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RESEARCH ARTICLE

New Contrive Protocol for Synthesis of Pyrimidine Derivatives

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ABSTRACT

Synthesis of a series of ***4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-N-(substituted-phenyl)-2-thiooxopyrimidine-5-carboxamide***. ***(4a-j)*** was achieved from different N-(substituted phenyl)-4-methyl-3-oxopentanamide, 2-chloro-6-fluorobenzaldehyde and thiourea using few drops of conc. hydrochloric acid added and refluxed with ethanol so to the fine yield. The structures of the products were supported by FTIR, ^{1}H NMR and mass spectral data.

KEYWORDS

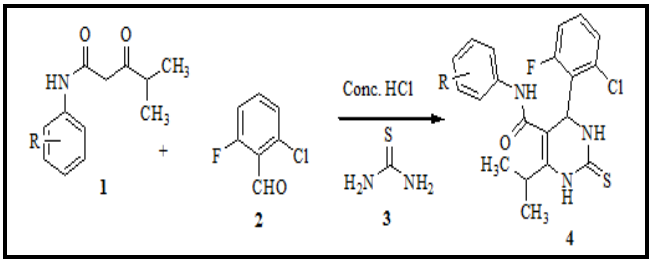
2-Chloro-6-Fluorobenzaldehyde; Hydrochloric Acid, Thiourea Only Refluxed

INTRODUCTION

1,2,3,4-Tetrahydropyrimidine (DHPM) calcium channel blockers are important class of drugs which induce relaxation of vascular smooth muscle, preferentially in arteries, and display a negative inotropic effect on isolated cardiac muscle[1]. They exert these effects by binding to a high affinity binding site in L-type voltage dependent Ca^{2+} channels[2]. So, this class of drug is effective in the treatment of hypertension, angina pectoris and other cardiovascular disorder[3].

DHPMs may lead to other beneficial effects such as regression of left ventricular pressure and vascular hypertrophy, renal protection, weak anti-platelet, anti-ischemic and anti- atherogenic activity[4-7]. Several marine natural products with interesting biological activities containing pyrimidine core have recently been isolated[8]. Most notably among these are the batzelladine alkaloids A and B which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy.

Dihyropyrimidine is a bioisoster of Dihydropyridine which shows very good calcium channel blocking activity and antihypertensive activity. 4-thiazolidinones and its arylidene derivatives possess good pharmacological properties[9,10]. Also these compounds are known to exhibit antitubercular[11], antibacterial[12] and antifungal[13] activities. We have developed a new decorum for the synthesis 4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-N-(substitutedphenyl)-2-thioxopyrimidine-5-carboxamide ***(4a-j)*** with the advantage of fine yield and environmentally easiness (**Scheme-1**).



Scheme 1

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EXPERIMENTAL

To the mixture of N-(substituted phenyl)-4-methyl-3-oxopentanamide, 2-chloro-6-fluoro-benzaldehyde and thiourea in 10 ml ethanol was added one/two drops of Conc. HCl with stirring for 20 hrs. at ambient temperature. After 20 hrs total reaction mass pour in water, Insoluble solid was generated, then filter and crystallization by ethanol.

4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-N-(2-methoxyphenyl)-2-thioxo pyrimidine-5-carboxamide (4a)

Yield: 58%; mp 177ºC; Anal. Calcd. for $C_{21}H_{21}ClFN_3O_2S$: C, 58.13; H, 4.88; Cl, 8.17; F, 4.38; N, 9.68; O, 7.37; S, 7.39; Found: C, 58.10; H, 4.91; Cl, 8.15; F, 4.40; N, 9.70; O, 7.35; S, 7.38%; IR (cm^{-1}): 3323 (N-H stretching of amide), 3094 (C-H stretching of aromatic ring), 2946 (C-H asymmetrical stretching of CH_3 group), 2875 (C-H symmetrical stretching of CH_3 group), 1650 (C=O stretching of amide), 1593 (N-H deformation of pyrimidine ring), 1521 (C=C stretching of aromatic ring), 1485 (C-H asymmetrical deformation of CH_3 group), 1410 (C-H symmetrical deformation of CH_3 group), 1341 (C-N-C stretching vibration of pyrimidine ring), 1276 (C-O-C stretching), 1191 (C=S stretching), 1106 (C-F stretching), 1065 (C-H in plane deformation of aromatic ring), 831 (para-substituted), 785 (C-H in out plane deformation of aromatic ring), 668 (C-Cl stretching); ^1H NMR (DMSO-*d6*) δ ppm: 1.17 (s, 3H, H), 1.18 (s, 3H, H), 3.52-3.54 (m, 1H, H), 3.98 (s, 3H, H), 6.51 (s, 1H, H), 6.83-6.89 (m, 3H, H), 7.19-7.23 (m, 2H, H), 7.54-7.57 (m, 2H, H), 8.53 (s, 1H, H), 10.05 (s, 1H, H), 10.08 (s, 1H, H); MS: *m/z* 434.

4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-N-(3-methoxy -phenyl)-2-thioxo pyrimidine-5-carboxamide (4b)

Yield: 61%; mp 174ºC; Anal. Calcd. for $C_{21}H_{21}ClFN_3O_2S$: C, 58.13; H, 4.88; Cl, 8.17; F, 4.38; N, 9.68; O, 7.37; S, 7.39; Found: C, 58.10; H, 4.85; Cl, 8.19; F, 4.37; N, 9.70; O, 7.39; S, 7.40%; IR (cm^{-1}): 3398 (N-H stretching of amide), 3100 (C-H stretching of aromatic ring), 2978 (C-H asymmetrical stretching of CH_3 group), 2856 (C-H symmetrical stretching of CH_3 group), 1649 (C=O stretching of amide), 1576 (N-H deformation of pyrimidine ring), 1519 (C=C stretching of aromatic ring), 1459 (C-H asymmetrical deformation of CH_3 group), 1401 (C-H symmetrical deformation of CH_3 group), 1346 (C-N-C stretching vibration of pyrimidine ring), 1242 (C-O-C stretching), 1106 (C=S stretching), 1091 (C-F stretching), 1003 (C-H in plane deformation of aromatic ring), 838 (para-substituted), 767 (C-H in out plane deformation of aromatic ring), 658 (C-Cl stretching); ^1H NMR (DMSO-*d6*) δ ppm: 1.12 (s, 3H, H), 1.14 (s, 3H, H), 3.53-3.57 (m, 1H, H), 3.80 (s, 3H, H), 6.51 (s, 1H, H), 6.87-6.89 (m, 2H, H), 7.13-7.16 (m, 2H, H), 7.41 (s, 1H, H), 7.54-7.58 (m, 2H, H), 8.50 (s, 1H, H), 10.01 (s, 1H, H), 10.07 (s, 1H, H); MS: *m/z* 434.

4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-N-(4-methoxy -phenyl)-2-thioxo pyrimidine-5-carboxamide (4c)

Yield: 51%; mp 172ºC; Anal. Calcd. for $C_{21}H_{21}ClFN_3O_2S$: C, 58.13; H, 4.88; Cl, 8.17; F, 4.38; N, 9.68; O, 7.37; S, 7.39; Found: C, 58.13; H, 4.90; Cl, 8.15; F, 4.40; N, 9.66; O, 7.34; S, 7.42%; IR (cm^{-1}): 3389 (N-H stretching of amide), 3023 (C-H stretching of aromatic ring), 2974 (C-H asymmetrical stretching of CH_3 group), 2862 (C-H symmetrical stretching of CH_3 group), 1634 (C=O stretching of amide), 1575 (N-H deformation of pyrimidine ring), 1516 (C=C stretching of aromatic ring), 1454 (C-H asymmetrical deformation of CH_3 group), 1409 (C-H symmetrical deformation of CH_3 group), 1349 (C-N-C stretching vibration of pyrimidine ring), 1234 (C-O-C stretching), 1197 (C=S stretching), 1106 (C-F stretching), 1055 (C-H in plane deformation of aromatic ring), 845 (para-substituted), 767 (C-H in out plane deformation of aromatic ring), 670 (C-Cl stretching); ^1H NMR (DMSO-*d6*) δ ppm: 1.19 (s, 3H, H), 1.29 (s, 3H, H), 3.12 (s, 3H, H), 3.30-3.37 (m, 1H, H), 6.49 (s, 1H, H), 6.95-6.99 (m, 1H, H), 7.06-7.08 (d, 2H, H), 7.10-7.12 (d, 2H, H), 7.27-7.30 (m, 2H, H), 8.96 (s, 1H, H), 9.69 (s, 1H, H), 9.79 (s, 1H, H); MS: *m/z* 434.

4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-N-(2-chloro -phenyl)-2-thioxo pyrimidine-5-carboxamide (4d)

Yield: 53%; mp 172ºC; Anal. Calcd. for $C_{20}H_{18}Cl_2FN_3OS$: C, 54.80; H, 4.14; Cl, 16.18; F, 4.33; N, 9.59; O, 3.65; S, 7.32; Found: C, 54.80; H, 4.13; Cl, 16.19; F, 4.34; N, 9.58; O, 3.67; S, 7.30%; IR (cm^{-1}): 3357 (N-H stretching of amide), 3101 (C-H stretching of aromatic ring), 2972 (C-H asymmetrical stretching of CH_3 group), 2873 (C-H symmetrical stretching of CH_3 group), 1643 (C=O stretching of amide), 1576 (N-H deformation of pyrimidine ring), 1521 (C=C stretching of aromatic ring), 1467 (C-H asymmetrical deformation of CH_3 group), 1405 (C-H symmetrical deformation of CH_3 group), 1348 (C-N-C stretching vibration of pyrimidine ring), 1268 (C-N stretching), 1167 (C=S stretching), 1097 (C-F stretching), 1038 (C-H in plane deformation of aromatic ring), 834 (para-substituted), 743 (C-H in out plane deformation of aromatic ring), 653 (C-Cl stretching); ^{1}H NMR (DMSO-*d6*) δ ppm: 1.17 (s, 3H, H), 1.21 (s, 3H, H), 3.50-3.53 (m, 1H, H), 6.41 (s, 1H, H), 6.84-6.90 (m, 3H, H), 7.19-7.21 (m, 2H, H), 7.51-7.54 (m, 2H, H), 8.60 (s, 1H, H), 9.78 (s, 1H, H), 9.97 (s, 1H, H); MS: *m/z* 438.

4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-N-(3-chloro -phenyl)-2-thioxo pyrimidine-5-carboxamide (4e)

Yield: 59%; mp 176ºC; Anal. Calcd. for $C_{20}H_{18}Cl_2FN_3OS$: C, 54.80; H, 4.14; Cl, 16.18; F, 4.33; N, 9.59; O, 3.65; S, 7.32; Found C, 54.82; H, 4.17; Cl, 16.15; F, 4.37; N, 9.55; O, 3.65; S, 7.30%; IR (cm^{-1}): 3349 (N-H stretching of amide), 3095 (C-H stretching of aromatic ring), 2946 (C-H asymmetrical stretching of CH_3 group), 2870 (C-H symmetrical stretching of CH_3 group), 1658 (C=O stretching of amide), 1582 (N-H deformation of pyrimidine ring), 1534 (C=C stretching of aromatic ring), 1451 (C-H asymmetrical deformation of CH_3 group), 1420 (C-H symmetrical deformation of CH_3 group), 1350 (C-N-C stretching vibration of pyrimidine ring), 1257 (C-N stretching), 1146 (C=S stretching), 1097 (C-F stretching), 1009 (C-H in plane deformation of aromatic ring), 838 (para-substituted), 753 (C-H in out plane deformation of aromatic ring), 657 (C-Cl stretching); ^{1}H NMR (DMSO-*d6*) δ ppm: 1.14 (s, 3H, H), 1.17 (s, 3H, H), 3.54-3.57 (m, 1H, H), 6.46 (s, 1H, H), 6.88-6.91 (m, 2H, H), 7.12-7.15 (m, 2H, H), 7.46 (s, 1H, H), 7.57-7.61 (m, 2H, H), 8.75 (s, 1H, H), 9.67 (s, 1H, H), 9.92 (s, 1H, H); MS: *m/z* 438.

4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-N-(4-chloro -phenyl)-2-thioxo pyrimidine-5-carboxamide (4f)

Yield: 59%; mp 170ºC; Anal. Calcd. for $C_{20}H_{18}Cl_2FN_3OS$: C, 54.80; H, 4.14; Cl, 16.18; F, 4.33; N, 9.59; O, 3.65; S, 7.32; Found C, 54.82; H, 4.12; Cl, 16.16; F, 4.35; N, 9.55; O, 3.69; S, 7.30%; IR (cm^{-1}): 3375 (N-H stretching of amide), 3111 (C-H stretching of aromatic ring), 2953 (C-H asymmetrical stretching of CH_3 group), 2883 (C-H symmetrical stretching of CH_3 group), 1650 (C=O stretching of amide), 1590 (N-H deformation of pyrimidine ring), 1521 (C=C stretching of aromatic ring), 1471 (C-H asymmetrical deformation of CH_3 group), 1412 (C-H symmetrical deformation of CH_3 group), 1342 (C-N-C stretching vibration of pyrimidine ring), 1273 (C-N stretching), 1182 (C=S stretching), 1108 (C-F stretching), 1061 (C-H in plane deformation of aromatic ring), 831 (para-substituted), 781 (C-H in out plane deformation of aromatic ring), 664 (C-Cl stretching); ^{1}H NMR (DMSO-*d6*) δ ppm: 1.17 (s, 3H, H), 1.23 (s, 3H, H), 3.31-3.35 (m, 1H, H), 6.43 (s, 1H, H), 6.97-6.99 (m, 1H, H), 7.09-7.11 (d, 2H, H), 7.13-7.15 (d, 2H, H), 7.25-7.31 (m, 2H, H), 8.91 (s, 1H, H), 9.76 (s, 1H, H), 9.92 (s, 1H, H); MS: *m/z* 438.

4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-N-(2-fluoro -phenyl)-2-thioxo pyrimidine-5-carboxamide (4g)

Yield: 56%; mp 178ºC; Anal. Calcd. for $C_{20}H_{18}ClF_2N_3OS$: C, 56.94; H, 4.30; Cl, 8.40; F, 9.01; N, 9.96; O, 3.79; S, 7.60; Found: C, 56.92; H, 4.30; Cl, 8.38; F, 9.01; N, 9.98; O, 3.77; S, 7.55%; IR (cm^{-1}): 3333 (N-H stretching of amide), 3103 (C-H stretching of aromatic ring), 2956 (C-H asymmetrical stretching of CH_3 group), 2878 (C-H symmetrical stretching of CH_3

group), 1650 (C=O stretching of amide), (N-H deformation of pyrimidine ring), 1528 (C=C stretching of aromatic ring), 1473 (C-H asymmetrical deformation of CH_3 group), 1411 (C-H symmetrical deformation of CH_3 group), 1340 (C-N-C stretching vibration of pyrimidine ring), 1271 (C-N stretching), 1185 (C=S stretching), 1102 (C-F stretching), 1062 (C-H in plane deformation of aromatic ring), 673 (C-Cl stretching); ^{1}H NMR (DMSO-*d6*) δ ppm: 1.19 (s, 3H, H), 1.21 (s, 3H, H), 3.55-3.59 (m, 1H, H), 6.49 (s, 1H, H), 6.83-6.87 (m, 3H, H), 7.17-7.20 (m, 2H, H), 7.50-7.54 (m, 2H, H), 8.68 (s, 1H, H), 9.88 (s, 1H, H), 9.98 (s, 1H, H); MS: *m/z* 421.

4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-N-(3-fluoro -phenyl)-2-thioxo pyrimidine-5-carboxamide (4h)

Yield: 52%; mp 174ºC; Anal. Calcd. for $C_{20}H_{18}ClF_2N_3OS$: C, 56.94; H, 4.30; Cl, 8.40; F, 9.01; N, 9.96; O, 3.79; S, 7.60; Found C, 56.92; H, 4.32; Cl, 8.38; F, 9.04; N, 9.99; O, 3.75; S, 7.54%; IR (cm^{-1}): 3384 (N-H stretching of amide), 3065 (C-H stretching of aromatic ring), 2978 (C-H asymmetrical stretching of CH_3 group), 2875 (C-H symmetrical stretching of CH_3 group), 1650 (C=O stretching of amide), 1583 (N-H deformation of pyrimidine ring), 1542 (C=C stretching of aromatic ring), 1430 (C-H asymmetrical deformation of CH_3 group), 1420 (C-H symmetrical deformation of CH_3 group), 1340 (C-N-C stretching vibration of pyrimidine ring), 1271 (C-N stretching), 1170 (C=S stretching), 1045 (C-F stretching), 1043 (C-H in plane deformation of aromatic ring), 670 (C-Cl stretching); ^{1}H NMR (DMSO-*d6*) δ ppm: 1.17 (s, 3H, H), 1.19 (s, 3H, H), 3.53-3.56 (m, 1H, H), 6.56 (s, 1H, H), 6.84-6.90 (m, 2H, H), 7.13-7.17 (m, 2H, H), 7.42 (s, 1H, H), 7.56-7.60 (m, 2H, H), 8.88 (s, 1H, H), 9.69 (s, 1H, H), 9.91 (s, 1H, H); MS: *m/z* 421.

4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-N-(4-fluoro -phenyl)-2-thioxo pyrimidine-5-carboxamide (4i)

Yield: 54%; mp 176ºC; Anal. Calcd. for $C_{20}H_{18}ClF_2N_3OS$: C, 56.94; H, 4.30; Cl, 8.40; F, 9.01; N, 9.96; O, 3.79; S, 7.60; Found: C, 56.90; H, 4.34; Cl, 8.44; F, 9.00; N, 9.91; O, 3.75; S, 7.64%; IR (cm^{-1}): 3365 (N-H stretching of amide), 3070 (C-H stretching of aromatic ring), 2952 (C-H asymmetrical stretching of CH_3 group), 2875 (C-H symmetrical stretching of CH_3 group), 1640 (C=O stretching of amide), 1561 (N-H deformation of pyrimidine ring), 1536 (C=C stretching of aromatic ring), 1441 (C-H asymmetrical deformation of CH_3 group), 1413 (C-H symmetrical deformation of CH_3 group), 1330 (C-N-C stretching vibration of pyrimidine ring), 1268 (C-N stretching), 1169 (C=S stretching), 1064 (C-F stretching), 1002 (C-H in plane deformation of aromatic ring), 666 (C-Cl stretching); ^{1}H NMR (DMSO-*d6*) δ ppm: 1.21 (s, 3H, H), 1.27 (s, 3H, H), 3.29-3.33 (m, 1H, H), 6.55 (s, 1H, H), 6.93-6.97 (m, 1H, H), 7.13-7.16 (d, 2H, H), 7.18-7.20 (d, 2H, H), 7.27-7.30 (m, 2H, H), 8.90 (s, 1H, H), 9.84 (s, 1H, H), 9.99 (s, 1H, H); MS: *m/z* 421.

4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-N-(2-bromo -phenyl)-2-thioxo pyrimidine-5-carboxamide (4j)

Yield: 48%; mp 175ºC; Anal. Calcd. for $C_{20}H_{18}ClBrFN_3OS$: C, 49.75; H, 3.76; Br, 16.55; Cl, 7.34; F, 3.94; N, 8.70; O, 3.31; S, 6.64; Found: C, 49.73; H, 3.72; Br, 16.54; Cl, 7.32; F, 3.91; N, 8.73; O, 3.35; S, 6.60%; IR (cm^{-1}): 3365 (N-H stretching of amide), 3008 (C-H stretching of aromatic ring), 2928 (C-H asymmetrical stretching of CH_3 group), 2874 (C-H symmetrical stretching of CH_3 group), 1647 (C=O stretching of amide), 1571 (N-H deformation of pyrimidine ring), 1527 (C=C stretching of aromatic ring), 1451 (C-H asymmetrical deformation of CH_3 group), 1411 (C-H symmetrical deformation of CH_3 group), 1342 (C-N-C stretching vibration of pyrimidine ring), 1271 (C-N stretching), 1174 (C=S stretching), 1095 (C-F stretching), 1053 (C-H in plane deformation of aromatic ring), 742 (C-Br stretching), 671 (C-Cl stretching); ^{1}H NMR (DMSO-*d6*) δ ppm: 1.14 (s, 3H, H), 1.20 (s, 3H, H), 3.53-3.57 (m, 1H, H), 6.43 (s, 1H, H), 6.84-6.88 (m, 3H, H), 7.19-7.23 (m, 2H, H), 7.50-7.53 (m, 2H, H), 8.77 (s, 1H, H), 9.82 (s, 1H, H), 9.97 (s, 1H, H); MS: *m/z* 482.

CONCLUSION

In climax, we include synthesized of original pyrimidine derivatives using simple and suitable method. This method produces these products in first-class yields and trouble-free workup. Product is isolated by simple filtration. The isolated products are very pure and do not need any column purification. This study opens up a new area of beneficial synthesis of potentially biologically active novel pyrimidine derivatives compounds.

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