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Research Article

Synthesis and structural evaluation of some novel tetra hydro pyrimidines from Mannich condensation of three components

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ABSTRACT

In this paper we discuss about the synthesis of three new series of N-(2-chloro-4-(trifluoromethyl) phenyl)-4-(sub-phenyl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide **(PY-1 to 12)** are synthesized. The synthesis of **(PY-1 to 12)** was achieved by an acid catalyzed cyclocondensation of N-(2-chloro-4-(trifluoromethyl) phenyl)-oxobutanamide, substituted urea/thiourea and Benzaldehydes. The desired substituted compounds are show potent biological activity. The compounds were characterized by IR, NMR, Mass and elemental analysis. This includes the condensation of substituted Benzaldehyde (2) with either urea or thiourea or N-methyl urea (3 or 3a) to form hemiaminal with some similarities to the Mannich condensation. Hemiaminal undergoes dehydration in presence of acid catalyst to produce iminium cation as an intermediate. The examine (iminium cation) generated acts as an electrophile for the nucleophilic addition of keto enroll of N-(2-chloro-4-(trifluoromethyl)phenyl)-3-oxobutanamide(1) with removal of proton to produce an intermediate, undergoes intramolecular condensation in presence of acid between oxygen of ketone and amino group of urea or thiourea or N-methyl urea to give the cyclized targeted product(4) (PY-1 to 12) (Scheme-1&2) (Table-1).

Keywords: Pyrimidine, urea, thiourea and benzaldehyde.

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CHEMISTRY RESEARCH A RTICLE

Synthesis and structural evaluation of some novel tetra hydro pyrimidines from Mannich condensation of three components

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ABSTRACT

In this paper we discuss about the synthesis of three new series of N-(2-chloro-4-(trifluoromethyl) phenyl)-4-(sub-phenyl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide **(PY-1 to 12)** are synthesized. The synthesis of **(PY-1 to 12)** was achieved by an acid catalyzed cyclocondensation of N-(2-chloro-4-(trifluoromethyl) phenyl)-oxobutanamide, substituted urea/thiourea and Benzaldehydes. The desired substituted compounds are show potent biological activity. The compounds were characterized by IR, NMR, Mass and elemental analysis.

This includes the condensation of substituted Benzaldehyde (2) with either urea or thiourea or N-methyl urea (3 or 3a) to form hemiaminal with some similarities to the Mannich condensation. Hemiaminal undergoes dehydration in presence of acid catalyst to produce iminium cation as an intermediate. The examine (iminium cation) generated acts as an electrophile for the nucleophilic addition of keto enroll of N-(2-chloro-4-(trifluoromethyl)phenyl)-3-oxobutanamide(1) with removal of proton to produce an intermediate, undergoes intramolecular condensation in presence of acid between oxygen of ketone and amino group of urea or thiourea or N-methyl urea to give the cyclized targeted product(4) (PY-1 to 12) (Scheme-1&2) (Table-1).

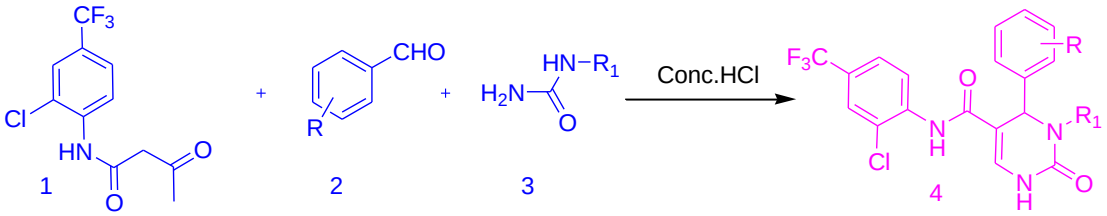
Keywords: Pyrimidine, urea, thiourea and benzaldehyde.

1. INTRODUCTION

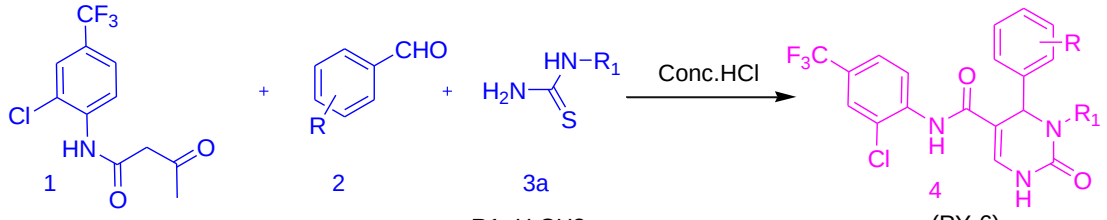
Pyrimidine is a six membered heterocyclic compound consisting of two nitrogen atoms at one and three positions of heterocyclic ring. Generally pyrimidine derivatives such as 2-hydroxy-substitutedpyrimidine, 2-mercapto- substituted-pyrimidine and 2-amino-substituted pyrimidine are studied. Pyrimidines have been isolated from the nucleic acid hydrolysates. Pyrimidines are among those molecules that make life possible, have been some of the building blocks of DNA and RNA. Several analogues of pyrimidines have been used as compounds that interfere with the synthesis and functioning of nucleic acids e.g. fluorouracil, which has been used in cancer treatment. Also there are some thiouracil derivatives, which produce adverse reduction in susceptible patients and found more potent and less likely to produce side effects and is being widely used.

There are several other important groups of pyrimidines with medicinal uses. Pyrimidine ring carrying various substituents may be built up from two or three aliphatic fragments by the principle synthesis or by a variety of other syntheses, which are complimentary rather than alternative to it.

An alternative method of synthesis is the summarization or break down of another heterocyclic such as hydration of purine, but such methods are rarely used. From last ten decades pyrimidine and its derivative were studied because of their biological activity. The 1, 2, 3, 4-tetrahydropyrimidines have many pharmacological and medicinal application *viz*: antimicrobial and radio protective.



Scheme_1



Scheme_2

Table-1Physical Data of compounds (PY-1 to 12).

Code	R1	M.F.	M.W.	M.P.0C	Yield %	Rf1	Rf2
PY-1	2-OCH3	$C_{20}H_{17}ClF_3N_3O_3$	440	207	68	0.48	0.65
PY-2	2-F	$C_{19}H_{14}ClF_4N_3O_2$	428	202	59	0.49	0.58
PY-3	4-Cl	$C_{19}H_{14}Cl_2F_3N_3O_2$	445	224	71	0.41	0.68
PY-4	4-CH3	$C_{20}H_{17}ClF_3N_3O_2$	424	201	69	0.59	0.68
PY-5	4-F	$C_{19}H_{14}ClF_4N_3O_2$	428	195	55	0.55	0.71
PY-6	4-Cl	$C_{19}H_{14}Cl_2F_3N_3OS$	460	220	71	0.48	0.58
PY-7	3-Cl	$C_{20}H_{16}Cl_2F_3N_3O_2$	458	222	63	0.51	0.61
PY-8	2-F	$C_{20}H_{16}ClF_4N_3O_2$	442	215	59	0.52	0.70
PY-9	4-OCH3	$C_{21}H_{19}ClF_3N_3O_3$	454	228	75	0.47	0.75
PY-10	4-Cl	$C_{20}H_{16}Cl_2F_3N_3O_2$	458	197	71	0.56	0.65
PY-11	3,4-DiCl	$C_{20}H_{15}Cl_3F_3N_3O_2$	493	232	71	0.52	.067
PY-12	4-Br	$C_{20}H_{16}BrClF_3N_3O_2$	503	195	67	0.50	0.68

TLC Solvent system Rf1:- Hexane: Ethyl acetate –:4, Rf2:-Chloroform: methanol –9; 1.

2. MATERIALS AND METHOD

General procedure for the synthesis N-(2-chloro-4-(trifluoromethyl) phenyl)-4- (sub- phenyl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (PY-1 to PY-12).

N-(2-chloro-4-(trifluoromethyl)phenyl)-3-oxobutanamide , Benzaldehydes , urea derivatives (0.015M) aPY small quantity of HCl in ethyl alcohol (25ml) were heat to 80- 85°C for 10 to 12 hrs. After that cool the reaction mixture to 25-35°C for 20 hrs. Crude product was dissolves in ethyl alcohol and reprecipited to give desire compounds.

3. RESULTS AND DISCUSSIONS

Products were monitored by TLC analysis of ***(PY-1 to PY-12)*** all the compounds melting point were

checked. IR, NMR and elemental analysis were done and reported.

N-(2-chloro-4-(trifluoromethyl) phenyl)-4-(2-methoxyphenyl)-1, 2, 3, tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (PY-1)

Yield:68%; Melting point 207ºC; Molecular formula :C20H17ClF3N3O3 Carbon: 54.62; Hydrogen : 3.90; Chlorine : 8.06; Fluorine : 12.96; Nitrogen:9.55; Oxygen : 10.91 Obtained Carbon : 54.42; Hydrogen : 3.81; Chlorine : 8.00; Fluorine, 12.90; Nitrogen, 9.55; Oxygen, 10.91%; IR spectra : 3410 (For -NH), 3070 (For -C-H, of Phenyl ring), 1660 (C=O, amide carbonyl stretching), 1600 (N-H, pyrimidine ring), 1525 (C=C, Phenyl ring stretching), 1344 (For -C-N-C of pyrimidine),1247 (C-O-C, asymmetrical stretching of OCH3), 44 (C-F stretching); Mass: 440; 1H NMR (Solvent : DMSO-*d6*) δppm: 2.28 (s, 3(H), Hi), 3.72 (s, 3(H), Hii), 5.15 (s, 1(H), Hiii), 6.87 (s, 1(H), Hiv,), 6.97- 7.14 (m , 2(H), Hv), 7.28-7.30 (d, 2(H), Hvi',), 7.48-7.50 (d , 2(H), Hviii'), 8.37 (s, 1(H), Hviii), 8.44-8.47 (m , 1(H), Hix,), 8.90 (s, 1H, Hl).

N-[(2-chloro-4-(trifluoro methyl) phenyl)-4-(2-fluorophenyl)]-1, 2, 3, 4- tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (PY-2)

Yield: 59%; Melting point: 202ºC Molecular formula: C19H14ClF4N3O2; Carbon: 53.35; Hydrogen: 3.30; Chlorine: 8.29; Fluorine: 17.76; Nitrogen: 9.82; Oxygen, 7.48; Results: Carbon: 53.21; Hydrogen: 3.10; Chlorine: 8.08; Fluorine: 17.12; Nitrogen: 9.71; Oxygen: 7.40%; MS: *m/z* 428.

N-[(2-chloro-4-(trifluoro methyl) phenyl)-4-(4-chlorophenyl)]-1, 2, 3, 4- tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (PY-3)

Practical yield: 71%; Melting point 224ºC; Molecular formula: C19H14Cl2F3N3O2; Carbon: 51.37; Hydrogen: 3.18; Chlorine: 15.96; Fluorine: 12.83; Nitrogen: 9.46;
Oxygen: 7.20; Results: Carbon: 51.20; Hydrogen: 3.03; Chlorine: 15.56; Fluorine: 12.66; Nitrogen: 9.22; Oxygen: 7.10%; MS: *m/z 445*;

N-[(2-chloro-4-(trifluoro methyl) phenyl)-4-(4-methylphenyl)]-1, 2, 3, 4- tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (PY-4)

Yield: 69%; Melting point 201ºC; Molecular formula: C20H17ClF3N3O2; Carbon: 56.68; Hydrogen: 4.04; Chlorine: 8.37; Fluorine: 13.45; Nitrogen: 9.91; Oxygen: 7.55; Results: Carbon: 56.24; Hydrogen: 4.00; Chlorine: 8.22; Fluorine: 13.24; Nitrogen: 8.5; Oxygen: 7.35%; MS: *m/z* 424.

N-[(2-chloro-4-(trifluoro methyl) phenyl)-4-(4-fluorophenyl)]-1, 2, 3, 4- tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (PY-5)

Yield: 55%; Melting point 195ºC; Molecular formula C19H14ClF4N3O2; Carbon: 53.35; Hydrogen: 3.30; Chlorine: 8.29; Fluorine: 17.76; Nitrogen: 9.82; Oxygen: 7.48; Results: Carbon: 53.09; Hydrogen: 3.12; Chlorine: 8.11; Fluorine: 17.23; Nitrogen: 9.45; Oxygen: 7.24%; MS: *m/z* 428.

4-(4-chlorophenyl)-N-[2-chloro-4-(trifluoro methyl) phenyl]-6-methyl-2- thioxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (PY-6)

Yield: 71%; Melting point 220ºC; Molecular formula C19H14Cl2F3N3OS: Carbon: 49.53; Hydrogen: 3.04; Chlorine: 15.40; Fluorine: 12.38; Nitrogen: 9.12; Oxygen: 3.48; Sulphur: 6.97; Results: Carbon: 49.57; Hydrogen: 3.08; Chlorine: 15.23; Fluorine: 12.24; Nitrogen: 9.17; Oxygen: 3.23; Sulphur: 6.81%; IR cm-1: 3363 (For -NH) , 3109 (For -C-H, of Phenyl ring), 2955 (C-H, CH3 group stretching), 2871 (C-H, CH3 group stretching), 1666 (C=O, amide carbonyl stretching), 1597 (N-H pyrimidine ring), 1523 (C=C Phenyl ring stretching), 1423 (C-H, CH3 group asymmetrical deformation), 1342 (C-H, CH3 group symmetrical deformation), 70 (C-N-C pyrimidine ring stretching), 1269/1246 (C-N, stretching), 14 (C-F stretching), 677 (C-Cl starching) Mass: 460; Proton NMR (Solvent :Dimethyl sulfoxide-*d6*) δppm: 2.02 (s, 3(H),Ha), 5.43 (s, 1(H),Hb), 6.95-6.98 (d, 1(H),Hc,), 7.10 (s, 1(H),Hd),7.27-7.29 (d, 2(H),Hef,), 7.51-7.53 (m, 1(H),Hg), 7.66 (s, 1(H),Hh), 8.19-8.22 (m, 1(H), Hi,), 8.81 (s,1(H),Hj), 8.84 (s,1(H),Hk), 9.70 (s, 1(H),Hl).

4-(3-chlorophenyl)-N-[2-chloro-4-(trifluoro methyl) phenyl]-3, 6-dimethyl-2- oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (PY-7)

Yield: 63%; Melting point 222ºC; Molecular formula C20H16Cl2F3N3O2: Carbon: 52.42; Hydrogen: 3.52; chlorine: 15.47; Fluorine: 12.44; Nitrogen: 9.17; Oxygen: 6.98; Results: Carbon: 52.02; Hydrogen: 3.46; Chlorine: 15.23; Fluorine: 12.13; Nitrogen: 9.08; Oxygen: 6.43%; MS: *m/z* 458. IR: 3260, 3130 (For -NH), 2960 (For -C-H, of Phenyl ring), 1695 (For C=O, carbonyl), 48 (For -C-F).

N-[2-chloro-4-(trifluoro methyl) phenyl]-4-(2-fluorophenyl)-3,6-dimethyl-2- oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (PY-8)

Yield: 59%; Melting point 215ºC; Molecular formula C20H16ClF4N3O2: Carbon: 54.37; Hydrogen: 3.65; Chlorine: 8.02; Fluorine: 17.20; Nitrogen: 9.51; Oxygen: 7.24; Results: Carbon: 54.30; Hydrogen: 3.52; Chlorine: 7.89; Fluorine: 17.10; Nitrogen: 9.42; Oxygen: 7.14%; MS: *m/z* 442. IR: 3255, 3120 (For -NH), 2958 (For -C-H of phenyl ring), 1691 (For C=O, carbonyl), 48 (For C-F).

N-[2-chloro-4-(trifluoro methyl) phenyl]-4-(4-methoxyphenyl)-3, 6-dimethyl- 2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (PY-9)

Yield: 75%; Melting point 228ºC; Molecular formula C21H19ClF3N3O3; Carbon: 55.58; Hydrogen: 4.22; Chlorine: 7.81; Fluorine: 12.56; Nitrogen: 9.26; Oxygen: 10.58; Results: Carbon: 55.40; Hydrogen: 4.32; Chlorine: 7.75; Fluorine: 12.24; Nitrogen: 9.32; Oxygen: 10.42%; MS: *m/z* 454. IR: 3263, 37 (For -NH), 2962 (For -C-H, of Phenyl ring), 1692 (For C=O, carbonyl), 48 (For -C-F).

4-(4-chlorophenyl)-N-[2-chloro-4-(trifluoro methyl) phenyl]-3,6-dimethyl-2- oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (PY-10)

Yield:71%; Melting point 197ºC; Molecular formula C20H16Cl2F3N3O2: Carbon: 52.42; Hydrogen: 3.52; Chlorine: 15.47; Fluorine: 12.44; Nitrogen: 9.17; Oxygen: 6.98; Results: Carbon: 52.40; Hydrogen: 3.42; Chlorine: 15.25; Fluorine: 12.21; Nitrogen 9.12; Oxygen: 6.23%; IR : 3315 (For -NH) , 3070 (For -C-H, of Phenyl ring), 2923 (C- H, CH3 group stretching), 2868 (C-H CH3 group stretching), 1680 (C=O amide stretching), 1600 (N-H, pyrimidine ring), 1529 (C=C, Phenyl ring stretching), 1491 (C-H, CH3 group asymmetrical deformation), 114 (C-H, CH3 group symmetrical deformation), 1344 (C-N-C, pyrimidine ring stretching), 1267 (C-N, stretching), 32 (C-F stretching), 653 (C-Cl starching) ; Mass: 458; 1H NMR (Solvent: Dimethyl sulfoxide-*d6*) δppm: 2.19 (s,3(H),Ha), 3.09 (s, 3(H),Hb), 5.33-5.32 (s, 1(H),Hc), 7.08-7.10 (d, 1(H),Hd,), 7.23-7.26 (d, 1(H),He), 7.32-7.39(m, 3(H),Hf-h,), 7.88-7.90 (m,1(H),Hi), 8.43-8.46 (m, 1(H),Hj), 8.88-8.89 (d, 1(H),Hk,), 10.07 (s, 1(H), Hl).

N-[2-chloro-4-(trifluoro methyl) phenyl]-4-(3, 4-dichlorophenyl)-3, 6- dimethyl-2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (PY-11)

Yield: 71%; Melting point 232ºC; Molecular formula C20H15Cl3F3N3O2: Carbon: 48.75; Hydrogen: 3.07; Chlorine: 21.59; Fluorine: 11.57; Nitrogen: 8.53; O: 6.49; Results: Carbon: 48.70; Hydrogen: 3.10; Chlorine: 21.29; Fluorine: 11.34; Nitrogen 8.52; Oxygen: 6.31%; MS: *m/z* 493. IR: 3254, 3134 (For -NH), 2954 (For -C-H, of Phenyl ring), 1684 (For -C=O, carbonyl), 44 (For -C-F).

4-(4-bromophenyl)-N-[2-chloro-4-(trifluoro methyl) phenyl]-3, 6-dimethyl-2- oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (PY-12)

Yield: 67%; Melting point 195ºC; Molecular formula C20H16BrClF3N3O2: Carbon: 47.78; Hydrogen: 3.21; Bromine: 15.89; Chlorine: 7.05; Fluorine: 11.34; Nitrogen: 8.36; Oxygen: 6.37; Results: Carbon: 47.60; Hydrogen: 3.22; Bromine: 15.74; Chlorine: 7.00; Fluorine: 11.25; Nitrogen: 8.33; Oxygen: 6.22%; MS: *m/z* 503. IR: 3247, 39 (For -NH), 2957 (For -C-H, of Phenyl ring), 1692 (For -C=O, carbonyl), 40(For - C-F).

4. CONCLUSION

A variety of biomedical advantage and with a vision to more determine the pharmacological report of bi/tricyclic aromatic heterocycles linked to pyrimidines, three different heterocyclic scaffolds related to pyrimidines (1,2,3,4-tetrahydropyrimidines have been synthesized in the work.

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