317).

**(2e)4-amino-5-( piperonyl -5-yl)naphtho[2,3-g]pyrimido[5,4-c]quinoline-8,13-dione:**

Brown powder, yield %(81%), m.p °C (292-294), T.L.C( $R_f$ ) (0.57) ;  $^1\text{H-NMR}$  ( $\delta$  ppm): (s,3.45, $\text{NH}_2$ ) (s,6.71, $\text{CH}_2$ -piperonal); (m,6.93-6.97,piperonal); (m,7.29-8.16,aromatic);. FT-IR ( $\text{cm}^{-1}$ ): 3362,3439 ( $\text{NH}_2$ ) , 3031 (=C-H) , 1626 (C=C) , 1587 (C=N) , 1281 (C-O-C asym.) , 1163 (C-O-C sym.), 1674(C=O). U.V  $\lambda_{\text{max}}$  (nm):(444,370).

**Synthesis compound 4-amino pyrimidine (2-one) and (2-thion) (3<sub>a-e</sub>) , (4<sub>a-e</sub>) (El-Gazzar, Hegab, Swelam, & Aly, 2002; Fawzy et al., 2018) :**

Equimolar (0.00025 mol) of compound (1a-e) and urea (thiourea) were dissolved in absolute ethanol (15ml) in basic media of tri ethyl amine. The reaction mixture was refluxed for (5-6 hrs.) (under T.L.C control) followed by cooling and poured into ice-water (20ml) with stirring, the formed precipitate was collected by filtration, dried and recrystallized from appropriate solvent to give compounds (3a-e) and (4a-e) respectively. Table (3),(4) respectively.

**(3a)4-amino-5-(piperonyl-5-yl)-1,10a-dihydro-2H-pyrimido[5,4-e]thiazolo[3,2-a]pyrimidin-2-one:**

Light brown powder, yield %(82%), m.p °C(185-186), T.L.C(R<sub>f</sub>) (0.325); <sup>1</sup>H-NMR (δ ppm):( s,2.42,NH<sub>2</sub>); (s, 2.56, NH); (s,2.60,CH<sub>2</sub>-piperonal);(m,3.79-3.97,piperonal);(d-d,3.41-3.42,thiazole);(b,6.15,aromatic).

FT-IR (cm<sup>-1</sup>): 3349,3430 (NH<sub>2</sub>),3233 (NH) , 3014 (=C-H) , 1633 (C=O) , 1562 (C=C) , 1442(C=N), 1245 asym. and 1098 sym. (C-O-C), 1033(C-S). U.V λ<sub>max</sub> (nm):(371,340).

**(3b) 4-amino-5-(piperonyl-5-yl)-1,11a-dihydro-2H-[1,2-a]pyrimidopyrimidine[5',4'-e] pyrimidin-2-one:**

Light Orange powder, yield %(65%), m.p °C(200-203), T.L.C(R<sub>f</sub>) (0.404) ;FT-IR (cm<sup>-1</sup>): 3344,3448 (NH<sub>2</sub>) ,3235 (NH) , 3024 (=C-H) , 1638 (C=O) , 1553 (C=C) , 1491(C=N), 1248 asym. and 1096 sym. (C-O-C). U.V λ<sub>max</sub> (nm):(341,328).

**(3c)4-amino-5-( piperonyl -5-yl)-9-nitropyrimido[5,4-c][1,8]naphthyridin-2(1H)-one:**

Brown powder, yield %(75%), m.p °C (189-192), T.L.C(R<sub>f</sub>) (0.258); FT-IR (cm<sup>-1</sup>) : 3245,3352 (NH<sub>2</sub>), 3199 (NH), 3085(=C-H), 1589(C=O), 1547 (C=C) , 1452(C=N), 1200 asym. and 1032 sym. (C-O-C) 1442 asym. and 1273 sym. (NO<sub>2</sub>). U.V λ<sub>max</sub> (nm):(343,214).

**(3d) 1-amino-14-( piperonyl -5-yl)naphtho[2,3-h]pyrimido[5,4-c]quinoline-3,7,12-(4H)-trione :**

Black plate, yield %(82%), m.p °C (140-143), T.L.C(R<sub>f</sub>) (0.73) ; FT-IR (cm<sup>-1</sup>) : 3390,3434 (NH<sub>2</sub>),3064 (NH) , 2914 (=C-H) , 1672 (C=O) , 1591 (C=C) , 1580(C=N), 1274 asym. and 1031 sym. (C-O-C). U.V λ<sub>max</sub> (nm):(371,340).

**(3e)4-amino-5-( piperonyl -5-yl)naphtho[2,3-g]pyrimido[5,4-c]quinoline-2,8,13(1H)-trione:**

Black plate, yield %(58%), m.p °C (204-207), T.L.C(R<sub>f</sub>) (0.5) ;. FT-IR (cm<sup>-1</sup>): 3383,3437 (NH<sub>2</sub>), 3187 (NH) , 3166(=C-H) , 1670(C=O) , 1584 (C=C) , 1573(C=N), 1244 asym. and 1029 sym. (C-O-C) 1442 asym. and 1273 sym. (NO<sub>2</sub>). U.V λ<sub>max</sub> (nm):(474,370).

**(4a)4-amino-5-(piperonyl-5-yl)-1,10a-dihydro-2H-pyrimido[5,4-e]thiazolo[3,2a]pyrimidine-2-thione:**

Brown powder, yield %(91%), m.p °C (186-187), T.L.C(R<sub>f</sub>) (0.279) ; FT-IR (cm<sup>-1</sup>): 3347,3446 (NH<sub>2</sub>), 3237(NH) , 3076 (=C-H) , 1553(C=C) , 1491 (C=N) , 1347 asym. and 1245 sym. (C-O-C), 1098(C=S) , 1033(C-S). U.V λ<sub>max</sub> (nm):(371,348).

**(4b)4-amino-5-( piperonyl -5-yl)-1,6a-dihydro-2H-[1,2-a]pyrimidopyrimidine[5',4'-e] pyrimidin-2-thione:**

Orange powder, yield %(58%), m.p °C (207-210), T.L.C(R<sub>f</sub>) (0.5) ; FT-IR (cm<sup>-1</sup>): 3339,3440 (NH<sub>2</sub>), 3227(NH) , 3030 (=C-H) , 1565(C=C) , 1484 (C=N) , 1369 asym. and 1245 sym. (C-O-C), 1096(C=S) . U.V λ<sub>max</sub> (nm):(341,329).

**(4c)4-amino-5-( piperonyl -5-yl)-9-nitropyrimido[5,4-c][1,8]naphthyridine-2(1H)-thione:**

Deep green powder, yield %(74%), m.p °C (235-238), T.L.C( $R_f$ ) (0.4) ;  $^1\text{H-NMR}$  ( $\delta$  ppm): (s,3.26  $\text{NH}_2$ ) , (s,3.45 NH) , (s,3.54,  $\text{CH}_2$ -piperonal) , (m,6.49-6.51, piperonal) , (m,7.56-8.86, aromatic). FT-IR ( $\text{cm}^{-1}$ ): 3352,3390 ( $\text{NH}_2$ ) , 3314(NH) , 2971(=C-H) , 1695(C=C) , 1647 (C=N) , 1295 asym. and 1075 sym. (C-O-C) , 1086(C=S) , 1523( $\text{NO}_2$  asym.) , 1380( $\text{NO}_2$  sym.) . U.V  $\lambda_{\text{max}}$  (nm):(370,340).

**(4d)1-amino-14-(piperonyl-5-yl)-3-thioxo-3,4-dihydronaphtho[2,3-h]pyrimido[5,4-c]quinoline-7,12-dione:**

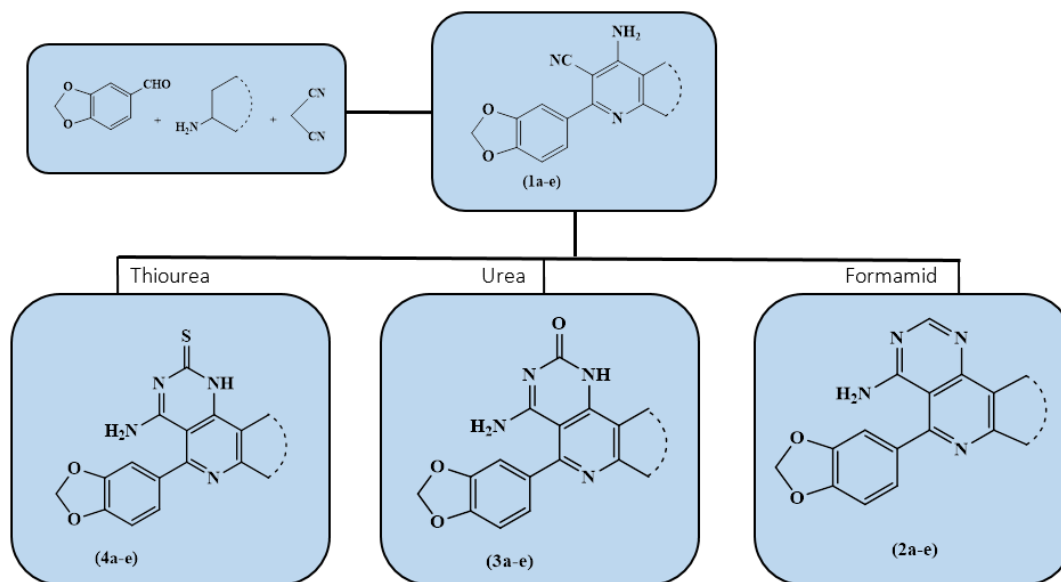
Black plate, yield %(83%), m.p °C (211-214), T.L.C( $R_f$ ) (0.28) ; FT-IR ( $\text{cm}^{-1}$ ): 3413,3435 ( $\text{NH}_2$ ) , 3347(NH) , 3072 (=C-H) , 1635(C=C) , 1591 (C=N) , 1273 asym. and 1037 sym. (C-O-C) , 1076(C=S) , 1672(C=O) . U.V  $\lambda_{\text{max}}$  (nm):(370,340).

**(4e)4-amino-5-(piperonyl-5-yl)-2-thioxo-1,2-dihydronaphtho[2,3-g]pyrimido[5,4-c]quinoline-8,13-dione:**

Black plate, yield %(62%), m.p °C (76-79), T.L.C( $R_f$ ) (0.63) ; FT-IR ( $\text{cm}^{-1}$ ): 2395,3421 ( $\text{NH}_2$ ) , 3105(NH) , 3005 (=C-H) , 1589(C=C) , 1575 (C=N) , 1327 asym. and 1020 sym. (C-O-C) , 1288(C=S) , 1670(C=O) . U.V  $\lambda_{\text{max}}$  (nm):(370,340).

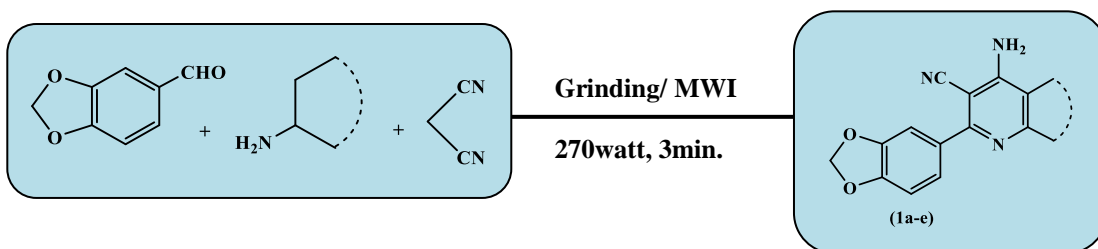
### 3 Results and Discussions

All compounds were prepared according to the following path way, Scheme (1):



Scheme 1. Synthetic pathway of compounds ( $2_{a-e}$ ), ( $3_{a-e}$ ), ( $4_{a-e}$ )

Piperonal, aromatic amine and malononitrile was underwent one-pot three component reaction in neutral media to afford fused 4-amino nicotinonitrile ( $1_{a-e}$ ), this reaction assumed proceed initially through a solvent free Knoevenagel condensation reaction between piperonal and malononitrile to afford the intermediate (I) which then undergoes Michael addition with aromatic amine to achieve the compounds ( $1_{a-e}$ ) (Borah, Dwivedi, & Chowhan, 2021) .



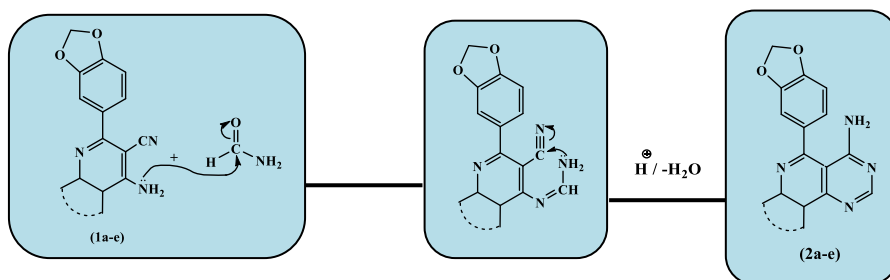
Scheme 2. synthetic equation of compounds (1a-e)

The structure of compounds (1a-e) were illustrated by spectral data so, they show two types of absorption in u.v spectroscopy at  $\lambda$  max (nm), (475) and (271) refer to  $n \rightarrow \pi^*$  and  $\pi \rightarrow \pi^*$  respectively. Whereas in FT-IR these compounds gave a significant absorption peak for amino group at (3341-3435)  $\text{cm}^{-1}$  while the cyano group appears as a weak peak at (2687)  $\text{cm}^{-1}$  additionally to the other spectral data listed in the experimental part. The  $^1\text{H-NMR}$  for compounds (1a, 1c and 1e) shown clear a singlet peak at ( $\delta$  ppm) (8.38, 9.82 and 9.81) refer to the amino group in addition to the other absorption peaks listed in experimental section, which came in agreement with the suggested structure.

Table 1  
Spectrum properties of compounds (1a-e)

Comp. No.	Structure of amine	Structure of enamine	FT- IR ( $\text{cm}^{-1}$ )					C-O-C	Others	U.V/MeOH $\lambda$ max (nm)
			NH	=C-H	C $\equiv$ N	C=C	C=N			
1a			3372,34 29	303 0	222 4	161 2	156 8	1289 1032	C-S 1111	375,340
1b			3371,34 02	303 0	222 4	161 2	156 8	1290 1032	—	371,327
1c			3322,34 00	303 0	219 4	166 8	158 9	1281 1091	NO <sub>2</sub> asym. 1490 sym. 1330	302,271
1d			3320,34 15	303 7	237 7	160 0	158 8	1232 1095	C=O 1676	475,340
1e			3341,34 35	306 4	268 7	162 4	158 7	1281 1090	C=O 1672	444,323

After proving the structural formula, compounds (1a-e) then used as active precursor to prepare the fused pyrimidines. actually, compounds (1a-e) were reacted with formamide to afford Fused-2-amino pyrimidine (2a-e) through cycloaddition reaction in presence of catalytic amount of acetic acid as acid catalyst as shown in the following mechanism, (Scheme 3) (Ghorab et al., 2006):



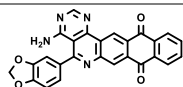
Scheme 3. Synthetic mechanism of compounds (2a-e)

The cyclization reaction occurred through elimination of water molecular followed by intra cyclization reaction by the action of the amino group on the cyano functional group to achieve the compounds (2a-e). By using the spectroscopic methods, the structures were proved on the bases of it's spectral data. So, in FT-IR these compounds revealed the absence of cyano functional group, while the absorption band for amino group still appear, Table (2). The  $^1\text{H-NMR}$  spectroscopy for compound (2c and 2e) and because of the decreasing of electronegativity of molecule by losing of cyano functional group, they shown low significant peaks at  $\delta$  (3.26 and 3.45 ppm) as a singlet peak refer to the  $\text{NH}_2$  functional group as well as to the other absorption peaks listed in the experimental section which came in agreement with the suggested structure.

Table 2  
Spectrum properties of compounds (2a-e)

Comp. No.	Structure of pyrimidine	FT- IR ( $\text{cm}^{-1}$ )				Others		U.V/MeOH $\lambda$ max (nm)	
		$\text{NH}_2$	$=\text{C}-\text{H}$	$\text{C}=\text{C}$	$\text{C}=\text{N}$	$\text{C}-\text{O}-\text{C}$			
				asym. sym.					
2a		3320,3384	3091	1590	1546	1248	1103	C-S 1033	376,366
2b		3320,3368	3082	1560	1493	1257	1104	—	370,317
2c		3314,3368	3015	1687	1594	1238	1104	$\text{NO}_2$ asym. 1488 sym. 1290	346,209
2d		3427,3489	3066	1604	1544	1280	1167	$\text{C}=\text{O}$ 1672	378,317

2e



3362,3439

3031

1626

1587

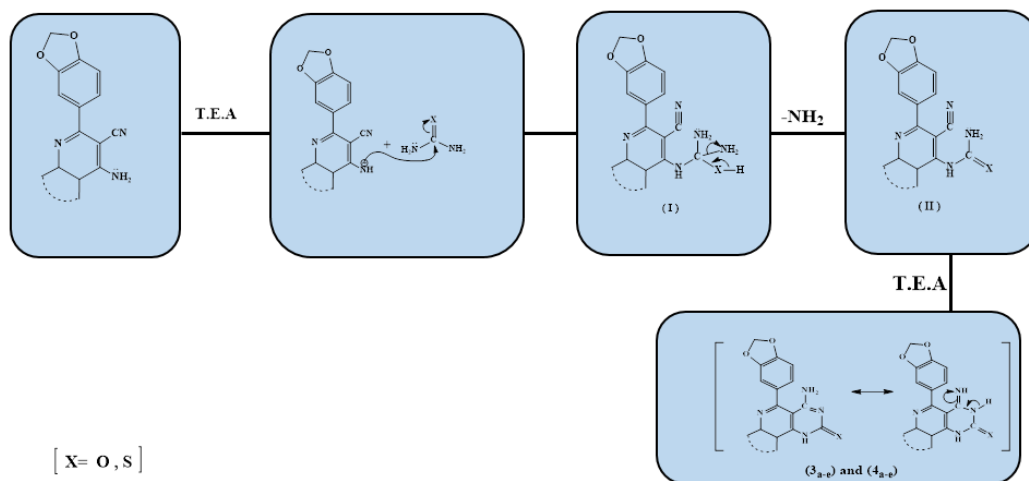
1281

1163

C=O  
1674

444,370

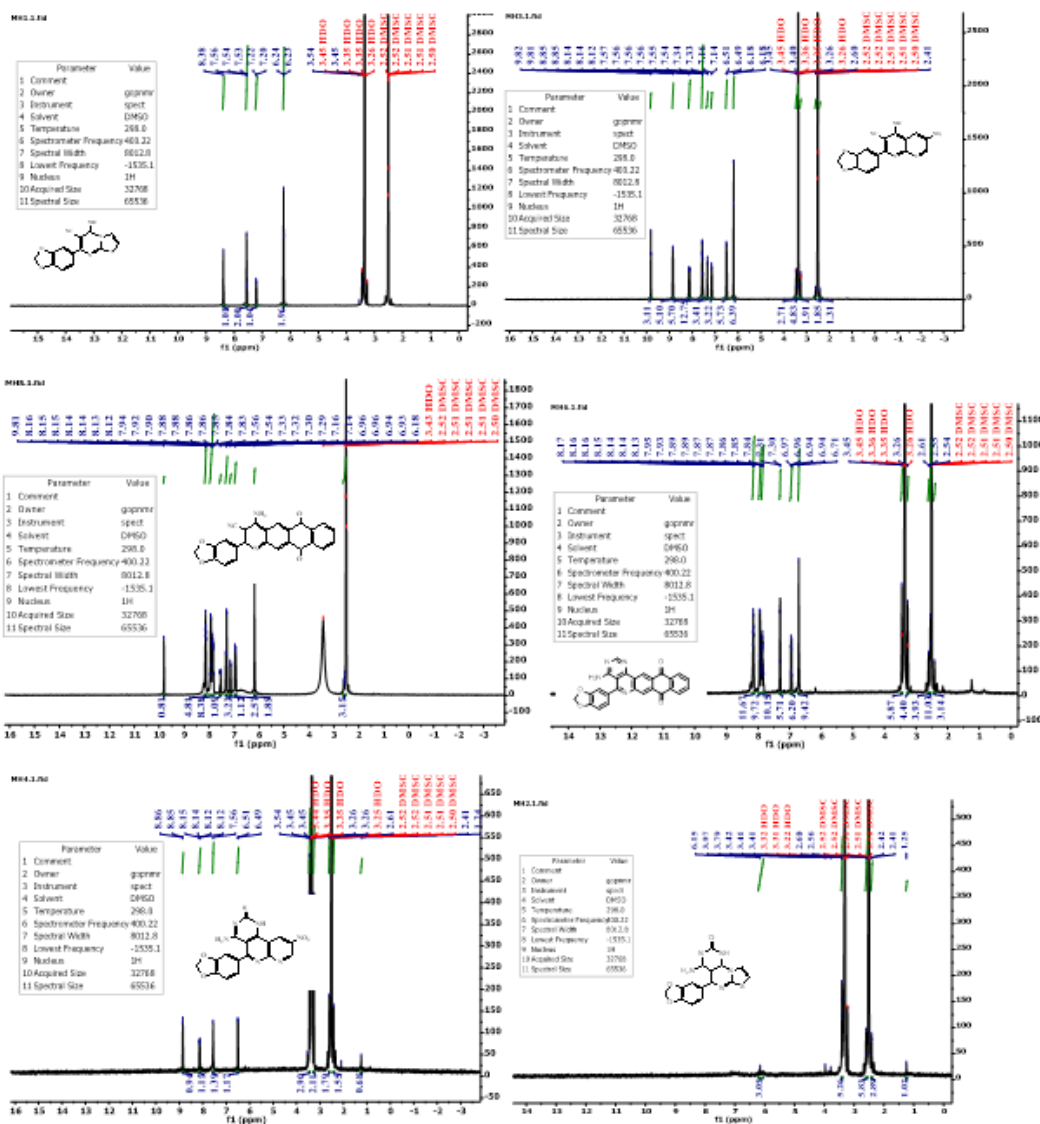
On the other hand, fused 4-amino pyrimidine 2-one (thion) (3a-e) and (4a-e) respectively were obtained through the reaction of compounds (1a-e) with urea and thiourea with catalytic amount of tri ethyl amine (TEA) as basic catalyst, (Scheme 4) (Aslam et al., 2018):



Scheme 4. Synthetic mechanism for compounds (3a-e) , (4a-e)

Tri ethyl amine were used to achieve the negative charge on amino pyridine which attack the thion group to afford the intermediate (I) followed by losing of ammonia molecule to give the intermediate (II) which in turn underwent the intracyclization reaction by the action of amino group to give the fused 4-amino pyrimidines-2-one (thion) (3a-e) and (4a-e) respectively. The  $^1\text{H-NMR}$  spectrum for compounds (3a and 4c) as examples showed a singlet peak at ( $\delta\text{ppm}$ ): (2.6 and 3.45) belong to the primary amine ( $\text{NH}_2$ ) and at (2.42 and 3.26) refer to the secondary amine ( $\text{NH}$ ) of pyrimidine ring. Whereas in FT-IR spectroscopy these compounds display absorption bands refer to the  $\text{NH}_2$ ,  $\text{NH}$ , ( $\text{C}=\text{O}$ ) and ( $\text{C}=\text{S}$ ) functional groups, in addition to the other absorption bands listed in Table (3) and (4).





#### 4 Conclusion

Green chemistry approaches represented by solid phase one-pot multicomponent reaction, grinding and microwave irradiation have been used in the first step under free solvent, catalyst and fusion conditions which lead to afford five novel 4-amino nicotine nitriles (1<sub>a-e</sub>) in high yield and simple working out. 4-amino nicotine nitriles shown active behavior toward preparing new series of fused pyrimidines derivatives in very simple procedures. As well as thin layer chromatography has an effective and simple role to determining the reaction time and measuring the purity of the prepared compounds.

## References

- Amer, A., El-Eraky, W. I., & Mahgoub, S. (2018). Synthesis, characterization and antimicrobial activity of some novel quinoline derivatives bearing pyrazole and pyridine moieties. *Egyptian Journal of Chemistry*, 61(Conference issue (14th Ibn Sina Arab Conference on Heterocyclic Chemistry and its Applications (ISACHC 2018), 30 March-2 April 2018, Hurgada, Egypt).), 1-8.
- Aslam, N., White, J., Zafar, A. M., Jabeen, M., Ghafoor, A., Sajjid, N., . . . Khan, M. A. (2018). 4H-Pyrano [2, 3-c] pyrazoles: a review.
- Bariwal, J. B., Trivedi, J. C., & Eycken, E. V. (2010). Microwave irradiation and multicomponent reactions. *Synthesis of Heterocycles via Multicomponent Reactions II*, 169-230.
- Boger, D. L., Ishizaki, T., Wysocki Jr, R. J., Munk, S. A., Kitos, P. A., & Suntornwat, O. (1989). Total synthesis and evaluation of (.+.-)-N-(tert-butoxycarbonyl)-CBI,(.+.-)-CBI-CDPI1, and (.+.-)-CBI-CDPI2: CC-1065 functional agents incorporating the equivalent 1, 2, 9, 9a-tetrahydrocyclopropa [1, 2-c] benz [1, 2-e] indol-4-one (CBI) left-hand subunit. *Journal of the American Chemical Society*, 111(16), 6461-6463.
- Borah, B., Dwivedi, K. D., & Chowhan, L. R. (2021). Applications of pyrazolone in multicomponent reactions for the synthesis of dihydropyrano [2, 3-c] pyrazoles and spiro-pyrano [2, 3-c] pyrazoles in aqueous medium. *ARKIVOC: Online Journal of Organic Chemistry*, 2021.
- Darwish, E. S., Abdelrahman, M. A., & Salaheldin, A. M. (2011). Enamines in Heterocyclic Synthesis: A Novel Simple and Efficient Route to Condensed Pyridazines. *Zeitschrift für Naturforschung B*, 66(6), 597-602.
- El-Gazzar, A., Hegab, M., Swelam, S., & Aly, A. (2002). Studies with polyfunctionality substituted heterocycles: Novel syntheses of thienopyrimido-1, 2, 4-triazoles. *Phosphorus, Sulfur, and Silicon and the Related Elements*, 177(1), 123-136.
- Farghaly, A. M., AboulWafa, O. M., Elshaiar, Y. A., Badawi, W. A., Haridy, H. H., & Mubarak, H. A. (2019). Design, synthesis, and antihypertensive activity of new pyrimidine derivatives endowing new pharmacophores. *Medicinal Chemistry Research*, 28(3), 360-379.
- Farouk Elsadek, M., Mohamed Ahmed, B., & Fawzi Farahat, M. (2021). An overview on synthetic 2-aminothiazole-based compounds associated with four biological activities. *Molecules*, 26(5), 1449.
- Fathalla, O., Zeid, I., Haiba, M., Soliman, A., Abd-Elmoez, S. I., & El-Serwy, W. (2009). Synthesis, antibacterial and anticancer evaluation of some pyrimidine derivatives. *World J Chem*, 4(2), 127-132.
- Fawzy, N. M., Roaiah, H. M., Awad, E. M., Wietrzyk, J., Milczarek, M., & Soliman, A. M. (2018). Synthesis of new indole derivatives using one-pot multicomponent reaction with antiproliferative towards normal and cancer cell lines. *Egyptian Pharmaceutical Journal*, 17(2), 85.
- Ghorab, M. M., Noaman, E., Ismail, M. M., Heiba, H. I., Ammar, Y. A., & Sayed, M. Y. (2006). Novel antitumor and radioprotective sulfonamides containing pyrrolo [2, 3-d] pyrimidines. *Arzneimittelforschung*, 56(06), 405-413.
- Kumar, S., Deep, A., & Narasimhan, B. (2019). A review on synthesis, anticancer and antiviral potentials of pyrimidine derivatives. *Current Bioactive Compounds*, 15(3), 289-303.

- Maddila, S., Gorle, S., Seshadri, N., Lavanya, P., & Jonnalagadda, S. B. (2016). Synthesis, antibacterial and antifungal activity of novel benzothiazole pyrimidine derivatives. *Arabian Journal of Chemistry*, 9(5), 681-687.
- Mahfoudh, M., Abderrahim, R., Leclerc, E., & Campagne, J. M. (2017). Recent approaches to the synthesis of pyrimidine derivatives. *European Journal of Organic Chemistry*, 2017(20), 2856-2865.
- Mallikarjunaswamy, C., Mallesha, L., Bhadregowda, D., & Pinto, O. (2017). Studies on synthesis of pyrimidine derivatives and their antimicrobial activity. *Arabian Journal of Chemistry*, 10, S484-S490.
- Mohamed, M. S., Rashad, A. E., Zaki, M. E., & Fatahala, S. S. (2005). Synthesis and antimicrobial screening of some fused heterocyclic pyrroles. *Acta Pharmaceutica*, 55(3), 237-249.
- Naik, T., & Chikhalia, K. (2007). Studies on synthesis of pyrimidine derivatives and their pharmacological evaluation. *E-Journal of Chemistry*, 4(1), 60-66.
- Orlov, P. V. (2018). *Application of derivatives of pyrazolotriazinones to improve the vegetative growth of barley*. paper presented at the chemistry of nitrogen containing heterocycles, Kharkiv, Ukraine.
- Prachayasittikul, S., Pingaew, R., Worachartcheewan, A., Sinthupoom, N., Prachayasittikul, V., Ruchirawat, S., & Prachayasittikul, V. (2017). Roles of pyridine and pyrimidine derivatives as privileged scaffolds in anticancer agents. *Mini Reviews in Medicinal Chemistry*, 17(10), 869-901.
- Raghavendra, M., Bhojya Naik, H. S., & Sherigara, B. S. (2006). Microwave induced synthesis of thieno [2, 3-b] quinoline-2-carboxylic acids and alkyl esters and their antibacterial activity. *Journal of Sulfur Chemistry*, 27(4), 347-351.
- Shi, F., Tu, S., Fang, F., & Li, T. (2005). One-pot synthesis of 2-amino-3-cyanopyridine derivatives under microwave irradiation without solvent. *Arkivoc*, 2005(1), 137-142.
- Thakur, V. (2011). *Synthesis of enamines and their bromination*.