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RESEARCH ARTICLE

Synthesis of Certain Fluoro Containing Pyrimidine Derivatives

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ABSTRACT

Synthesis of a series of ***4-(4-(2,6-difluoro-4-nitrophenoxy)phenyl)-N-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide***. ***(4a-j)*** was achieved from different N-(4-substitutedphenyl)-3-oxobutanamide, 4-(2,6-difluoro-4-nitrophenoxy) benzaldehyde and urea 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

4-(2,6-Difluoro-4-Nitrophenoxy) Benzaldehyde; Hydrochloric Acid, Urea Only Refluxed

INTRODUCTION

NSAIDs show side effects such as gastrointestinal irritation and lesions, renal toxicity and inhibition of platelet aggregation, while the use of opioids is limited to severe pain because of adverse secondary reactions as respiratory depression, dependence, sedation, and constipation[1,2]. Hence there is always a need for those drugs which have improved analgesic activity and less adverse effects. Pyrimidines exhibit a range of pharmacological activity such as antibacterial[3,4,5] antifungal[6,7], anticancer[8,9], anti-inflammatory[10,11] and cardioprotective effects[12]. Pyrimidine compounds are also used as hypnotic drugs for the nervous system[13], calcium-sensing receptor antagonists[14] and also for antagonists of the human A2A adenosine receptor[15]. Like pyrimidine, coumarin also exhibits diverse biological properties[16,17]. We have developed a new decorum for the synthesis 4-(4-(2,6-difluoro-4-nitrophenoxy)phenyl)-N-(substitutedphenyl) -1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide ***(4a-j)*** with the advantage of fine yield and environmentally easiness (**Scheme-a**).

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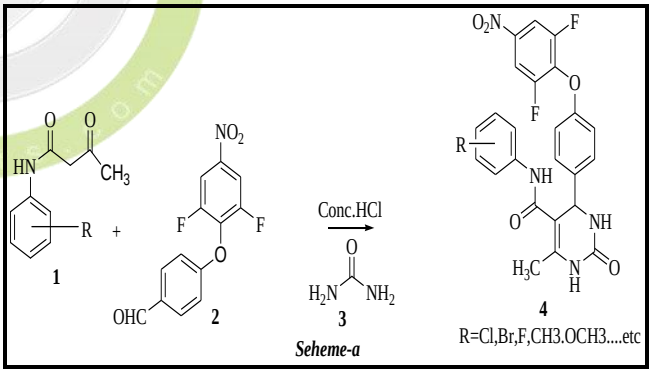

Scheme- a

EXPERIMENTAL

To the mixture of N-(4-substitutedphenyl)-3-oxobutanamide, 4-(2,6-difluoro-4-nitrophenoxy) benzaldehyde and urea in 20 ml ethanol was added few drops of Conc. HCl with stirring for 24 hrs. at ambient temperature. After 24 hrs total reaction mass pour in water, Insoluble solid was generated, then filter and crystallization by ethanol.

4-(4-(2, 6-difluoro-4-nitrophenoxy)phenyl)-N-(2-methoxyphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4a)

Yield: 57%; mp 191ºC; Anal. Calcd. for $C_{25}H_{20}F_2N_4O_6$: C, 58.82; H, 3.95; F, 7.44; N, 10.98; O, 18.81; Found: C, 58.84; H, 3.99; F, 7.47; N, 10.95; O, 18.75%; IR (cm^{-1}): 3413 (N-H stretching of amide), 3097 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of CH_3 group), 2867 (C-H symmetrical stretching of CH_3 group), 1660 (C=O stretching of amide), 1564 (C=O stretching of cyclic) 1546 (N-H deformation of pyrimidine ring), 1527 (C=C stretching of aromatic ring), 1498 (C-H asymmetrical deformation of CH_3 group), 1410 (C-H symmetrical deformation of CH_3 group), 1330 (C-NO2 symmetrical deformation of NO_2 group), 1305 (C-N-C stretching vibration of pyrimidine ring), 1242 (C-O-C stretching), 1141 (C-F stretching), 1087 (C-H in plane deformation of aromatic ring), 819 (para-substituted), 794 (C-H in out plane deformation of aromatic ring); ^1H NMR (DMSO-*d6*) δ ppm: 1.20 (s, 3H, H), 3.79 (s, 3H, H), 6.36 (s, 1H, H), 6.70-6.72 (dd', 2H, H), 6.98-7.00 (dd', 2H, H), 7.10-7.15 (m, 2H, H), 7.38-7.43 (m, 2H, H), 7.53-7.57 (m, 2H, H), 8.37 (s, 1H, H), 9.72 (s, 1H, H), 10.12 (s, 1H, H); MS: *m/z* 510.

4-(4-(2, 6-difluoro-4-nitrophenoxy)phenyl)-N-(3-methoxyphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4b)

Yield: 59%; mp 201ºC; Anal. Calcd. for $C_{25}H_{20}F_2N_4O_6$: C, 58.82; H, 3.95; F, 7.44; N, 10.98; O, 18.81; Found: C, 58.81; H, 3.97; F, 7.42; N, 10.94; O, 18.85%; IR (cm^{-1}): 3417 (N-H stretching of amide), 3095 (C-H stretching of aromatic ring), 2965 (C-H asymmetrical stretching of CH_3 group), 2871 (C-H symmetrical stretching of CH_3 group), 1668 (C=O stretching of amide), 1572 (C=O stretching of cyclic) 1550 (N-H deformation of pyrimidine ring), 1523 (C=C stretching of aromatic ring), 1491 (C-H asymmetrical deformation of CH_3 group), 1408 (C-H symmetrical deformation of CH_3 group), 1324 (C-NO_2 symmetrical deformation of NO_2 group), 1300 (C-N-C stretching vibration of pyrimidine ring), 1240 (C-O-C stretching), 1140 (C-F stretching), 1081 (C-H in plane deformation of aromatic ring), 823 (para-substituted), 756 (C-H in out plane deformation of aromatic ring); ^1H NMR (DMSO-*d6*) δ ppm: 1.22 (s, 3H, H), 3.74 (s, 3H, H), 6.32 (s, 1H, H), 6.77-6.79 (dd', 2H, H), 6.96-6.98 (dd', 2H, H), 7.09-7.13 (m, 2H, H), 7.39-7.43 (m, 3H, H), 7.54 (s, 1H, H), 8.26 (s, 1H, H), 9.67 (s, 1H, H), 10.01 (s, 1H, H); MS: *m/z* 510.

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

Yield: 63%; mp 198ºC; Anal. Calcd. for $C_{25}H_{20}F_2N_4O_6$: C, 58.82; H, 3.95; F, 7.44; N, 10.98; O, 18.81; Found: C, 58.84; H, 3.98; F, 7.49 N, 10.99; O, 18.72%; IR (cm^{-1}): 3421 (N-H stretching of amide), 3090 (C-H stretching of aromatic ring), 2968 (C-H asymmetrical stretching of CH_3 group), 2875 (C-H symmetrical stretching of CH_3 group), 1668 (C=O stretching of amide), 1575 (C=O stretching of cyclic) 1552 (N-H deformation of pyrimidine ring), 1527 (C=C stretching of aromatic ring), 1498 (C-H asymmetrical deformation of CH_3 group), 1410 (C-H symmetrical deformation of CH_3 group), 1330 (C-NO_2 symmetrical deformation of NO_2 group), 1305 (C-N-C stretching vibration of pyrimidine ring), 1242 (C-O-C stretching), 1141 (C-F stretching), 1087 (C-H in plane deformation of aromatic ring), 819 (para-substituted), 794 (C-H in out plane deformation of aromatic ring); ^1H NMR (DMSO-*d6*) δ ppm: 1.20 (s, 3H, H), 3.50 (s, 3H, H), 6.51 (s, 1H, H), 6.74-6.76 (dd', 2H, H), 6.96-6.98 (dd', 2H, H), 7.13-7.19 (m, 2H, H), 7.37-7.39 (dd', 2H, H), 7.45-7.47 (dd', 2H, H), 8.47 (s, 1H, H), 9.68 (s, 1H, H), 10.03 (s, 1H, H); MS: *m/z* 510.

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

Yield: 59%; mp 182ºC; Anal. Calcd. for $C_{24}H_{17}ClF_2N_4O_5$: C, 55.99; H, 3.33; Cl, 6.89; F, 7.38; N, 10.88; O, 15.54; Found: C, 55.91; H, 3.39; Cl, 6.85; F, 7.39; N, 10.89; O, 15.59%; IR (cm^{-1}): 3385 (N-H stretching of amide), 3091 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of CH_3 group), 2864 (C-

H symmetrical stretching of CH_3 group), 1668 (C=O stretching of amide), 1581 (C=O stretching of cyclic) 1566 (N-H deformation of pyrimidine ring), 1510 (C=C stretching of aromatic ring), 1475 (C-H asymmetrical deformation of CH_3 group), 1404 (C-H symmetrical deformation of CH_3 group), 1325 (C-NO_2 symmetrical deformation of NO_2 group), 1305 (C-N-C stretching vibration of pyrimidine ring), 1220 (C-N stretching), 1139 (C-F stretching), 1072 (C-H in plane deformation of aromatic ring), 827 (para-substituted), 734 (C-H in out plane deformation of aromatic ring), 659 (C-Cl stretching); ^{1}H NMR (DMSO-*d6*) δ ppm: 1.17 (s, 3H, H), 6.41 (s, 1H, H), 6.72-6.74 (dd', 2H, H), 6.88-6.90 (dd', 2H, H), 7.06-7.09 (m, 2H, H), 7.32-7.35 (m, 2H, H), 7.52-7.57 (m, 2H, H), 8.39 (s, 1H, H), 9.66 (s, 1H, H), 10.00 (s, 1H, H); MS: *m/z* 514.

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

Yield: 53%; mp 187ºC; Anal. Calcd. for $C_{24}H_{17}ClF_2N_4O_5$: C, 55.99; H, 3.33; Cl, 6.89; F, 7.38; N, 10.88; O, 15.54; Found: C, 55.95; H, 3.39; Cl, 6.87; F, 7.39; N, 10.89; O, 15.59%; IR (cm^{-1}): 3379 (N-H stretching of amide), 3099 (C-H stretching of aromatic ring), 2979 (C-H asymmetrical stretching of CH_3 group), 2869 (C-H symmetrical stretching of CH_3 group), 1667 (C=O stretching of amide), 1587 (C=O stretching of cyclic) 1560 (N-H deformation of pyrimidine ring), 1507 (C=C stretching of aromatic ring), 1471 (C-H asymmetrical deformation of CH_3 group), 1408 (C-H symmetrical deformation of CH_3 group), 1319 (C-NO2 symmetrical deformation of NO2 group), 1311 (C-N-C stretching vibration of pyrimidine ring), 1213 (C-N stretching), 1111 (C-F stretching), 1078 (C-H in plane deformation of aromatic ring), 837 (para-substituted), 737 (C-H in out plane deformation of aromatic ring), 673 (C-Cl stretching); ^{1}H NMR (DMSO-*d6*) δ ppm: 1.19 (s, 3H, H), 6.44 (s, 1H, H), 6.73-6.75 (dd', 2H, H), 6.94-6.96 (dd', 2H, H), 7.09-7.13 (m, 2H, H), 7.35-7.41 (m, 3H, H), 7.59 (s, 1H, H), 8.40 (s, 1H, H), 9.78 (s, 1H, H), 10.07 (s, 1H, H); MS: *m/z* 514.

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

Yield: 50%; mp 181ºC; Anal. Calcd. for $C_{24}H_{17}ClF_2N_4O_5$: C, 55.99; H, 3.33; Cl, 6.89; F, 7.38; N, 10.88; O, 15.54; Found: C, 55.93; H, 3.38; Cl, 6.85; F, 7.38; N, 10.82; O, 15.72%; IR (cm^{-1}): 3376 (N-H stretching of amide), 3074 (C-H stretching of aromatic ring), 2974 (C-H asymmetrical stretching of CH_3 group), 2864 (C-H symmetrical stretching of CH_3 group), 1656 (C=O stretching of amide), 1561 (C=O stretching of cyclic) 1543 (N-H deformation of pyrimidine ring), 1502 (C=C stretching of aromatic ring), 1454 (C-H asymmetrical deformation of CH_3 group), 1402 (C-H symmetrical deformation of CH_3 group), 1323 (C-NO_2 symmetrical deformation of NO_2 group), 1310 (C-N-C stretching vibration of pyrimidine ring), 1210 (C-N stretching), 1101 (C-F stretching), 1048 (C-H in plane deformation of aromatic ring), 846 (para-substituted), 743 (C-H in out plane deformation of aromatic ring), 663 (C-Cl stretching); ^{1}H NMR (DMSO-*d6*) δ ppm: 1.25 (s, 3H, H), 6.54 (s, 1H, H), 6.78-6.80 (dd', 2H, H), 6.95-6.96 (dd', 2H, H), 7.15-7.21 (m, 2H, H), 7.38-7.40 (dd', 2H, H), 7.44-7.46 (dd', 2H, H), 8.32 (s, 1H, H), 9.63 (s, 1H, H), 10.06 (s, 1H, H); MS: *m/z* 514.

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

Yield: 56%; mp 173ºC; Anal. Calcd. for $C_{24}H_{17}F_3N_4O_5$: C, 57.84; H, 3.44; F, 11.44; N, 11.24; O, 16.05; Found: C, 57.88; H, 3.44; F, 11.40; N, 11.28; O, 16.07%; IR (cm^{-1}): 3376 (N-H stretching of amide), 3084 (C-H stretching of aromatic ring), 2973 (C-H asymmetrical stretching of CH_3 group), 2879 (C-H symmetrical stretching of CH_3 group), 1661 (C=O stretching of amide), 1576 (C=O stretching of cyclic) 1550 (N-H deformation of pyrimidine ring), 1509 (C=C stretching of aromatic ring), 1467 (C-H asymmetrical deformation of CH_3 group), 1411 (C-H symmetrical deformation of CH_3 group), 1319 (C-NO_2 symmetrical deformation of NO_2 group), 1301 (C-N-C stretching vibration of

pyrimidine ring), 1210 (C-N stretching), 1064 (C-F stretching); ^{1}H NMR (DMSO-*d6*) δ ppm: 1.26 (s, 3H, H), 6.34 (s, 1H, H), 6.71-6.73 (dd', 2H, H), 6.87-6.89 (dd', 2H, H), 7.07-7.10 (m, 2H, H), 7.32-7.37 (m, 2H, H), 7.53-7.57 (m, 2H, H), 8.54 (s, 1H, H), 9.76 (s, 1H, H), 10.13 (s, 1H, H); MS: *m/z* 498.

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

Yield: 61%; mp 177ºC; Anal. Calcd. for $C_{24}H_{17}F_3N_4O_5$: C, 57.84; H, 3.44; F, 11.44; N, 11.24; O, 16.05; Found: C, 57.88; H, 3.44; F, 11.40; N, 11.28; O, 16.07%; IR (cm^{-1}): 3376 (N-H stretching of amide), 3089 (C-H stretching of aromatic ring), 2976 (C-H asymmetrical stretching of CH_3 group), 2870 (C-H symmetrical stretching of CH_3 group), 1661 (C=O stretching of amide), 1573 (C=O stretching of cyclic) 1550 (N-H deformation of pyrimidine ring), 1504 (C=C stretching of aromatic ring), 1472 (C-H asymmetrical deformation of CH_3 group), 1411 (C-H symmetrical deformation of CH_3 group), 1321 (C-N-C stretching vibration of pyrimidine ring), 1213 (C-N stretching), 1075 (C-F stretching), 1034 (C-H in plane deformation of aromatic ring), ^{1}H NMR (DMSO-*d6*) δ ppm: 1.27 (s, 3H, H), 6.47 (s, 1H, H), 6.72-6.74 (dd', 2H, H), 6.93-6.95 (dd', 2H, H), 7.08-7.11 (m, 2H, H), 7.36-7.40 (m, 3H, H), 7.58 (s, 1H, H), 8.31 (s, 1H, H), 9.69 (s, 1H, H), 9.99 (s, 1H, H); MS: *m/z* 498.

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

Yield: 60%; mp 179ºC; Anal. Calcd. for $C_{24}H_{17}F_3N_4O_5$: C, 57.84; H, 3.44; F, 11.44; N, 11.24; O, 16.05; Found: C, 57.86; H, 3.43; F, 11.43; N, 11.29; O, 16.02%; IR (cm^{-1}): 3375 (N-H stretching of amide), 3093 (C-H stretching of aromatic ring), 2972 (C-H asymmetrical stretching of CH_3 group), 2877 (C-H symmetrical stretching of CH_3 group), 1664 (C=O stretching of amide), 1577 (C=O stretching of cyclic) 1554 (N-H deformation of pyrimidine ring), 1508 (C=C stretching of aromatic ring), 1475 (C-H asymmetrical deformation of CH_3 group), 1413 (C-H symmetrical deformation of CH_3 group), 1311 (C-N-C stretching vibration of pyrimidine ring), 1217 (C-N stretching), 1074 (C-F stretching), 1031 (C-H in plane deformation of aromatic ring); ^{1}H NMR (DMSO-*d6*) δ ppm: 1.18 (s, 3H, H), 6.46 (s, 1H, H), 6.79-6.81 (dd', 2H, H), 6.97-6.99 (dd', 2H, H), 7.13-7.18 (m, 2H, H), 7.36-7.38 (dd', 2H, H), 7.46-7.48 (dd', 2H, H), 8.41 (s, 1H, H), 9.69 (s, 1H, H), 10.10 (s, 1H, H); MS: *m/z* 498.

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

Yield: 49%; mp 171ºC; Anal. Calcd. for $C_{24}H_{17}BrF_2N_4O_5$: C, 51.54; H, 3.06; Br, 14.29; F, 6.79; N, 10.02; O, 14.30; Found: C, 51.52; H, 3.03; Br, 14.28; F, 6.80; N, 10.06; O, 14.31%; 3371 (N-H stretching of amide), 3094 (C-H stretching of aromatic ring), 2973 (C-H asymmetrical stretching of CH_3 group), 2874 (C-H symmetrical stretching of CH_3 group), 1661 (C=O stretching of amide), 1575 (C=O stretching of cyclic) 1552 (N-H deformation of pyrimidine ring), 1507 (C=C stretching of aromatic ring), 1472 (C-H asymmetrical deformation of CH_3 group), 1411 (C-H symmetrical deformation of CH_3 group), 1312 (C-N-C stretching vibration of pyrimidine ring), 1214 (C-N stretching), 1070 (C-F stretching), 1035 (C-H in plane deformation of aromatic ring) 744 (C-Br stretching); ^{1}H NMR (DMSO-*d6*) δ ppm: 1.23 (s, 3H, H), 6.46 (s, 1H, H), 6.74-6.76 (dd', 2H, H), 6.88-6.90 (dd', 2H, H), 7.08-7.11 (m, 2H, H), 7.34-7.37 (m, 2H, H), 7.55-7.59 (m, 2H, H), 8.54 (s, 1H, H), 9.76 (s, 1H, H), 10.13 (s, 1H, H); MS: *m/z* 559.

CONCLUSION

In climax, we include synthesized of original fluoro containing pyrimidine derivatives using simple and suitable method. This method produces these products in first-class yields and difficulty-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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