Research Article

Synthesis and Antitubercular Activity of Some Novel {1[(1phenylethylidene) amino] naphtho [2,1-B]furan-2- yl}4-substituted pyrimidin-2-amine Derivatives

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ABSTRACT

4-{1- [(1-phenylethylidene) amino] naphtha [2,1-b] furan-2-yl} 4-(4- substituted) pyrimidin-2-amine derivatives(4a-4j) were synthesized by the cyclization of guanidine and various chalcone s(3) which were synthesized by the condensation of 1-(1-{[(1*Z*)-1-phenylethylidene]amino}naphtho[2,1-*b*]furan-2-yl)ethanone (2) with various substituted aromatic aldehydes. 1-(1-{[(1*Z*)-1-phenylethylidene]amino}naphtho[2,1-*b*]furan-2-yl)ethanone (2) were synthesized by the condensation of 1-(1-aminonaphtho[2,1-*b*]furan-2-yl)ethanone (1) with acetophenone. The startingmaterial2-hydroxy-1-naphthonitrile was treated with chloroacetone and anhydrous potassium carbonate to give 1-(1-aminonaphtho[2,1-*b*]furan-2-yl)ethanone (1). All newly synthesized compounds has been developed under conventional heating and microwave irradiation. The structures of the newly synthesized compounds were established on the basis of elemental and spectral (IR, ^{1}H NMR and Mass) studies. Further newly synthesized compounds were showed moderate to potent antitubercular activity.

Keywords: Pyrimidine-2-amine, Microwave Irradiation, Antitubercular activity.

INTRODUCTION

Pyrimidine is the most important member of all the diazine as this ring system occurs widely in living organisms. Pyrimidine is a versatile lead molecules for a broad range of biological effects, including antifungal,[1]anti-inflammatory,[2] cardiovascular,[3]analgesic,[4] antiviral,[5] antimalarial,[6]antioxidant,[7] antimicrobial,[8] anthelmintic,[8] anti-HIV,[9] antitumor,[10] activities has been ascribed to these partly reduced pyrimidine derivatives. Additionally, dihydropyrimidines have been found active to transport medication across biological membranes. Several marine alkaloids containing the DHPMs is founding nature and in potent HIV-gp-120-CD4 inhibitors. In recent years microwave assisted organic synthesis has gained the popularity among the organic chemists due to their reduced reaction time, ecofriendliness, enhanced selectivity and better workup procedures.[11] Our research group has been interested in the synthesis of some novel {1[(1phenylethylidene) amino] naphtho [2,1-*b*]furan-2-yl}4-Substituted pyrimidin-2-amine derivatives using microwave irradiation and their antitubercularactivity.

MATERIALS AND METHODS

All reagents and solvents used were of laboratory (LR) grade and were obtained from SD fine chemicals (Mumbai, India), Merck (Mumbai, India) and Sigma-Aldrich (Mumbai, India) and were used without further purification. Precoated silica gel F_{254} plates, obtained from Merck (Mumbai, India), were used for analytical and preparative TLC. Melting points were determined in an open capillary tube on Chemline CL726 melting point apparatus and were uncorrected. IR spectra were recorded on a Shimadzu FT-IR 157 spectrophotometer using KBr pellets. ^{1}HNMR (δ, ppm) spectra were recorded onBruker advance III 500 MHz NMR spectrophotometer in $CDCl_3$ or DMSO-d_6. In the ^{1}H NMR spectra was used TMS as internal reference. Mass spectra were obtained on a Shimadzu GC-MS QP 2010 mass spectrometer. Elemental analyses were performed on a ElementarVario EL III analyzer.

General procedure of 1-(1-aminonaphtho[2,1-*b*]furan-2-yl)ethanone (1)

To a solution of 2-hydroxy-1-naphthonitrile (0.02 mol) in dry acetone (100ml), chloroacetone (0.02 mol) and anhydrous potassium carbonate (0.2 mol) were added and the reaction mixture was refluxed on water bath for 8 hr. The potassium salt was filtered off and washed thoroughly with acetone. Removal of solvent from the filtrate and recrystallized from ethanol. The yield of the product was 89% and M.P 187-190°C.

General procedure of 1-(1-{[1-Phenyl ethylidene]amino} naphtho[2,1-*b*]furan-2-yl)ethanone (2)

A mixture of compound (1) (0.01 mol), appropriate acetophenone (0.01 mol) and DMF (5drops) was subjected to microwave irradiation at 200 watts intermittently at 10 sec intervals for specified time. On completion of reaction (monitored by TLC), the reaction mixture was cooled and digested with water. The solid obtained was filtered and recrystallized from ethanol. The yield of the product was 78% and M.P 203-207°C.

General procedure of substituted chalcone (3)

Equimolar quantities (0.01 mol) of Aromatic aldehyde and compound (2) (0.01 mol) were taken in 100ml conical flask and dissolved in 20ml of ethanol to this (0.03 mol) of

NaOH in minimum quantity of water was added. The mixture was stirred on a magnetic stirrer and the reaction was monitored with TLC. Reaction mixture was diluted with water and acidified with concentrated hydrochloric acid. The precipitated chalcone was filtered and recrystallized from absolute ethanol. The yield of the product was 69% and M.P 195-200°C.

General procedure of 4-{1- [(1-phenylethylidene) amino] naphtha [2,1-b] furan-2-yl} 4-(4- substituted) pyrimidin-2-amine derivatives (4a-4j)

Conventional method

A compound (3) (0.01 mol) and guanidine hydrochloride (0.01 mol) were dissolved in absolute alcohol (20 ml). Few drops of concentrated HCl were added and the reaction mixture was refluxed and the reaction was monitored by TLC. After completion of reaction, it was poured into 250ml of ice cold water and kept for some time. The crude solid was filtered and subjected to column chromatography. Elution with solvent ethyl acetate/petroleum ether (60-80°) gave pure compound and recrystallized from appropriate solvent.

Microwave Assisted Method

The condensation of the compound (3) (0.001 mol) with guanidine hydrochloride (0.001 mol) in alkaline medium *viz*, in potassium hydroxide (0.003 mol) in the presence of ethanol (10 mL), the entire reaction mixture was microwave irradiated at 180 watts for about 2-16 minutes, then kept aside for 2-3hrs, resulted the formation of corresponding pyrimidine derivatives Reaction completion was identified by TLC precoated plates and recrystallized from appropriate solvent.

{1[(1phenylethylidene) amino] naphtho [2,1-*b*]furan-2-yl}4-phenyl pyrimidin-2-amine (4a)

M.P 182-185°C.IR: 3254.02 cm^{-1}(N-H str), 2989.76 cm^{-1}(ArC-H str), 2837.38 cm^{-1}(Al C-H str),1294.28 cm^{-1}(C-C str), 1681.98 cm^{-1}(C=Nstr),1626.05 cm^{-1}(C=C str),1421.58 cm^{-1}(C-Nstr), 1058.96 cm^{-1}(C-O-Cstr).^{1}HNMR(CDCl3): 6.49(s,2H,NH_2) D_2O exchangable, 1.84(s,3H,CH_3),7.57-8.52(m,17H,Ar-H).MS: *m/z* 455 (M^+); Anal. Calcd. for$C_{30}H_{22}N_4O$: C, 79.27; H, 4.88; N, 12.33. Found: C, 79.29; H, 4.90; N, 12.36%.

{1[(1phenylethylidene) amino] naphtho [2,1-*b*]furan-2-yl}4-(4-methoxy phenyl) pyrimidin-2-amine (4b)

M.P 172-175°C.IR: 3259.81 cm^{-1}(N-H str), 2956.97 cm^{-1}(Ar C-H str), 2839.31 cm^{-1}(Al C-H str),1292.35 cm^{-1}(C-C str),1683.91 cm^{-1}(C=N str),1626.05 cm^{-1}(C=C str),1427.37 cm^{-1}(C-N str),1058.95 cm^{-1}(C-O-C str).^{1}HNMR(CDCl3): 6.70(s,2H,NH_2) D_2O exchangable, 1.92(s,3H,CH_3), 3.48(s,3H,OCH_3),6.70-8.88(m,16H,Ar-H).MS: *m/z* 484 (M^+); Anal. Calcd. for$C_{31}H_{24}N_4O_2$: C, 76.84; H, 4.99; N, 11.56. Found: C, 76.87; H, 5.12; N, 11.59%.

{1[(1phenylethylidene) amino] naphtho [2,1-*b*]furan-2-yl}4--(2-chloro phenyl)pyrimidin-2-amine (4c)

M.P 188-192°C.IR: 3259.81 cm^{-1}(N-H str), 2978.19 cm^{-1}(Ar C-H str), 2845.10 cm^{-1}(Al C-H str), 1269.20 cm^{-1}(C-C str), 1685.84 cm^{-1}(C=N str), 1624.12 cm^{-1}(C=C str), 1427.37 cm^{-1}(C-N str), 1057.96 cm^{-1}(C-O-C str) , 717.54 cm^{-1}(C-Clstr). ^{1}HNMR(CDCl3): 6.79(s,2H,NH_2) D_2O exchangable, 1.92(s,3H,CH_3), 6.86-8.88(m,16H,Ar-H).MS: *m/z* 490(M+1); Anal. Calcd. for$C_{30}H_{21}ClN_4O$: C, 73.69; H, 4.33; N, 11.46. Found: C, 73.71; H, 4.35; N, 11.49%.

{1[(1phenylethylidene) amino] naphtho [2,1-*b*]furan-2-yl}4--(2-hydroxy phenyl)pyrimidin-2-amine (4d)

M.P 160-162°C.IR: 3490.87 cm^{-1}(O-H str),3194.23 cm^{-1}(N-H str), 2972.40 cm^{-1}(Ar C-H str), 2860.53 cm^{-1}(Al C-H str), 1261.49 cm^{-1}(C-C str), 1658.84 cm^{-1}(C=N str), 1597.11 cm^{-1}(C=C str), 1446.66 cm^{-1}(C-N str), 1070.53 cm^{-1}(C-O-C str).^{1}HNMR(CDCl3): 6.79(s,2H,NH_2) D_2O exchangeable, 1.86(s,3H,CH_3),9.06(s,1H,OH),6.86-8.88(m,16H,Ar-H).MS: *m/z* 471(M+1); Anal. Calcd. for$C_{30}H_{22}N_4O_2$: C, 76.58; H, 4.71; N, 11.91. Found: C, 76.59; H, 4.74; N, 11.95%.

{1[(1phenylethylidene) amino] naphtho [2,1-*b*]furan-2-yl}4--(2-hydroxy naphthyl)pyrimidin-2-amine (4e)

M.P 150-155°C.IR: 3548.89 cm^{-1}(O-H str),3192.30 cm^{-1}(N-H str), 2976.26 cm^{-1}(Ar C-H str), 2862.46 cm^{-1}(Al C-H str), 1261.49 cm^{-1}(C-C str), 1658.84 cm^{-1}(C=N str), 1593.25 cm^{-1}(C=C str), 1473.66 cm^{-1}(C-N str), 1134.18 cm^{-1}(C-O-C str).^{1}HNMR(CDCl3): 6.70(s,2H,NH_2) D_2O exchangeable, 1.85(s,3H,CH_3),9.87(s,1H,OH),6.72-8.88(m,18H,Ar-H).MS: *m/z* 520.4(M^+); Anal. Calcd. for$C_{34}H_{24}N_4O_2$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.49; H, 4.68; N, 10.79%.

{1[(1phenylethylidene) amino] naphtho [2,1-*b*]furan-2-yl}4--(4-bromo phenyl)pyrimidin-2-amine (4f)

M.P 156-161°C.IR: 3196.15 cm^{-1}(N-H str), 2953.12 cm^{-1}(Ar C-H str), 2858.60 cm^{-1}(Al C-H str), 1251.84 cm^{-1}(C-C str), 1662.69 cm^{-1}(C=N str), 1595.18 cm^{-1}(C=C str), 1429.30 cm^{-1}(C-N str), 1068.60 cm^{-1}(C-O-C str),651.96 cm^{-1} (C-Br str). ^{1}HNMR (CDCl3): 6.85(s,2H,NH_2) D_2O exchangeable 2.67(s,3H,CH_3), 7.08-8.33(m,16H,Ar-H). MS: *m/z* 535.3 (M+2); Anal. Calcd. for$C_{30}H_{21}BrN_4O$: C, 67.55; H, 3.97; N, 10.50. Found: C, 67.58; H,3.10; N, 10.54%.

{1[(1phenylethylidene) amino] naphtho [2,1-*b*]furan-2-yl}4--(4-N,N dimethyl amino phenyl) pyrimidin-2-amine (4g)

M.P 166-168°C.IR: 3196.15 cm^{-1}(N-H str), 2974.33 cm^{-1}(Ar C-H str), 2806.52 cm^{-1}(Al C-H str), 1269.20 cm^{-1}(C-C str), 1656.91 cm^{-1}(C=N str), 1597.11 cm^{-1}(C=C str), 1413.87 cm^{-1}(C-N str), 1072.46 cm^{-1}(C-O-C str).^{1}HNMR(CDCl3): 6.70(s,2H,NH_2) D_2O exchangeable, 1.80(s,3H,CH_3), 2.45(s,3H,CH_3), 6.72-8.87(m,16H,Ar-H).MS: *m/z* 497 (M^+); Anal. Calcd. for$C_{32}H_{27}N_5O$: C, 77.24; H, 5.47; N, 14.07. Found: C, 77.27; H, 5.49; N, 14.10%.

{1[(1phenylethylidene) amino] naphtho [2,1-*b*]furan-2-yl}4--(4-hydroxy3-methoxyphenyl) pyrimidin-2-amine (4h)

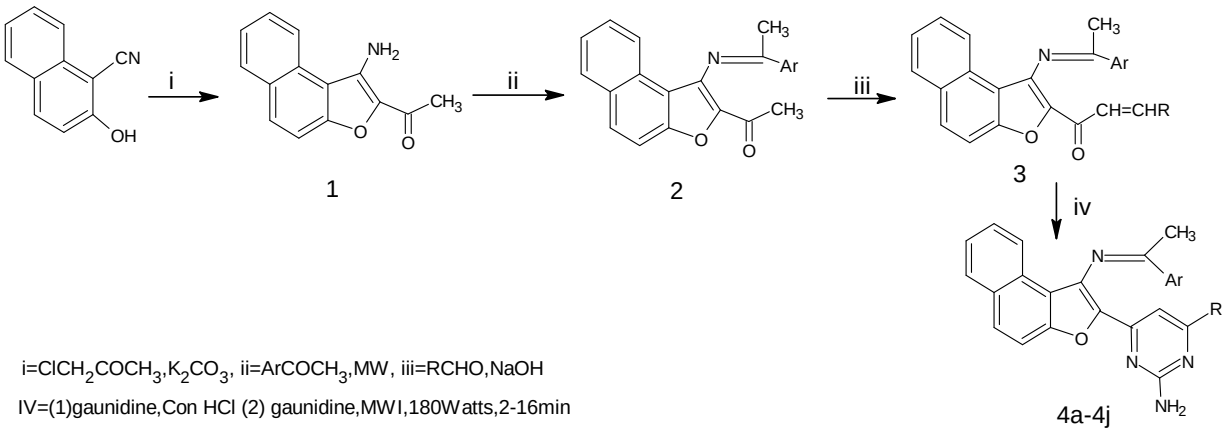
M.P 145-148°C.IR: 3473.66 cm^{-1}(O-H str),3151.79 cm^{-1}(N-H str), 2904.89 cm^{-1}(Ar C-H str), 2808.45 cm^{-1}(Al C-H str), 1267.27 cm^{-1}(C-C str), 1666.91 cm^{-1}(C=N str), 1595.18 cm^{-1}(C=C str), 1415.80 cm^{-1}(C-N str), 1070.53 cm^{-1}(C-O-C str). ^{1}HNMR(CDCl3): 7.26(s,2H,NH_2) D_2O exchangeable, 1.59(s,3H,CH_3), 3.72(s,1H,OCH_3),9.67(s,1H,OH),7.43-8.48(m,15H,Ar-H).MS: *m/z* 500 (M^+); Anal. Calcd. for$C_{31}H_{24}N_4O_3$: C, 74.39; H, 4.83; N, 11.19. Found: C, 74.42; H, 4.86; N, 11.21%.

{1[(1phenylethylidene) amino] naphtho [2,1-*b*]furan-2-yl}4- --(3,4,5-trimethoxy phenyl)pyrimidin-2-amine (4i)

M.P 196-201°C.IR: 3194.23 cm^{-1}(N-H str), 2970.48 cm^{-1}(Ar C-H str), 2843.17 cm^{-1}(Al C-H str), 1249.91 cm^{-1}(C-C str), 1656.93 cm^{-1}(C=N str), 1595.18 cm^{-1}(C=C str), 1467.88 cm^{-1}(C-N str), 1072.46 cm^{-1}(C-O-C str). ^{1}HNMR(CDCl3): 6.75(s,2H,NH_2) D_2O exchangeable, 1.89(s,3H,CH_3), 3.17(s,3H,OCH_3),7.09-7.84(m,14H,Ar-H).MS: *m/z* 545 (M+1); Anal. Calcd. for$C_{33}H_{28}N_4O_4$: C, 72.78; H, 5.18; N, 10.29. Found: C, 72.79; H, 5.19; N, 10.31%.

{1[(1phenylethylidene) amino] naphtho [2,1-*b*]furan-2-yl}4---(4-methyl phenyl)pyrimidin-2-amine (4j)

M.P 139-142°C.IR: 3200.01 cm^{-1}(N-H str), 2978.19 cm^{-1}(Ar C-H str), 2821.95 cm^{-1}(Al C-H str), 1259.56 cm^{-1}(C-C str), 1660.77 cm^{-1}(C=N str), 1600.97 cm^{-1}(C=C str), 1491.02 cm^{-1}(C-N str), 1076.32 cm^{-1}(C-O-C str). ^{1}HNMR(CDCl3): 7.22(s,2H,NH_2) D_2O exchangeable, 1.52(s,3H,CH_3), 2.5(s,3H,OCH_3),7.24-7.81(m,16H,Ar-H).MS: *m/z* 469 (M+1); Anal. Calcd. for$C_{31}H_{24}N_4O$: C, 79.46; H, 5.16; N, 11.96. Found: C, 79.48; H, 5.18; N, 11.99%.



i=ClCH$_2$COCH$_3$,K$_2$CO$_3$, ii=ArCOCH$_3$,MW, iii=RCHO,NaOH

IV=(1)gaunidine,Con HCl (2) gaunidine,MWI,180Watts,2-16min

Ar=phenyl ,R=4-OMeC$_6$H$_5$-, C$_6$H$_5$-,2-ClC$_6$H$_5$-,2-OHC$_6$H$_5$-, 2-OHC$_{10}$H$_6$-, 4-(CH$_3$)$_2$NC$_6$H$_5$-,4-Br C$_6$H$_5$-,3-OMe 4-OHC$_6$H$_5$-, 3,4,5-OMeC$_6$H$_5$-, 4-CH$_3$C$_6$H$_5$-

Scheme 1 Synthetic route of Compounds 4a-4j

RESULTS AND DISCUSSION

A mixture of chalcone and guanidine in ethanol in presence alkaline medium i.e. potassium hydroxide under microwave irradiation resulted in the formation of final product. This present route, besides being advantageous in simple reaction conditions and easy work-up procedures, less time consuming and eco-friendly, has resulted in better yields over the conventional methods. All the three synthetic methods are compared in terms of yield and reaction time. All the synthesized compounds (4a-4j) were screened for their antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ by the broth dilution method according to recommended procedure by the National Committee for Clinical Laboratory Standards for the determination of minimum inhibitory concentration (MIC). The results of antitubercular activity are shown in Table 2.The investigation of antitubercular screening revealed that some of the tested compounds 4b, 4c and 4hshowed moderate to good antitubarcular activity.

Table 1: Comparison Between Various Synthetic Methods of {1[(1phenylethylidene) amino] naphtho [2,1-*b*]furan-2-yl}4-Substituted pyrimidin-2-amine derivatives.(4a-4j)

Compds.	Conventional method		Microwave assisted method	
	Reaction time (hr)	% Yield*	Reaction time (min)	% Yield*
4a	6.0	67	5.0	73
4b	6.0	52	5.5	67.8
4c	6.0	57	4.5	70.4
4d	6.0	53	5.5	65.3
4e	6.0	50.6	10	70.2
4f	6.0	47.3	6.5	63.8
4g	6.0	56	6.5	77
4h	6.0	55	5.0	64.2
4i	6.0	53	6.0	66
4j	6.0	45	6.5	61.7

* Yield refers to pure isolated products

Table 2 Antitubercular activity of 4{1[(1phenylethylidene) amino] naphtha [2, 1-*b*]furan-2-yl}4-Substituted pyrimidin-2-amine derivatives**.**(4a-4j)

Compds.	MIC (µg/mL) Acid fast *M. tuberculosis*
4a	>100
4b	50
4c	100
4d	>100
4e	>100
4f	>100
4g	>100
4h	100
4i	>100
4j	>100

CONCLUSION

A simple, quick and efficient method for the synthesis of 4{1[(1phenylethylidene) amino] naphtha [2, 1-*b*]furan-2-yl}4-Substituted pyrimidin-2-amine derivatives by condensation of Chalcone and guanidine in presence of con. HCl has been developed. Ease of separation of pure product, selectively and in high yields. A novel, microwave assisted eco-friendly convenient route, for the synthesis 4{1[(1phenylethylidene) amino] naphtha [2, 1-*b*]furan-2-yl}4-Substituted pyrimidin-2-amine derivatives has been developed which gave excellent yields in short reaction times.

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