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Microwave-assisted synthesis of pyrido[4,3-d]pyrimidine derivatives and their biological evaluation

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ABSTRACT

In the present study, we report the important role of solvent-free conditions coupled with microwave activation and their advantages in heterocyclic synthesis. This eco-friendly approach, which was found application in facile organic synthesis, is applied to the rapid assembly of heteroatom organic compounds via cyclocondensation reactions. Combinatorial heterocyclic synthesis under solvent-free conditions is described having allowed to build a library of such heterocyclic compounds of pharmacological interest. Some of the discussed compounds show *in vitro* antimicrobial activity against Mycobacterium tuberculosis H37Rv (MTB) compared with some standard drugs.

KEYWORDS

Pyridopyrimidines;
Microwave irradiation;
Multicomponent reaction;
Solvent–free synthesis;
Green chemistry;
Antibacterial activity.

INTRODUCTION

Since the appearance of the reference first papers[1] on the application of microwave irradiation in organic syntheses, the field has seen a steady growth to point where a variety of transformations are now possible with microwave heating[2,15-21]. Carrying out the reactions using microwave heating, as opposed to conventional heating, has the major advantage of shorter reaction times because of the rapid heating. Consequently, reactions exhibit cleaner products made more facile work- up procedures.

Pyridopyrimidines are biologically interesting molecules that have established utility in the pharmaceutical and the agrochemical industries. Compounds with these ring systems have diverse pharmacological activity such as antitumor[22,23], cardiotonic[24,25], hepatoprotective[24], antihypertensive[24], antibronchitic[26], antifungal[27], antibacterial[28] and antifolate[29]. Therefore these fused heterocycles have been extensively investigated and their synthetic preparations are well documented[30-32]. As a result, a number of reports appeared in literature; however they usually require forcing conditions[33], long reaction times[34,35] and complex synthetic pathways[29]. So new routes for thesynthesis of these molecules have attracted a considerable attention as a rapid entry for the formation of these heterocycles[36,37].

On this account, our target is to perform a facile and efficient one-pot, four- component, green synthesis of pyridopyrimidines via microwave heating and to evaluate the bioactivity of the prepared compounds.

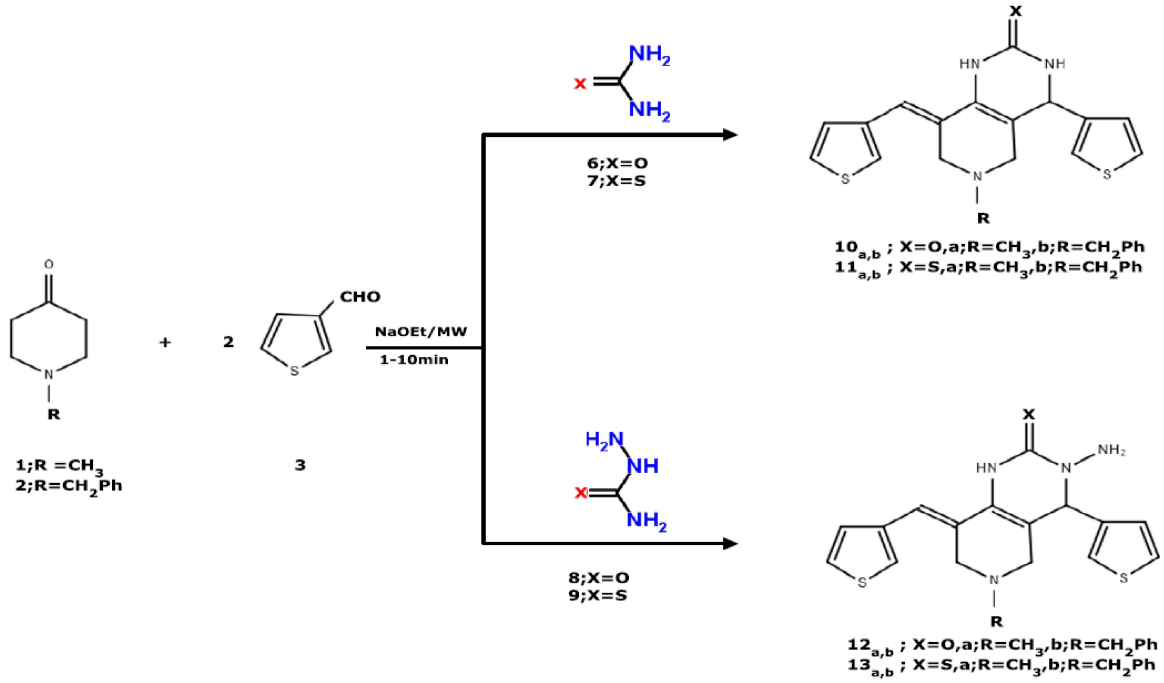
RESULTS AND DISCUSSION

Chemistry

In the present study, we are going to synthesize a series of polysubstituted [4,3-d] pyridopyrimidines via one- pot multicomponent reaction of N- substituted

piperidones (**(1)** and **(2)**) with heterocyclic aldehydes (**(3)**,**(4)** and **(5)**) and compounds containing amide moiety, namely, urea, thiourea, semicarbazide and thiosemicarbazide under microwave irradiation in absence of solvent. The structure of the studied compounds is established on the basis of elemental analysis and spectral data. The resulting products, the pyrido[4,3-d] pyrimidine-2- ones (**(10)**,**(12)**,**(14)**,**(16)**,**(18)** and **(20)**), and the pyrido[4,3-d] pyrimidine-2- thiones (**(11)**,**(13)**,**(15)**,**(17)**,**(19)** and **(21)**) are obtained in one-pot reaction on irradiating a mixture of compounds (**(1)** and **(2)**), heterocyclic aldehydes(**(3)**,**(4)** and **(5)**), and urea, semicarbazide, thiourea, and thiosemicarbazide, respectively, in presence of solid sodium ethoxide as a catalyst, with MW irradiation at the ambient temperature.

On irradiating N- substituted piperidones (**(1)** and **(2)**), thiophene-3- carboxyaldehyde **(3)** and urea **(6)**, thiourea **(7)**, semicarbazide **(8)**, and thiosemicarbazide **(9)** with MW irradiation for few minutes under free-solvent condition and in presence of sodium ethoxide as a catalyst affords the corresponding pyrido [4,3-d] pyrimidine derivatives (**$10_{a,b}$-$13_{a,b}$**) (examined by TLC),respectively (Scheme 1).



Scheme 1

Using similar conditions (MW / NaOEt and in absence of solvent) N-substituted piperidones (**(1)** and **(2)**) react with 5-chloro-3-furaldehyde **(3)** and urea **(6)** to give pyrido[4,3-d] pyrimidin-2- ones (**$14_{a,b}$**), respectively. Replacement of urea by thiourea(7), semicarbazide **(8)** and thiosemicarbazide **(9)** affords the corresponding pyridopyrimidine- 2- thiones (**$15_{a,b}$**) and the amino derivatives of pyridopyrimidine (**$16_{a,b}$**,**$17_{a,b}$**), respectively (Scheme 2).

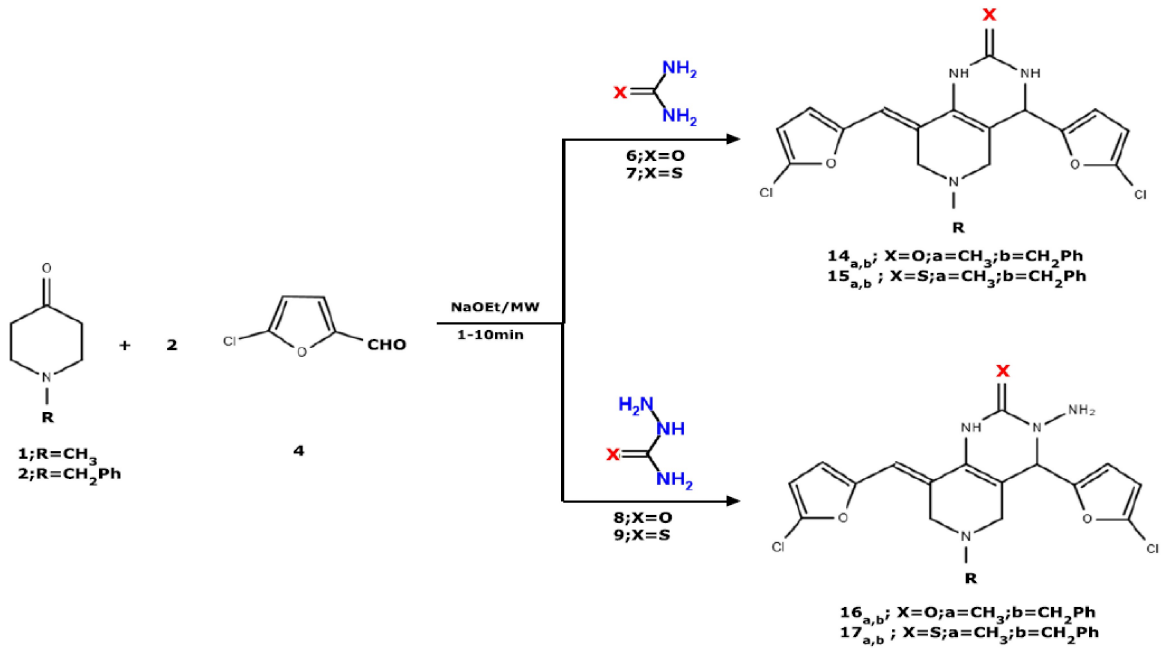
Similarly, pyridopyrimidine–ones (**$18_{a,b}$**), pyridopyrimidine-thiones (**$19_{a,b}$**) and 2-aminopyridopyrimidine derivatives (**$20_{a,b}$**,**$21_{a,b}$**) are produced by the reaction of N-substituted piperidones (**(1)** and **(2)**) with pyridine-4-aldehyde **(5)**, urea **(6)**, thiourea **(7)**, semicarbazide **(8)** and thiosemicarbazide **(9)**, respectively (Scheme 3)

The reaction of N- substituted piperidones with heterocyclic aldehydes and compounds containing amide moiety is believed to proceed via the cyclization of the isomeric intermediate **(22)** to afford the desired products **(10-21)** (Scheme 4).

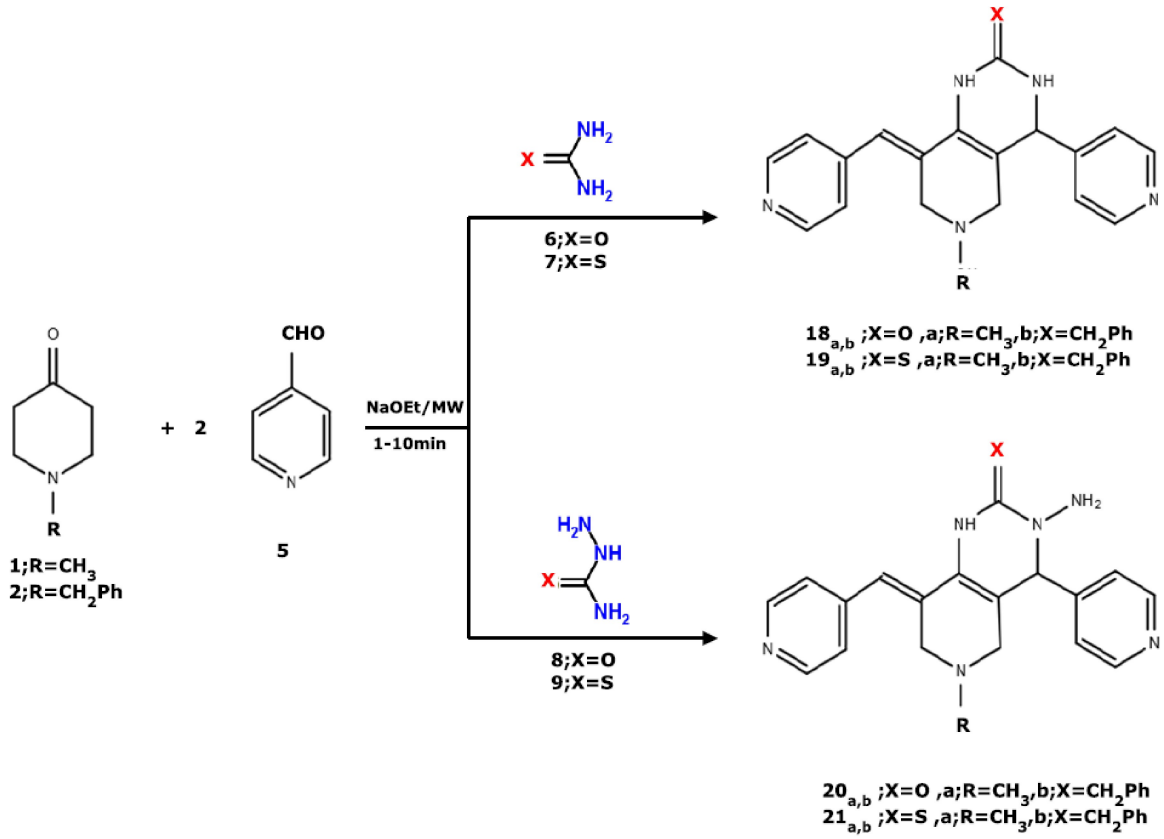
The elemental analyses and spectral data for the synthesized compounds are in accordance with the assigned structures **(10-21)**.

Biological screening

In vitro antimicrobial screening of the synthesized compounds **(10-21)** were evaluated against Mycobacterium tuberculosis H37Rv (MTB). Activities of the



Scheme 2

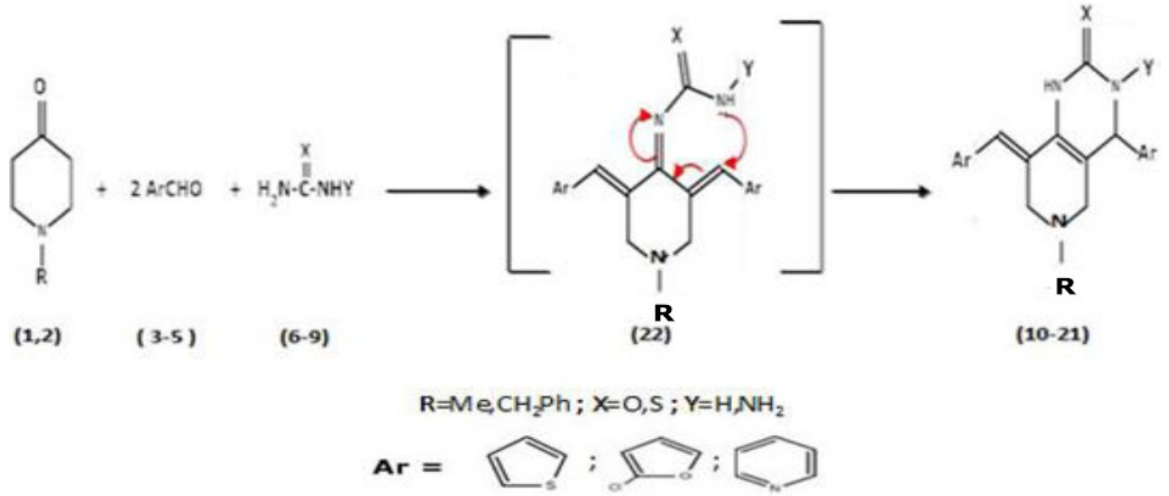


Scheme 3

compounds and the minimum inhibitory concentration (MIC) of the tested compounds required to inhibit 99% of bacterial growth, were evaluated by agar diffusion method. Compounds **(14_b),(15_b)**, **(16_a),(16_b)** and **(17_b)**, exhibited significant activity against (MTB) as compared with the reference drugs.

From the results obtained we can conclude that :

1) The N- benzyl pyridopyrimidines show better ac-



Scheme 4

TABLE 1 : MIC (µM) values of pyridopyrimidines (10-21) against MTB

Tested samples	MIC (µM)	Tested samples	MIC (µM)	Tested samples	MIC (µM)
10_a	30.2	14_a	55.9	18_a	14.6
10_b	48.2	14_b	5.1	18_b	21.6
11_a	28.5	15_a	50.3	19_a	11.4
11_b	48.7	15_b	3	19_b	20.1
12_a	69.6	16_a	5.1	20_a	21.8
12_b	51.7	16_b	2.2	20_b	39.4
13_a	64.3	17_a	51	21_a	60
13_b	42.1	17_b	6	21_b	57

TABLE 2 : MIC (µM) values of standard drugs

Standard reference	MIC (µM)	Standard reference	MIC (µM)
Ethambutol	7.6	Isoniazid	0.4
Ciprofloxacin	4.7	Rifampicin	0.1

tivity than their N- methyl analogs.

2) The presence of heterocyclic ring enhanced activity.

EXPERIMENTAL SECTION

Melting points were determined on open glass capillaries using an electrothermal I A 9000 digital melting point apparatus and are uncorrected. IR spectra are recoded (KBr) on PyeUnicam SP-1000 instrument spectrophotometer. ^{1}H NMR spectra are obtained on a Varian Mercury VXR -300 MHz spectrometer ($CDCl_3$) using tetramethylsilane (TMS) as an internal reference. Chemical shifts are expressed as δ (ppm). Mass spectra are recorded on an MS 30 or MS 9 (AEI) mass spectrometer operating at 70 e V. The elemental analyses are formed at Micro Analytical center at CairoUniversity and the Micro Analytical unit at the National Research Center. Follow up the reactions and checking the purity of the compounds are made by TLC on silica gel – precoated aluminum sheets (Type 60 F 254, Merck, Darmstadt, Germany), and the spots are detected by exposure to UV lamp at λ_{365} nm for few seconds. The antimicrobial activity against Mycobacterium tuberculosis is evaluated by Micro analytical center, Microbiology Department, Cairo University. Microwave reactions are carried out in domestic 1000W microwave oven. All the chemicals purchased from Sigma-Aldrich company, and are used as received without further purification.

Synthesis of N - substituted pyridopyrimidine - 2-ones ($10_{a,b}$), ($14_{a,b}$) and ($18_{a,b}$)

A mixture of N- substituted -4- piperidone, namely, N-methyl and N- benzyl -4-piperidone (1mmol), heterocyclic aldehyde, namely, 4-pyridine carboxaldehyde, 3-thiophene carboxaldehyde and 5-chloro-2- furan carboxaldehyde (2mmol), urea (0.06,1mmol) and sodium ethoxide (2.04g, 3mmol) are subjected to microwave irradiation for about ½-3 min. After completion of the reaction as evident from TLC, water (50 ml) is added to the mixture and the product is filtered off and dried.The crude product is crystallized from the proper solvent.

8- (3-Thienylmethylene) -4- (3- thienyl)- 6- methyl-3,4,5,6,7,8- hexahydropyrido [4,3-d] pyrimidine

– 2- one (10_a)

Yield(87.76%); mp180-183ºc(n-hexane); IR(KBr, ν cm^{-1}) : 3373, 3338 (NH), 1657 (C=O); ^{1}H NMR ($CDCl_3$) δ : 7.92 - 7. 88 (2s, 2H, thiophene -H), 7.43-7. 28 (2d, 2H, thiophene – H), 7.25 – 6.93 (2d, 2H, thiophene – H), 7.79 (s, 1H, NH), 7.85 (s, 1H, NH), 6.67 (s, 1H,- CH=), 5.06 (s, 1H, pyrimidine –H), 3.22-3.26(2d, 4H, $2CH_2$, pyridine –H), 2.80 (s, 3H, N-Me); MS, m/z (%) : 343 [M^+] (27), 260 [M^+ -C_4H_3S] (65),177 [260 – C_4H_3S] (13), 162 [177 –CH_3](100); Anal. Calcd% for $C_{17}H_{17}N_3OS_2$ 343 (found) C 59.48 (59.45); H 4.96 (4.92); N 12.24 (12.20); S 18.66 (18.61).

8-(5-Chloro-2-furylmethylene)-4-(5-chloro-2-furyl)-6-methyl-3,4,5,6,7,8-hexahydropyrido[4,3-d] pyrimidine- 2-one (14_a)

Yield (76%); mp 172-175 ºC (n-hexane); IR (KBr, ν cm^{-1}) : 3373, 3338 (NH), 1685 (C=O); ^{1}H NMR ($CDCl_3$) δ : 7.85 (s, 1H, NH), 7.79 (s, 1H, NH), 6.88 – 6.33 (4d, 4H, furan – H), 6.82 (s, 1H,- CH=), 5.18 (s, 1H, pyrimidine –H), 3.28-3.25 (2d, 4H, $2CH_2$, pyridine –H), 2.35 (s, 3H, N-Me); MS, m/z (%) : 380 [M^+] (56), 278.5 [M^+ -C_4H_2OCl] (100), 177[278.5-C_4H_2OCl] (45),162 [177-CH_3] (18); Anal. Calcd% for $C_{17}H_{15}N_3O_3Cl_2$ 380 (found) C 53.68 (53.61); H 3.95 (3.95); N 11.05 (10.9); Cl 18.68 (18.55).

8- (4-Pyridinylmethylene) -4- (4- pyridinyl)- 6-methyl- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- one (18_a)

Yield(89%); mp178-180ºC (ethanol); IR (KBr, ν cm^{-1}) : 3444, 3140 (NH) and 1665 (C=O); ^{1}H NMR ($CDCl_3$) δ : 8.7 – 7. 2 (4d, 8H, pyridine-H), 7.9 (s, 1H, NH), 7.8 (s, 1H, NH), 7.15 (s, 1H,- CH=), 5.3 (s, 1H, pyrimidine –H), 3.25-3.21 (2d, 4H, $2CH_2$, pyridine –H), 2.43 (s, 3H, N-Me); MS, m/z (%) : 333 [M^+] (37), 255 [M^+ -C_5H_4N] (100), 177 [255 -C_5H_4N] (31), 162[177 –CH_3] (22). Anal.Calcd% for for $C_{19}H_{19}N_5O$ 333 (found) C 68.39(68.47); H 5.70(5.71); N 21.02(21).

6-Benzyl -8-(3-thienylmethylene) -4- (3- thienyl)-3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- one (10_b)

Yield(91%); mp120-122º C(ethanol); IR (KBr, ν cm^{-1}) : 3420, 3380 (NH), 1710 (C=O);^{1}H NMR ($CDCl_3$) δ : 7.9 - 7. 7(2s, 2H, thiophene – H), 7.63 - 7. 59 (2d, 2H, thiophene – H), 7 – 6.9 (2d, 2H, thiophene – H), 7.89 (s, 1H, NH), 7.4 (s, 1H, NH), 7.1-7.1 (m,5H,aromatic-H), 6.82 (s, 1H,- CH=), 5.1 (s, 1H, pyrimidine –H), 3.72 (s, 2H, CH_2Ph), 2.8-2.1 (2d, 4H, $2CH_2$, pyridine –H); MS, m/z (%) : 419 [M^+] (57), 336 [M^+ -C_4H_3S] (100), 253 [336 – C_4H_3S] (36), 176[253 –C_6H_5] (81), 162[176-CH_2](28); Anal. Calcd% for $C_{23}H_{21}N_3OS_2$ 419 (found) C 65.87 (65.8); H 5.01 (4.9); N 10.02 (10); S 15.27 (14.88).

6-Benzyl -8-(5-Chloro-2-furylmethylene) -4- (5-chloro-2-furyl)- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- one (14_b)

Yield (81%); mp 104-106ºC (n-hexane); IR (KBr, ν cm^{-1}) : 3410, 3370 (NH), 1720 (C=O);^{1}H NMR ($CDCl_3$) δ : 7.9(s, 1H, NH), 7.8 (s, 1H, NH), 7.1-6.9(m, 5H, aromatic-H) 6.89 – 6.32 (4d, 4H, furan – H), 6.62 (s, 1H,- CH=), 5.1 (s, 1H, pyrimidine –H), 3.26-3.23 (2d, 4H, $2CH_2$,pyridine –H), 3.69 (s, 2H, CH_2Ph) MS, m/z (%) : 456 [M^+] (65), 354.5 [M^+ -C_4H_2OCl] (100), 253[354.5- C_4H_2OCl] (37),176 [253-C_6H_5] (33), 162[176-CH_2](29); Anal. Calcd% for $C_{23}H_{19}N_3O_3Cl_2$ 456 (found) C 60.53(60.49); H 4.17 (4.13); N 9.21 (9.18); Cl 15.57 (15.56).

6-Benzyl -8-(4-pyridinylmethylene) -4- (4-pyridinyl)- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- one (18_b)

Yield(73%); mp131-133ºC(ethanol); IR (KBr, ν cm^{-1}) : 3420, 3380 (NH), 1710 (C=O); ^{1}H NMR ($CDCl_3$) δ : 8.5 – 7. 4 (4d, 8H, pyridine-H), 7.9 (s, 1H, NH), 7.8 (s, 1H, NH), 7.1 (s, 1H,- CH=), 5.3 (s, 1H, pyrimidine –H), 3.28-3.22 (2d, 4H, $2CH_2$, pyridine –H). 2.23 (s, 3H, N-Me); MS, m/z (%) : 409 [M^+] (33), 331 [M^+ -C_5H_4N] (100), 253 [331 -C_5H_4N] (62), 176[253 –C_6H_5] (70), 162 [176 -CH_2] (58) ; Anal. Calcd% for $C_{25}H_{23}N_5O$ 409 (found) C 73.35 (73.32); H 5.62 (5.6); N 17.11 (17.1).

Synthesis of N - substituted pyridopyrimidine -2-thiones ($11_{a,b}$), ($15_{a,b}$) and ($19_{a,b}$)

A mixture of N- substituted -4- piperidone, namely, N-methyl and N- benzyl -4-piperidone (1mmol), heterocyclic aldehyde, namely, 3-thiophenecarboxaldehyde, 5-chloro-2-furan carboxaldehyde and 4-pyridine carboxaldehyde

(2mmol), thiourea (0.76, 1mmol) and sodium ethoxide (2.04g, 3mmol) are subjected to microwave irradiation for about ½-3 min. After completion of the reaction as evident from TLC, water (50 ml) is added to the mixture and the product is filtered off and dried. The crude product is crystallized from the proper solvent.

8- (3-Thienylmethylene) -4- (3- thienyl)- 6- methyl- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- thione (11_a)

Yield(85%); mp186-188ºC (n-hexane); IR (KBr, ν cm^{-1}) : 3360, 3320 (NH); ^1H NMR ($CDCl_3$) δ : 7.85 – 7.80 (2s, 2H, thiophene – H), 7.40 - 7. 35 (2d, 2H, thiophene – H), 7.69 – 6.87 (2d, 2H, thiophene – H),7.79(s, 1H, NH), 7.85 (s, 1H, NH), 6.62 (s, 1H,- CH=), 5.3 (s, 1H, pyrimidine –H), 3.35-3.22 (2d, 4H, $2CH_2$, pyridine –H), 2.1 (s, 3H, N-Me); MS, m/z (%) : 359 [M^+] (39), 276 [M^+ -C_4H_3S] (86), 193 [276 – C_4H_3S] (100), 178[193 –CH_3](55); Anal. Calcd% for $C_{17}H_{17}N_3S_3$ 359 (found) C 56.82 (56.79); H 4.73(4.62); N 11.70 (11.60); S 26.74 (26.51).

8-(5-Chloro-2-furylmethylene) -4- (5-chloro-2-furyl)- 6- methyl- 3,4,5,6,7,8- hexahydropyrido [4,3-d] pyrimidine - 2- thione (15_a)

Yield(71%); mp180-183ºC (n-hexane); IR (KBr, ν cm^{-1}) : 3320, 3315 (NH); ^1H NMR ($CDCl_3$) δ : 6.90-6.31 (4d, 4H, furan – H), 7.8 (s, 1H, NH), 7.7 (s, 1H, NH), 6.65 (s, 1H,- CH=), 5.2 (s, 1H, pyrimidine –H), 3.28-3.25 (2d, 4H, $2CH_2$, pyridine –H), 2.32 (s, 3H, N-Me); MS, m/z (%) : 396 [M^+] (46), 294 [M^+ - C_4H_2OCl] (54), 193 [294 – C_4H_2OCl] (100), 178[193 –CH_3](33); Anal. Calcd% for $C_{17}H_{15}N_3O_2SCl_2$ 396 (found) C 51.52(51); H 3.79(3.62); N 10.61(10.60); S 8.08 (7.93), Cl 17.93 (17.8).

8- (4-Pyridinylmethylene) -4- (4- pyridinyl)- 6- methyl- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- thione (19_a)

Yield(73%); mp166-169ºC (ethanol); IR (KBr, ν cm^{-1}) : 3440, 3390 (NH); ^1H NMR ($CDCl_3$) δ : 8.7 – 7.49 (4d, 8H, pyridine-H), 7.8 (s, 1H, NH), 7.62 (s, 1H, NH), 7.22 (s, 1H,- CH=), 5.38 (s, 1H, pyrimidine –H), 2.15 (s, 3H, N-Me), 3.25-3.22 (2d, 4H, $2CH_2$, pyridine –H); MS, m/z (%) : MS, m/z (%) : 349 [M^+] (79%), 271 [M^+ -C_5H_4N] (83%), 193 [271- C_5H_4N] (100%), 178[193 –CH_3] (32%); Anal. Calcd% for $C_{19}H_{19}N_5S$ 349 (found) C 65.33 (65.15); H 5.44 (5.4) ; N 20.05 (19.7); S 9.16 (9.1).

6-Benzyl -8-(3-thienylmethylene) -4- (3- thienyl)- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- thione (11_b)

Yield(80%); mp148-149ºC (n-hexane); IR (KBr, ν cm^{-1}) : 3410, 3330 (NH); ^1H NMR ($CDCl_3$) δ : 7.90 – 7.86 (2s, 2H, thiophene – H), 7.48 - 7. 36 (2d, 2H, thiophene – H), 7.26 – 6.90 (2d, 2H, thiophene – H), 7.60 (s, 1H, NH), 7.55 (s, 1H, NH), 6.7 (s, 1H,- CH=), 5.34 (s, 1H, pyrimidine –H), 3.54 (s, 2H,CH_2Ph), 3.30-3.22 (2d, 4H, $2CH_2$, pyridine –H); MS, m/z (%) : 435 [M^+] (41), 352 [M^+ -C_4H_3S] (64%), 269 [352 – C_4H_3S](31%), 192[269 –C_6H_5] (26%), 178[192-CH_2] (100%); Anal. Calcd% for $C_{23}H_{21}N_3S_3$ 435 (found) C 63.45 (63.39); H 4.83 (4.79); N 9.66 (9.6); S 22.07 (22).

6-Benzyl -8-(5-chloro-2-furylmethylene) -4- (5-chloro-2-furyl)- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- thione (15_b)

Yield(69%); mp120-123ºC (n-hexane); IR (KBr, ν cm^{-1}) : 3410, 3370 (NH);^1H NMR ($CDCl_3$) δ : 6.87-6.30 (4d, 4H furan-H), 7.25 (s, H, NH), 7.1 (s, 1H, NH), 7.6-7.3 (m, 5H, aromatic-H), 6.62 (s, 1H,- CH=), 5.20(s, 1H, pyrimidine –H), 3.67 (s, 2H,CH_2Ph), 3.22-3.18 (2d, 4H, $2CH_2$, pyridine –H); MS, m/z (%) 472 [M^+] (35%), 370.5 [M^+ -C_4H_2OCl] (100%), 269 [370.5 - C_4H_2OCl] (42%), 192 [269 –C_6H_5] (57%), 178 [192-CH_2] (39%); Anal. Calcd% for $C_{23}H_{19}N_3O_2SCl_2$ 472 (found) C 58.47 (58.43) ; H 4.03 (4) ; N 8.90 (8.3); S 6.78 (6.57), Cl 15.04 (15).

6-Benzyl -8-(4-pyridinylmethylene) -4- (4-pyridinyl)- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- thione (19_b)

Yield(78%); mp164-166ºC (ethanol); IR (KBr, ν cm^{-1}) : 3425, 3360 (NH); ^1H NMR ($CDCl_3$) δ 8.60 – 7. 19 (4d, 8H, pyridine – H), 7.8 (s, 1H, NH), 7.6 (s, 1H, NH), 7.4-7.2 (m, 5H, aromatic-H), 6.65 (s, 1H,- CH=), 5.2 (s, 1H, pyrimidine –H), 3.72 (s, 2H,CH_2Ph), 3.26-3.20 (2d,4H, $2CH_2$, pyridine –H); MS, m/z (%) : MS, m/z (%) : 425 [M^+] (34%), 347 [M^+ -C_5H_4N] (100%), 269 [347 – C_5H_4N] (44%), 192[269 –C_6H_5] (52%), 178[192- CH_2] (33%); Anal. Calcd% for $C_{25}H_{23}N_5S$ 425 (found) C 70.59(70.51); H 5.41(5.39);

N 16.47(16.42); S 7.53 (7.5).

Synthesis of 3- Amino- N - substituted pyridopyrimidine -2- ones ($12_{a,b}$), ($16_{a,b}$) and ($20_{a,b}$)

A mixture of N- substituted -4- piperidone, namely, N-methyl and N- benzyl -4-piperidone (1mmol), heterocyclic aldehyde, namely, 4-pyridine carboxaldehyde, 3- thiophenecarboxaldehyde and 3- furan carboxaldehyde (2mmol), semicarbazide (0.75, 1mmol) and sodium ethoxide (2.04g, 3mmol) are subjected to microwave irradiation for about ½-3 min. After completion of the reaction as evident from TLC, water (50 ml) is added to the mixture and the product is filtered off and dried. The crude product is crystallized from the proper solvent.

3-Amino-8- (3-thienylmethylene) -4- (3- thienyl)- 6- methyl- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- one (12_a)

Yield(86%); mp158-160ºc(n-hexane); IR (KBr, ν cm^{-1}) : 3330(NH), 3345-3340 (NH_2),1657(C=O); ^{1}H NMR ($CDCl_3$) δ : 12.9 (s, 2H, NH_2), 7.94-7.88 (2s, 2H, thiophene – H), 7.48- 7. 30 (2d, 2H, thiophene – H), 7.26 – 6.92 (2d, 2H, thiophene – H), 7.79 (s, 1H, NH), 7.21 (s, 1H, - CH=), 5.2 (s, 1H, pyrimidine –H), 3.34-3.9 (2d, 4H, $2CH_2$, pyridine –H), 2.27 (s, 3H, N-Me); MS, m/z (%) : 358 [M^+] (29%), 275 [M^+ - C_4H_3S] (53%),192 [275 – C_4H_3S] (77%), 177[192 – CH_3] (40%),161[177-NH_2] (100%); Anal. Calcd% for $C_{17}H_{18}N_4OS_2$358 (found) C 56.98(56.82); H 5.03 (5.02); N 15.64(15.60); S 17.88 (17.80).

3-Amino-8-(5-chloro-2-furylmethylene) -4- (5-chloro-2- furyl)- 6- methyl- 3,4,5,6,7,8- hexahydropyrido [4,3-d] pyrimidine - 2- one (16_a)

Yield(80%); mp172-175ºC (n-hexane); IR (KBr, ν cm^{-1}) : 3373 (NH), 3350-3325 (NH_2), 1685 (C=O); ^{1}H NMR ($CDCl_3$) δ : 12.77 (s, 2H, NH_2), 6.88-6.31 (d, 4H, furan – H), 7.45 (s, 1H, NH), 6.8 (s, 1H, - CH=), 5.3 (s, 1H, pyrimidine –H), 2.23 (s, 3H, N-Me), 3.28-3.20 (2d, 4H, $2CH_2$, pyridine –H); MS, m/z (%) : 395 [M^+] (77%), 293.5 [M^+ -C_4H_2OCl] (66%), 192[293.5- C_4H_2OCl] (100%), 177 [192-CH_3] (35%), 161[177-NH_2] (56%); Anal. Calcd% for $C_{17}H_{16}N_4O_3Cl_2$ 395 (found) C 51.65(51.62); H 4.05 (4); N 14.18(14.16); S 17.97 (17.90).

3-Amino- 8- (4-pyridinylmethylene) -4- (4-pyridinyl)- 6- methyl- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- one (20_a)

Yield(69%); mp158-160ºC (ethanol); IR (KBr, ν cm^{-1}) : 3360 (NH), 3350-3325 (NH_2), 1672 (C=O); ^{1}H NMR ($CDCl_3$) δ : 10.90 (s, 2H, NH_2), 8.70 – 7. 20 (4d, 8H, pyridine-H), 6.89 (s, 1H, NH), 6.77 (s, 1H,- CH=), 5.30 (s, 1H, pyrimidine –H), 3.29-3.20 (2d, 4H, $2CH_2$, pyridine –H), 2.1 (s, 3H, N-Me); MS, m/z (%) : 348 [M^+] (100%), 270 [M^+ -C_5H_4N] (82%), 192 [255 - C_5H_4N] (58%), 177[192 –CH_3] (71%), 161[177-NH_2] (28%); Anal. Calcd% for $C_{19}H_{20}N_6O$ 348 (found) C 65.52 (65.49); H 5.75 (5.71); N 24.14 (24).

3-Amino-6-benzyl -8-(3-thienylmethylene) -4- (3-thienyl)- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- one (12_b)

Yield(75%); mp127-130ºC (ethanol); IR (KBr, ν cm^{-1}) : 3388 (NH), 3350-3325 (NH_2),1662 (C=O); ^{1}H NMR ($CDCl_3$) δ : 12.2 (s, 2H, NH_2), 7.96-7.89 (2s, 2H, thiophene – H), 7.41 - 7. 28 (2d, 2H, thiophene – H), 7.3 – 6.9 (2d, 2H, thiophene – H), 7.7 (s, 1H, NH), 7.4-7.1 (m, 5H, aromatic-H), 6.9 (s, 1H,- CH=), 5.38 (s, 1H, pyrimidine –H), 3.7 (s, 2H,CH_2Ph), 3.35-3.20 (2d, 4H, $2CH_2$, pyridine –H); MS, m/z (%): 434 [M^+] (35%), 351 [M^+ -C_4H_3S] (100%), 268 [351 – C_4H_3S](65%), 191[268 –C_6H_5] (28%), 177[191-CH_2] (30%),161 [177 –NH_2] (32%). Anal. Calcd% for $C_{23}H_{22}N_4OS_2$434 (found) C 63.59 (63.49); H 5.07 (5.01); N 12.90 (12.8); S 14.75 (14.6).

3- Amino-6-benzyl -8-(5-chloro-2-furylmethylene) -4- (5-chloro-2-furyl)- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine –2- one (16_b)

Yield(69%); mp142-144ºC (n-hexane); IR (KBr, ν cm^{-1}) : 3410 (NH), 3390-3380 (NH_2),1690 (C=O) ^{1}HNMR($CDCl_3$) δ : 11.9 (s, 2H, NH_2), 6.96 – 6. 33 (4d, 4H furan-H), 7.5 (s, H, NH), 7.1-6.9 (m, 5H, aromatic-H), 6.65 (s, 1H,- CH=), 5.5 (s, 1H, pyrimidine –H), 3.65-3. (s, 2H,CH_2Ph), 3.35-3.20 (2 d, 4H, $2CH_2$, pyridine –H); MS, m/z (%) : 471[M^+] (36%), 369.5 [M^+ -C_4H_2OCl] (61%), 268 [369.5 - C_4H_2OCl] (100%), 191 [268–C_6H_5] (80%), 177[191- CH_2] (30%),161 [177- NH_2] (18%); Anal. Calcd% for $C_{23}H_{20}N_4O_3Cl_2$ 471 (found) C 58.60 (58.52); H 4.25 (4.23); N 11.89 (11.75); Cl 15.07 (15.06).

3-Amino-6-benzyl -8-(4-pyridinylmethylene) -4- (4-pyridinyl)- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- one (20_b)

Yield(83%); mp177-179ºC (n-hexane); IR (KBr, ν cm^{-1}) : 3360 (NH), 3350-3310 (NH_2), 1690 (C=O) ;^{1}H NMR ($CDCl_3$) δ : 12 (s, 2H, NH_2), 8.74 – 7.30 (4d, 8H, pyridine – H), 7.7(s, 1H, NH), 7.3-7.1 (m, 5H, aromatic-H), 6.62 (s, 1H,- CH=), 5.43 (s, 1H, pyrimidine –H), 3.3 (s, 2H,CH_2Ph), 3.29-3.22 (2 d,4H, $2CH_2$, pyridine –H); MS, m/z (%) : 424 [M^+] (47%), 346 [M^+ -C_5H_4N] (100%), 268 [346 – C_5H_4N] (53%), 191[268–C_6H_5] (23%), 177[191-CH_2] (55%), 161[177-NH_2] (31%); Anal. Calcd% for $C_{25}H_{24}N_6O$ 424 (found) C 70.75 (70.63); H 5.66 (5.61); N 19.81 (19.7).

Synthesis of 3-Amino-N - substituted pyridopyrimidine -2- thiones ($13_{a,b}$), ($17_{a,b}$) and ($21_{a,b}$)

A mixture of N- substituted -4- piperidone, namely, N-methyl and N- benzyl -4-piperidone (1mmol), heterocyclic aldehyde, namely, 3-thiophenecarboxaldehyde, 5-chloro-2- furan carboxaldehyde and 4-pyridine carboxaldehyde (2mmol), thiosemicabazide (0.91, 1mmol) and sodium ethoxide (2.04g, 3mmol) are subjected to microwave irradiation for about ½-3 min. After completion of the reaction as evident from TLC, water (50 ml) is added to the mixture and the product is filtered off and dried. The crude product is crystallized from the proper solvent.

3-Amino-8-(3-thienylmethylene) -4- (3- thienyl)- 6-methyl- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- thione (13_a)

Yield(82%); mp130-134ºC (n-hexane); IR (KBr, ν cm^{-1}) : 3360 (NH), 3390-3320 (NH_2); ^{1}H NMR ($CDCl_3$) δ : : 12.6 (s, 2H, NH_2), 7.92-7.87 (2s, 2H, thiophene – H), 7.40 - 7. 26 (2d, 2H, thiophene – H), 7.28 – 6.94 (2d, 2H, thiophene – H), 7.8 (s, 1H, NH), 6.80 (s, 1H,- CH=), 5.48 (s, 1H, pyrimidine –H), 3.4-3.25 (2d, 4H, $2CH_2$, pyridine –H), 2.25 (s, 3H, N-Me); MS, m/z (%) : 374[M^+] (19%), 291[M^+ -C_4H_3S] (100%), 208[291 C_4H_3S] (76%), 193[208 –CH_3] (85%),177[193 –NH_2] (47%); Anal. Calcd% for $C_{17}H_{18}N_4S_3$374 (found) C 54.55 (54.49); H 4.81 (4.79); N 14.97 (14.93); S 25.67 (25.6).

3-Amino-8-(5-chloro-2-furylmethylene) -4- (5-chloro-2- furyl)- 6- methyl- 3,4,5,6,7,8-hexahydropyrido [4,3-d] pyrimidine - 2- thione (17_a)

Yield(78%); mp148-150ºC (n-hexane); IR (KBr, ν cm^{-1}) : 3388 (NH), 3390-3325 (NH_2); ^{1}HNMR($CDCl_3$) δ : 11.8 (s, 2H, NH_2), 6.75 – 6. 36 (4 d, 4H, furan – H), 7.65 (s, 1H, NH), 6.3 (s, 1H,-CH=), 5.1 (s, 1H, pyrimidine –H), 3.25-3.22 (2 d, 4H, $2CH_2$, pyridine –H), 1.91 (s,3H, N-Me); MS, m/z (%) : MS, m/z (%) : 411 [M^+] (27%), 309.5 [M^+ -C_4H_2OCl] (55%) 208 [309.5– C_4H_2OCl](100%), 193[208–CH_3] (40%),177[193 –NH_2] (62%); Anal. Calcd% for $C_{17}H_{16}N_4O_2SCl_2$ 411(found) C 49.64 (49.6); H 3.89(3.81); N 13.63 (13.59); S 7.79 (7.7), Cl 17.27 (17.21).

3-Amino- 8- (4-pyridinylmethylene) -4- (4-pyridinyl)- 6- methyl- 3,4,5,6,7,8-hexahydropyrido[4,3-d] pyrimidine – 2- thione (21_a)

Yield(72%); mp150-153ºC (ethanol); IR (KBr, ν cm^{-1}) : 3383, (NH), 3350-3325 (NH_2); ^{1}H NMR ($CDCl_3$) δ 10.90 (s, 2H, NH_2), 8.70 – 7. 20 (4d, 8H, pyridine-H), 7.79 (s, 1H, NH), 6.82 (s, 1H,- CH=), 5.42 (s, 1H, pyrimidine –H), 3.30-3.26 (2d, 4H, $2CH_2$, pyridine –H), 2.13 (s, 3H, N-Me); MS, m/z (%) : MS, m/z (%) : 364 [M^+] (34%), 286 [M^+ -C_5H_4N] (65%), 208 [286-C_5H_4N] (100%), 193[208–CH_3] (26%),177[193–NH_2] (21%); Anal. Calcd% for $C_{19}H_{20}N_6$ S 364 (found) C 62.64 (61.92); H 5.49 (5.41); N 23.07 (23); S 8.79 (8.63).

3-Amino-6-Benzyl -8-(3-thienylmethylene) -4- (3-thienyl)- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- thione (13_b)

Yield(82%); mp138-140ºc(n-hexane); IR (KBr, ν cm^{-1}) : 3420, (NH), 3350-3325 (NH_2).^{1}H NMR ($CDCl_3$) δ : 12.79 (s, 2H, NH_2), 7.90-7.88 (2s, 2H, thiophene – H), 7.44 - 7. 29 (2d, 2H, thiophene – H), 7.22 – 6.78 (2d, 2H, thiophene – H), 7.7 (s, 1H, NH), 7.5-7.1 (m, 5H, aromatic-H), 6.8 (s, 1H,- CH=), 5.1 (s, 1H, pyrimidine –H),3.7 (s, 2H,CH_2Ph), 3.35-3.24, (2d, 4H, $2CH_2$, pyridine –H); MS, m/z (%) : 450 [M^+] (86%), 367 [M^+ -C_4H_3S] (51%), 284 [367 –

C_4H_3S](33%), 207[284 –C_6H_5] (100%), 193[207-CH_2] (66%),177[193 –NH_2] (27%); Anal. Calcd% for $C_{23}H_{22}N_4S_3$ 450 (found) C 61.3 (61.1) ; H 4.89 (4.70) ; N 12.44 (14.40) ;S 21.33 (21.2).

3-Amino-6-benzyl-8-(5-chloro-2-furylmethylene) -4- (5-chloro-2-furyl)- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- thione (17_b)

Yield(77%); mp135-137ºC (n-hexane); IR (KBr, ν cm^{-1}) : 3410 (NH), 3350-3310 (NH_2); ^{1}HNMR($CDCl_3$) δ : 12.85 (s, 2H, NH_2), 6.98 – 6.36 (4 d, 4H furan-H), 6.97 (s, H, NH), 7.4-7.1 (m, 5H, aromatic-H), 6.55 (s, 1H,- CH=), 4.45 (s, 1H, pyrimidine –H), 3.4 (s,2H,CH_2Ph), 3.28-3.22 (2d, 4H, 2CH_2, pyridine –H); MS, m/z (%) : MS, m/z (%) : 487 [M^+] (71%), 385.5 [M^+ -C_4H_2OCl] (100%), 284 [385.5 -C_4H_2OCl] (40%), 207[284 –C_6H_5] (25%), 193[207-CH_2] (12%),177[193 –NH_2] (33%). Anal.Calcd% for $C_{23}H_{20}N_4O_2SCl_2$ 487 (found) C 56.67 (56.62) ; H 4.11 (4.10); N 11.50 (11.35); S 6.57(6.51), Cl 14.58 (14.48).

3-Amino-6-benzyl -8-(4-pyridinylmethylene) -4- (4-pyridinyl)- 3,4,5,6,7,8- hexahydropyrido[4,3-d] pyrimidine – 2- thione (21_b)

Yield(72%); mp166-168ºC (ethanol); IR (KBr, ν cm^{-1}) : 3380, (NH), 3350-3310 (NH_2); ^{1}H NMR ($CDCl_3$) δ 12.90 (s, 2H, NH_2), 8.6 – 7. 22 (4d, 8H, pyridine – H), 7.65 (s, 1H, NH), 7.59 (s, 1H, NH), 7.20-7.1 (m, 5H, aromatic-H), 6.63 (s, 1H,- CH=), 4.39 (s, 1H, pyrimidine –H),3.37 (s,2H,CH_2Ph), 3.26-3.2 (2d,4H, 2CH_2, pyridine –H); MS, m/z (%) : MS, m/z (%) : 440 [M^+] (63%), 362 [M^+ -C_5H_4N] (100%), 284 [362 – C_5H_4N] (27%), 207[284 –C_6H_5] (65%), 193[207- CH_2] (31%),177[193 –NH_2] (11%); Anal. Calcd% for $C_{25}H_{24}N_6S$ 440 (found) C 68.18 (68.13); H 5.45 (5.41); N 19.09 (18.90); S 7.27 (7.13).

CONCLUSION

- A simple, efficient and benign methodology for the syntheses of pyridopyrimidinederivatives is described.
- Under microwave irradiation and free-solvent condition, heterocyclic aldehydes, N-substituted acyclic ketones, and compounds containing amide moiety, cyclized to give fused pyrimidines in good yields.
- The biological activity of the compounds prepared in this study has been assessed in screens for antibacterial properties.
- The results reported in this study serve to illustrate the value of diversity oriented synthesis on heterocyclic templates in the discovery of biologically active compounds.

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