ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 3, 192-200

Chemistry & Biology Interface

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Research Paper

Microwave assisted synthesis and biological investigations of novel derivatives of pyrido[2,3-*d*]pyrimidines

Kamlesh Khokhani [*1], Taslim Khatri[2], Vijay Ram[2], Praful Patel[1]

[1]*Department of Chemistry, M M Science College, Morbi – 363 642, Gujarat, India*
[1]*Department of Chemistry, Kachchh University, Bhuj – 370 001, Gujarat, India*
3 April 2013; Accepted 20 June 2013

Keywords: Cyanopyridone; glacial acetic acid; anti bacterial; antifungal activity; microwave methods.

Abstract: A series of novel pyrido[2,3-*d*]pyrimidine was efficiently synthesized in higher yield and it was subjected to antibacterial and antifungal activity. Fourteen different 6-amino-1-(3,4-substituted phenyl)-2-oxo-4-(substituted phenyl)-1,2-dihydropyridine-3,5-dicarbonitrile **(1a-n)** were reacted with glacial acetic acid in presence of catalytic amount of concentrated sulphuric acid under microwave irradiation to obtain pyrido[2,3-*d*]pyrimidine derivatives **2(a-n)**. Purity of all the synthesized compounds was check by TLC. The structure of **2(a-n)** were confirmed by IR, ^{1}H-NMR, mass spectra and elemental analysis and screening against bacterial and fungal species was done using standard drug as reference.

Introduction

Bicyclic nitrogen-containing heterocyclic compounds, such as purines, [1-3] quinazolines, [4-6] pteridines and pyrido-pyrimidines[7-8] are well-known pharmacophore in drug discovery. Pyrido[2,3-*d*]pyrimidines have been the most thoroughly investigated of the four ring systems and hence, this scaffold is associated with a wide range of biological activities, such as dihydrofolate reductase (DHFR) inhibitory activity, antitumor activity, [9-11] adenosine kinase inhibition[12] and tyrosine kinase inhibition. [13]

Corresponding Author*
Email: khokhanikamlesh@gmail.com

In the last few years, most chemists will are using microwave energy for the chemical reactions at the laboratory scale [14-16], not only it reduces chemical reaction time significantly, but also known to reduce side reactions, increases yield and improves reproducibility. Recently Solid supported synthesis of structurally diverse dihydropyrido[2,3-*d*]pyrimidines was also performed using microwave irradiation [17], chemoselective synthesis of the derivatives have also been reported in microwave conditions [18]. Its application ranges from analytical chemistry to biochemistry [19], pathology [20] and medical treatments [21]. Somewhat surprisingly, microwave heating has only been implemented in organic

ISSN: 2249 –4820
Chemistry & Biology Interface, 2013, 3, 3, 192-200

synthesis since the mid-1980s. The first reports on the use of microwave heating to accelerate organic chemical transformations (MAOS) were published by the groups of Richard Gedye [22] and Raymond J. Giguere [23] in 1986. Several other researchers have explored this chemistry in recent years and fairly good reviews and publications are cited in the literature [24-30].

Pyrido[2,3-*d*]pyrimidine have been synthesized by the condensation of compound with thiourea, formamide and arylisocynate respectively [31]. The pyrido[2,3-*d*]pyrimidine having cyano groups at the 6 positions, various pyrido[2,3-*d*]pyrimidine have been reported in the literature.[32]

One of the most popular approaches to construct the pyrimidine ring is *via* synthesis of the suitably substituted ureas and thio ureas. In the first step, the amino group of any heterocyclic moiety is converted into urea by treatment with an isocyanides [33], potassium cyanide hydrochloride [34] or chlorosulfonyl isocyanides [35] and into a thiourea by reaction with an isothiocyanate [36] or thiophosgene and an amine [37]. The resulting ureas and thioureas readily undergo an intramolecular cyclization upon treatment with bases or acids to afford the fused pyrimidine ring systems.

Materials and Methods

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV. All the reactions were carried out in Samsung MW83Y Microwave Synthesizer which was locally modified for carrying out chemical reactions. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GCMS-QP-2010 model using Direct Injection Probe technique. 1H-NMR was determined in DMSO-d6 solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

Experimental

All the 6-amino-1-(3-chloro-4-fluoro phenyl)-2-oxo-4-(substituted phenyl)-1,2-dihydropyridine-3,5-dicarbonitriles and 6-amino-1-(3,4-dichlorophenyl)-2-oxo-4-(substituted phenyl)-1,2-dihydropyridine-3,5-dicarbonitriles **1(a-n)** were prepared by conventional method. The 0.01mole of 3,4-disubstituted cyanoacetamide, 0.01mole of substituted aldehyde and 0.01mole of malononitrile were refluxed for 22 hours on water bath in methanol (20 ml) using piperidine as base catalyst. After completion of the reaction the product was separated by filtration and was recrystallized from methanol.

General procedure for the synthesis of 8-(3,4-substitited phenyl)-2-methyl-4,7-dioxo-5-(substitutedphenyl)-3,4,7,8-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (2a-n):

0.01mole **1(a-n)** was dissolved in 20 ml of acetic acid which was used as a reactant as well as solvent. A few drops of Sulfuric acid were introduced as the acidic catalyst to promote the reaction. The reaction mixture was subjected to MWI for a 20min. at low power (180 W). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature; separated product was

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 3, 192-200

filter wash with methanol and crystallized from DMF.

8-(3-chloro-4-fluorophenyl)-2-methyl-4, 7-dioxo-5-phenyl3,4,7,8-tetrahydro pyrido [2,3-*d]* pyrimidine-6-carbonitrile (2a):

MP: >350^{0}C; IR (cm^{-1}): 3144, 2943, 2223, 1684, 1596, 1249, 715; MS: m/z = 406(M+), 408(M+2); ^{1}H NMR (DMSO-d_6) δppm: 2.19(s, 3H), 7.30-7.40(m, 5H), 7.60(s, 1H), 7.57-7.63(t, 1H), 7.69-7.72(d, 1H), 12.4(s, 1H); Elemental Analysis for $C_{21}H_{12}ClFN_4O_2$: Calculated: C, 62.00; H, 2.97; N, 13.77;%. Found: C, 61.00; H, 2.87; N, 13.67;%.

8-(3-chloro-4-fluorophenyl)-5-(4-methoxyphenyl)-2-methyl-4,7-dioxo-3,4,7,8-tetrahydro pyrido [2,3-*d]* pyrimidine-6-carbonitrile (2b):

MP: 330-335^{0}C; IR (cm^{-1}): 3144, 2943, 2223, 1684, 1596, 1249, 707; MS: m/z = 436(M+), 438(M+2); ^{1}H NMR (DMSO-d_6) δppm: 2.19(s, 3H), 3.84(s, 3H), 7.01-7.04(d, 2H, *j=12 Hz*), 7.28-7.31(d, 2H, *j=12 Hz*), 7.60(s, 1H), 7.57-7.63(t, 1H), 7.69-7.72(d, 1H), 12.7(s, 1H); Elemental Analysis for $C_{22}H_{14}ClFN_4O_3$: Calculated: C, 60.49; H, 3.23; N, 12.83;%. Found: C, 60.29; H, 3.13; N, 12.63; %.

8-(3-chloro-4-fluorophenyl)-5-(2-methoxyphenyl)-2-methyl-4,7-dioxo-3,4,7,8-tetrahydro pyrido [2,3-*d]* pyrimidine-6-carbonitrile (2c):

MP: 325-327^{0}C; IR (cm^{-1}): 3140, 2944, 2225, 1680, 1596, 1249, 705; MS: m/z = 436(M+), 438(M+2); ^{1}H NMR (DMSO-d_6) δppm: 2.15(s, 3H), 3.89(s, 3H), 6.94-6.96(m, 2H), 7.23-7.27(m, 2H), 7.63(s, 1H), 7.57-7.65(t, 1H), 7.69-7.70(d, 1H), 12.4(s, 1H); Elemental Analysis for $C_{22}H_{14}ClFN_4O_3$: Calculated: C, 60.49; H, 3.23; N, 12.83;%. Found: C, 60.39; H, 3.20; N, 12.73;%.

8-(3-chloro-4-fluorophenyl)-5-(4-nitrophenyl)-2-methyl-4,7-dioxo-3,4,7,8-tetrahydro pyrido [2,3-*d]* pyrimidine-6-carbonitrile (2d):

MP: 303-305^{0}C; IR (cm^{-1}): 3141, 2953, 2230, 1684, 1596, 1355, 1249, 707; MS: m/z = 451(M+), 453 (M+2); ^{1}H NMR (DMSO-d_6) δppm: 2.10(s, 3H), 7.43-7.41(d, 2H, *j=8 Hz*), 8.21-8.20(d, 2H, *j=4 Hz*), 7.57(s, 1H), 7.55-7.60(t, 1H), 7.69-7.70(d, 1H), 12.9(s, 1H); Elemental Analysis for $C_{21}H_{11}ClFN_5O_4$: Calculated: C, 55.83; H, 2.45; N, 15.50;%. Found: C, 55.73; H, 2.41; N, 15.40; %.

8-(3-chloro-4-fluorophenyl)-2-methyl-4,7-dioxo-5-(p-tolyl)-3,4,7,8- tetrahydro pyrido [2,3-*d]* pyrimidine-6-carbonitrile (2e):

MP: 342-345^{0}C; IR (cm^{-1}): 3150, 2943, 2219, 1680, 1596, 1249, 700; MS: m/z = 420(M+), 422(M+2); ^{1}H NMR (DMSO-d_6) δppm: 2.09(s, 3H), 2.34(s, 3H), 3.84(s, 3H), 7.10-7.08(d, 2H, *j=8 Hz*), 7.26-7.28(d, 2H, *j=8 Hz*), 7.60(s, 1H), 7.57-7.63(t, 1H), 7.69-7.72(d, 1H), 12.7(s, 1H); Elemental Analysis for $C_{22}H_{14}ClFN_4O_2$: Calculated: C, 62.79; H, 3.35; N, 13.31;%. Found: C, 61.31; H, 3.18; N, 13.17; %.

5-(4-bromophenyl)-8-(3-chloro-4-fluorophenyl)-2-methyl-4,7-dioxo-3,4,7,8-tetrahydro pyrido [2,3-*d]* pyrimidine-6-carbonitrile (2f):

MP: >330^{0}C; IR (cm^{-1}): 3149, 2940, 2232, 1688, 1590, 1249, 703, 642; MS: m/z = 484(M+), 486(M+2), 488(M+4); ^{1}H NMR (DMSO-d_6) δppm: 2.05(s, 3H), 7.55-7.56(d, 2H), 7.28-7.30(d, 2H, *j=8 Hz*), 7.52(s, 1H), 7.57-7.63(t, 1H), 7.69-7.72(d, 1H), 12.0(s, 1H); Elemental Analysis for $C_{21}H_{11}BrClFN_4O_2$: Calculated: C, 51.93; H, 2.28; N, 11.54;%. Found: C, 51.91; H, 2.25; N, 11.52;%.

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 3, 192-200

8-(3-chloro-4-fluorophenyl)-5-(4-chlorophenyl)-2-methyl-4,7-dioxo-3,4,7,8-tetrahydro pyrido [2,3-*d]* pyrimidine-6-carbonitrile (2g):

MP: >330^{0}C; IR (cm^{-1}): 3135, 2943, 2220, 1680, 1596, 1249, 720; MS: m/z = 440(M+), 442(M+2), 444 (M+4); ^{1}H NMR (DMSO-d_6) δppm: 2.11(s, 3H), 7.44-7.46(d, 2H, *j=8 Hz*), 7.30-7.32(d, 2H, *j=8 Hz*), 7.52(s, 1H), 7.57-7.63(t, 1H), 7.69-7.72(d, 1H), 12.7(s, 1H); Elemental Analysis for $C_{21}H_{11}Cl_2FN_4O_2$: Calculated: C, 57.16; H, 2.51; N, 12.70; %. Found: C, 57.08; H, 2.48; N, 12.69; %.

8-(3,4-dichlorophenyl)-2-methyl-4,7-dioxo-5-phenyl-3,4,7,8-tetrahydro pyrido [2,3-*d]* pyrimidine-6-carbonitrile (2h):

MP: 328-330^{0}C; IR (cm^{-1}): 3171, 2943, 2223, 1684, 1501, 719; MS: m/z = 422(M+), 424(M+2), 426(M+4); ^{1}H NMR (DMSO-d_6) δppm: 2.19(s, 3H), 7.30-7.40(m, 5H), 7.38-7.41(d, 1H, *j=12 Hz*), 7.76(s, 1H), 7.81-7.84(d, 1H, *j=12 Hz*), 12.9(s, 1H); Elemental Analysis for $C_{21}H_{12}ClFN_4O_2$: Calculated: C, 62.00; H, 2.97; N, 13.77;%. Found: C, 61.00; H, 2.87; N, 13.67;%.

8-(3,4-dichlorophenyl)-5-(4-methoxyphenyl)-2-methyl-4,7-dioxo-3,4,7,8-tetrahydro pyrido [2,3-*d]* pyrimidine-6-carbonitrile (2i):

MP: >350^{0}C; IR (cm^{-1}): 3173, 2942, 2848, 2223, 1685, 1480, 1170, 814, 733; MS: m/z = 452(M+), 454(M+2), 456(M+4); ^{1}H NMR (DMSO-d_6) δppm: 2.19(s, 3H), 3.84(s, 3H), 7.01-7.04(d, 2H, *j=12 Hz*), 7.28-7.31(d, 2H, *j=12 Hz*), 7.38-7.41(d, 1H, *j=12 Hz*), 7.76(s, 1H), 7.81-7.84(d, 1H, , *j=12 Hz*), 12.7(s, 1H); Elemental Analysis for $C_{22}H_{14}Cl_2N_4O_3$: Calculated: C, 58.29; H, 3.11; N, 12.36; % Found: C, 58.24; H, 3.05; N, 12.30; %.

8-(3,4-dichlorophenyl)-5-(2-methoxyphenyl)-2-methyl-4,7-dioxo-3,4,7,8-tetrahydro pyrido [2,3-*d]* pyrimidine-6-carbonitrile (2j):

MP: 333-335^{0}C; IR (cm^{-1}): 3170, 2945, 2842, 2228, 1683, 1480, 1170, 814, 730; MS: m/z = 452(M+), 454(M+2), 456(M+4); ^{1}H NMR (DMSO-d_6) δppm: 2.10(s, 3H), 3.83(s, 3H), 6.96-7.20 (m, 4H), 7.36-7.39(d, 1H, *j=12 Hz*), 7.71(s, 1H), 7.79-7.82(d, 1H, , *j=12 Hz*), 12.6(s, 1H); Elemental Analysis for C22H14Cl2N4O3: Calculated: C, 58.29; H, 3.11; N, 12.36; Found: C, 58.20; H, 3.09; N, 12.33; %.

8-(3,4-dichlorophenyl)-5-(4-nitrophenyl)-2-methyl-4,7-dioxo-3,4,7,8-tetrahydro pyrido [2,3-*d]* pyrimidine-6-carbonitrile (2k):

MP: 298-300^{0}C; IR (cm^{-1}): 3173, 2942, 2848, 2223, 1685, 1355, 1480, 1170, 814, 733; MS: m/z = 467 (M+), 469(M+2), 471(M+4); ^{1}H NMR (DMSO-d_6) δppm: 2.19(s, 3H), 3.84(s, 3H), 8.21-8.23(d, 2H, *j=8 Hz*), 7.43-7.44(d, 2H, *j=4 Hz*), 7.38-7.41(d, 1H, *j=12 Hz*), 7.76(s, 1H), 7.81-7.84(d, 1H, , *j=12 Hz*), 12.7(s, 1H); Elemental Analysis for C21H11Cl2N5O4: Calculated: C, 53.87; H, 2.37; N, 14.96; %. Found: C, 53.80; H, 2.33; N, 14.91; %.

8-(3,4-dichlorophenyl)-2-methyl-4,7-dioxo-5-(p-tolyl)-3,4,7,8-tetrahydropyrido[2,3-*d]* pyrimidine-6-carbonitrile (2l):

MP: 340-342^{0}C; IR (cm^{-1}): 3173, 2942, 2848, 2223, 1685, 1480, 1170, 814, 733; MS: m/z = 436(M+), 438(M+2); ^{1}H NMR (DMSO-d_6) δppm: 2.09(s, 3H), 2.30(s, 3H), 7.18-7.20(d, 2H, *j=8 Hz*), 7.26-7.27(d, 2H, *j=4 Hz*), 7.60(s, 1H), 7.53-7.54(d, 1H), 7.31-7.32(d, 1H), 12.7(s, 1H); Elemental Analysis for C22H14Cl2N4O2: Calculated: C, 60.43; H, 3.23; N, 12.81; %. Found: C, 60.40; H, 3.21; N, 12.75; %.

5-(4-bromopnenyl)-8-(3,4-dichlorophenyl)-2-methyl-4,7-dioxo-

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 3, 192-200

3,4,7,8-tetrahydro pyrido [2,3-*d]* pyrimidine-6-carbonitrile (2m):

MP: 346-330^{0}C; IR (cm^{-1}): 3173, 2942, 2848, 2223, 1685, 1480, 1170, 814, 723, 642; MS: m/z = 500(M+), 502(M+2), 504(M+4); ^{1}H NMR (DMSO-d_6) δppm: 2.09(s, 3H), 7.01-7.04(d, 2H, *j=12 Hz*), 7.28-7.31(d, 2H, *j=12 Hz*), 7.38-7.41(d, 1H, *j=12 Hz*), 7.76(s, 1H), 7.81-7.84(d, 1H, *j=12 Hz*), 12.7(s, 1H); Elemental Analysis for C21H11BrCl2N4O2: Calculated: C, 50.23; H, 2.21; N, 11.16; %.Found: C, 50.20; H, 2.18; N, 11.10; %.

5-(4-chloropnenyl)-8-(3,4-dichlorophenyl)-2-methyl-4,7-dioxo-3,4,7,8-tetrahydropyrido [2,3-*d]* pyrimidine-6-carbonitrile (2n):

MP: >350^{0}C; IR (cm^{-1}): 3183, 2932, 2847, 2233, 1680, 1482, 1160, 819, 720, MS: m/z = 456(M+), 458(M+2), 460(M+4); ^{1}H NMR (DMSO-d_6) δppm: 2.09(s, 3H), 7.44-7.46(d, 2H, *j=8 Hz*), 7.30-7.32(d, 2H, *j=8 Hz*), 7.38-7.41(d, 1H, *j=12 Hz*), 7.76(s, 1H), 7.81-7.84(d, 1H, , *j=12 Hz*), 12.7(s, 1H); Elemental Analysis for C21H11Cl3N4O2: Calculated: C, 55.11; H, 2.42; N, 12.24; %. Found: C, 55.10; H, 2.41; N, 12.20; %.

Result and discussion

Here in we report the synthesis of 6-amino-1-(3-chloro-4-fluoro phenyl)-2-oxo-4-(substituted phenyl)-1,2-dihydropyridine-3,5-dicarbonitriles and 6-amino-1-(3,4-dichlorophenyl)-2-oxo-4-(substituted phenyl)-1,2-dihydropyridine-3,5-dicarbonitriles **1(a-n)** using the different monosubstituted aromatic aldehyde, cyanoacetamide and malononitrile in presence of catalytic amount of piperidine by conventional method. The intermediate **1(a-n)** reacts with glacial acetic acid in presence of catalytic amount of con. sulphuric acid under microwave condition to give **2(a-n).** The combination of solvent-free reaction conditions and microwave irradiation leads to large reduction in reaction times, enhancement in conversion and sometimes in selectivity with several advantages of the eco-friendly approach, termed green chemistry.

All the synthesized compounds were characterized by spectroscopic methods and elemental analysis. IR spectra of each compound showed CN stretching vibrations for 2223cm^{-1}, while secondary amine and carbonyl of amide shown at 3144 cm^{-1} and 1664 cm^{-1} respectively. In case of ^{1}H-NMR the chemical shift value of secondary amine proton appeared at 12.7 δppm. All the synthesized compounds showed [M+] of 100% intensity as the molecular ion peak. Compound containing chlorine showed isotopic peak at [M+2] of about 33% intensity to that of parent ion peak whereas bromo derivative showed isotopic peak at [M+2] of about equal intensity. The results of elemental analyses were found in good agreement with the calculated values.

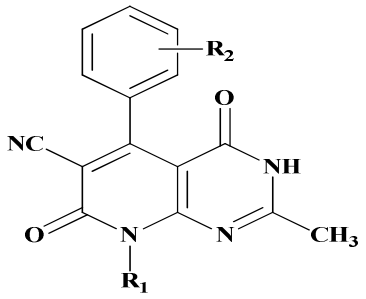
Conclusion

The compounds **2(a-n),** were tested for their antimicrobial activities using three fungal species *Candida albicans, Aspergillus niger, Aspergillus clavatus*, two gram positive bacterial species, *Staphylococcus aureus*, *Streptococcus pyogenes* and two gram negative bacterial species *Escherichia coli*, *Pseudomonas aeruginosa*. The results are depicted in Table 2. The results revealed that all compounds exhibited considerable inhibition action against Gram positive and Gram negative but found inactive against all the fungal fungal.

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 3, 192-200

Table-1 Synthesis of pyrido [2, 3-*d*] pyrimidine derivatives under microwave condition (2a-n).



Code	R_1	R_2	M.F.	M.W. (gm/mole)	M.P.(^{0}C)	% of yield
2a	3-Cl,4-F	H	$C_{21}H_{12}ClFN_4O_2$	406	>350	70
2b	3-Cl,4-F	4-OCH_3	$C_{22}H_{14}ClFN_4O_3$	436	330-335	76
2c	3-Cl,4-F	2-OCH_3	$C_{22}H_{14}ClFN_4O_3$	436	325-327	62
2d	3-Cl,4-F	4-NO_2	$C_{21}H_{11}ClFN_5O_4$	451	303-305	78
2e	3-Cl,4-F	4-CH_3	$C_{22}H_{14}ClFN_4O_2$	420	342-345	72
2f	3-Cl,4-F	4-Br	$C_{21}H_{11}BrClFN_4O_2$	487	>350	60
2g	3-Cl,4-F	4-Cl	$C_{21}H_{11}Cl_2FN_4O_2$	440	>350	71
2h	3,4-diCl	H	$C_{21}H_{12}Cl_2N_4O_2$	422	328-330	68
2i	3,4-diCl	4-OCH_3	$C_{22}H_{14}Cl_2N_4O_3$	452	>350	80
2j	3,4-diCl	2-OCH_3	$C_{22}H_{14}Cl_2N_4O_3$	452	333-335	73
2k	3,4-diCl	4-NO_2	$C_{21}H_{11}Cl_2N_5O_4$	467	298-300	70
2l	3,4-diCl	4-CH_3	$C_{22}H_{14}Cl_2N_4O_2$	436	340-342	60
2m	3,4-diCl	4-Br	$C_{21}H_{11}BrCl_2N_4O_2$	502	346-348	72
2n	3,4-diCl	4-Cl	$C_{21}H_{11}Cl_3N_4O_2$	456	>350	72

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 3, 192-200

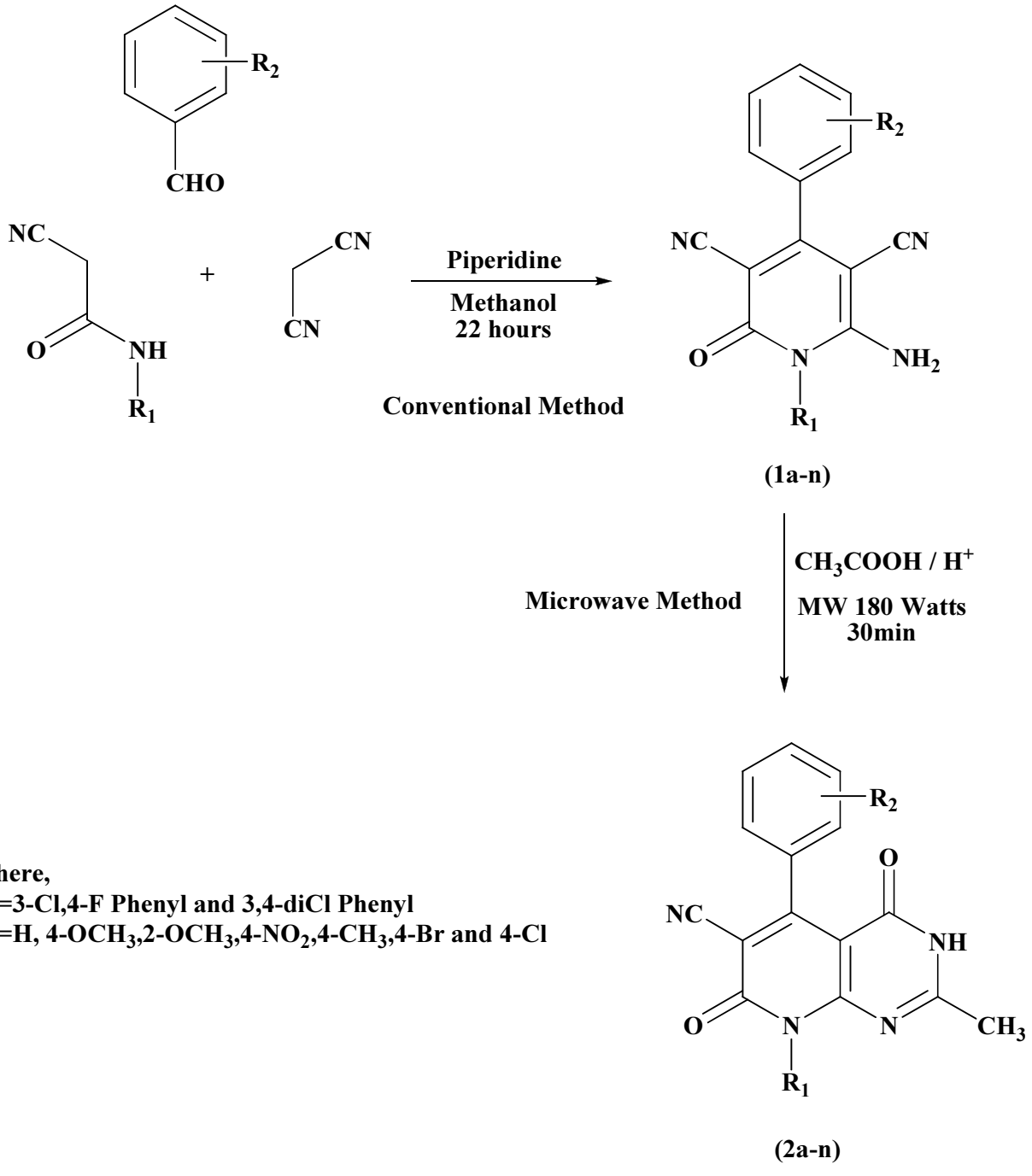
Table-2 Minimal inhibitory concentration (MIC) of all synthesized compounds

Code	S.a.	S.p.	E.c.	P.a.	C.a.	A.n.	A.c.
2a	100	250	200	200	500	>1000	>1000
2b	200	200	100	100	>1000	>1000	>1000
2c	250	250	100	250	500	1000	500
2d	500	500	200	200	1000	500	1000
2e	100	250	200	200	500	>1000	>1000
2f	500	500	62.5	200	>1000	1000	1000
2g	100	62.5	250	250	>1000	100	1000
2h	200	500	250	250	>1000	>1000	>1000
2i	200	250	200	100	500	1000	1000
2j	250	250	100	250	500	1000	500
2k	500	500	200	200	1000	500	1000
2l	100	250	200	200	500	>1000	>1000
2m	100	62.5	250	250	>1000	100	1000
2n	250	200	200	100	250	1000	1000
Ampicillin	250	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Ciprofloxacin	50	50	25	25	-	-	-
Nystatin	-	-	-	-	100	100	100
Greseofulvin	-	-	-	-	500	100	100

Reaction Scheme

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 3, 192-200



Where,
R_1=3-Cl,4-F Phenyl and 3,4-diCl Phenyl
R_2=H, 4-OCH_3,2-OCH_3,4-NO_2,4-CH_3,4-Br and 4-Cl

References

[1] Ding S.; Gray N. S.; X. Wu; Ding Q.; Schultz P., *J. Am. Chem. Soc.* **2002**, *124*, 1594-1596.

[2] Raboisson P.; Lugnier C.; Muller C.; Reimund J. M.; Schultz D.; Pinna G.; Le Bec A.; Basaran H.; Desaubry L.; Gaudiot F.; Seloum M.; Bourguignon J. J., *Eur. J. Med. Chem.* **2003**, *38*, 199-214.

[3] Manikowski A.; Verri A.; Lossani A.; Gebhardt B. M.; Gambino J.; Focher F.; Spadari S.; Wright G. E., *J. Med. Chem.* **2005**, *48*, 3919-3929.

[4] Pandey A.; Volkots D. L.; Seroogy J. M.; Rose J. W.; J. Yu; Lambing J. L.; Hutchaleelaha A.; Hollenbach S. J.; Abe K.; Giese N. A.; Scarborough R. M., *J. Med. Chem.* **2002**, 45, 3772-3793.

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 3, 192-200

[5] Antonello A.; Hrelia P.; Leonardi A.; Marucci G.; Rosini M.; Tarozzi A.; Tumiatti V.; Melchiorre C., *J. Med. Chem*. **2005**, 48, 28-31.
[6] Bathini Y.; Singh I.; Harvey P. J.; Keller P. R.; Singh R.; Micetich R. G.; Fry D. W.; Dobrusin E. M.; Toogood P. L., *Bio org. Med. Chem. Lett*. **2005**, 15, 3881-3885.
[7] Quintela J. M.; Peinador C.; Botana L.; Estevez M.; Riguera R., *Bio org. Med. Chem.* **1997**, 5, 1543-1553.
[8] Rosowsky A.; Chen H.; Fu H.; Queener S., *Bioorg. Med. Chem.* **2003**, 11, 59-67.
[9] Kovacs J. A.; Allegra C. J.; Swan J. C.; Parillo J. E.; Chabner B. A.; Masur H., *Antimicrob. Agents Chemother*. **1988**, *32*, 430-433.
[10] Gangjee A.; Adair O.; Queener S. F., *J. Med. Chem.* **1999**, *42*, 2447-2455.
[11] Gangjee A.; Adair O. O.; Queener S. F., *J. Med. Chem.* **2003**, *46*, 5074-5082.
[12] Lee K.; Jiang M.; Cowart M.; Gfesser G.; Perner R.; Kim K. H.; Gu Y. G; Williams M.; Jarvis M. F.; Kowaluk E. A.; Stewart A. O; Bhagwat S. S., *J. Med. Chem.* **2001**, 44, 2133-2138.
[13] Trumpp-Kallmeyer S.; Rubin J. R.; Humblet C.; Hamby J. M.; Showalter H. D. H., *J. Med. Chem*. **1998**, 41, 1752-1763.
[14] Leadbeater, N. *Chemistry World*, **2004**, *1*, 38.
[15] Adam, D. *Nature*, **2003**, *421*, 571.
[16] Anu, A.; Sharad, P.;Prem M. S. C., Letters in Organic Chemistry, **2006, 3,** 712.
[17] Anu, A.; Prem M.S.C.; Tetrahedron Lett., **2005**, 46,1345.
[18] Shujiang, T.; Chunmei, L.; Feng, S.; Dianxiang, Z.; Qingqing, S.; Longji, C.; Synthesis **2008**, 3, 369.
[19] Kingston, H. M.; Haswell S. J. *Microwave-Enhanced Chemistry: Fundamentals, Sample preparation and Applications, American Chemical Society*: Washington DC, Eds. **1997.**
[20] Giberson, R. T.; Demaree R. S. (Eds.) *Microwave Techniques and Protocols*, Humana Press: Totowa, New Jersey, **2001**.
[21] Prentice, W. E. *Therapeutic Modalities for Physical Therapists*, McGraw-Hill: New York, **2002**.
[22] Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279.
[23] Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945.
[24] Saeed, A., Sharma, A.P., Durani, N., Jain, R., Durani, S., Kapil, R.S. (**1990**) *J. Medicinal Chem.*, 95, p. 3626.
[25] Vishnu, J.R., Monika, V. **1994** *Indian J. Chem.*, 33 B, p. 808.
[26] El-Gaby, M.S.A., Zahran, M.A., Ismail, M.M.F., Ammar, Y.A. A novel synthesis of dibenzo[c,f]chromenes, dibenzo[c,h]chromenes and benzo[7,8]chromeno[3,4-f]isoindoles as anti-microbial agents **2000**, *Farmaco*, 55 (3), pp. 227-232.
[27] El-Agrody, A.M., El-Hakim, M.H., Abd El-Latif, M.S., Fakery, A.H., El Sayed, E.-S.M., El-Ghareab, K.A. Synthesis of pyrano[2,3-*d]*pyrimidine and pyrano[3,2-e][1,2,4]triazolo[2,3-c]pyrimidine derivatives with promising antibacterial activities **2000** *Acta Pharmaceutica*, 50 (2), pp. 111-120.
[28] El-Agrody, A.M., Eid, F.A., Emam, H.A., Mohamed, H.M., Bedair, A.H. Synthesis of 9-methoxy and 9-acetoxy-3-amino-1-(4-methoxyphenyl)-1H benzo[f]chromene-2-carbonitriles via 2-(imino-piperidin-1-yl-methyl)-3-(4 methoxyphenyl)acrylonitrile as intermediate **2002** *Zeitschriftfur Naturforschung - Section B Journal of Chemical Sciences*, 57 (5), pp. 579 585.
[29] Ammar, Y.A., Ismail, M.M.F., El-Gaby, M.S.A., Zahran, M.A. Some reactions with quinoxaline-2,3-dicarboxylic acid anhydride: Novel synthesis of thieno[2,3-*d]*pyrimidines and pyrrolo [3,4-b]quinoxalines as antimicrobial agents **2002** *Indian Journal of Chemistry - Section B Organic and Medicinal Chemistry*, 41 (7), pp. 1486-1491.
[30] Shaker, R.M. Synthesis and reactions of some new 4H-pyrano[3,2- c]benzopyran-5-one derivatives and their potential biological activities **1996** *Pharmazie*, 51 (3), pp. 148-151.
[31] Sangeeta Tiwari, Ashok K. Yadav & Mishra A. K. *E-Journal of Chemistry*, **2010**, 7(S1), S85-S92.
[32] Nikolai, M.; Igor, M. S. Artem, 2006, 8(5), 899-902.
[33] Russel, P. K.; Press, J. B.; Rampulla, R. A.; McNally, J. J.; Falotico, R.; Keiser, J. A.; Brigcht, D. A.; Tobia, A. *J. Med. Chem.* **1988**, 31, 1786.
[34] Croisier, P. BE769843, **1992**.
[35] Wamhoff, H.; Ertas, M. *Synthesis* **1985**, 190.
[36] Ibrachim, Y. A.; Elwahy, A. H. M.; Kadry, A. M. *Adv. Heterocycl. Chem.* **1996**, 65, 235
[37] Boehm, R.; Mueller, R.; Pech, R. *Pharmazie* **1990**, 45, 827.