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Synthesis and antimicrobial screening of 1,6-dihydropyrimidine derivatives

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Abstract

Some new dihydropyrimidines have been synthesized and their structures have been elucidated on the basis of IR, ^{1}H NMR and mass spectral data. The compounds were also assayed for their biological assay in DMF and DMSO. It is observed that DMSO is better solvent for the studied compounds and vanillin, salicyldehyde and furan-2-carbaldehyde are found to be most effective in the studied strains.

Key words: 1, 6-dihydropyrimidines, Anti-bacterial activities, Anti-fungal activity.

INTRODUCTION

Pyrimidine derivatives have attracted considerable attention because of their pharmacological properties [1-4] including antiviral, antitumor, antibacterial, antihypertensive etc. Thus, pyrimidines have been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological properties. In recent years, dihydropyrimidines represent a heterocyclic system with remarkable pharmacological efficiency which shows a very similar pharmacological profile to classical of dihydropyridine calcium channel modulators [5-11] e.g. Nifedipine.

Thus, in the present work, some new dihydropyrimidines have been synthesized. Their characterization was done by IR, NMR and mass spectral data. Further, their antimicrobial study was done in DMF and DMSO.

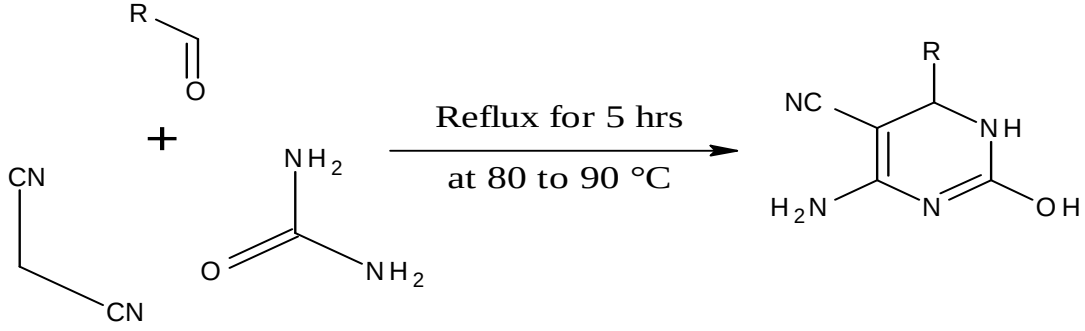
MATERIALS AND METHODS

The following 1, 6-dihydropyrimidines have been synthesized:
(1) 4-amino-2-hydroxy-6-phenyl-1,6-dihydropyrimidine-5-carbonitrile (SDU-1)
(2) 4-amino-2-hydroxy-6-[(E)-2-phenylethenyl]-1,6-dihydropyrimidine-5-carbonitrile (SDU-2)
(3) 4-amino-6-(3-chlorophenyl)-2-hydroxy-1,6-dihydropyrimidine-5-carbonitrile (SDU-3)
(4) 4-amino-6-(4-chlorophenyl)-2-hydroxy-1,6-dihydropyrimidine-5-carbonitrile (SDU-4)

(5) 4-amino-6-(4-fluorophenyl)-2-hydroxy-1,6-dihydropyrimidine-5-carbonitrile (SDU-5)
(6) 4-amino-2-hydroxy-6-(3-nitrophenyl)-1,6-dihydropyrimidine-5-carbonitrile (SDU-6)
(7) 4-amino-2-hydroxy-6-(4-hydroxyphenyl)-1,6-dihydropyrimidine-5-carbonitrile (SDU-7)
(8) 4-amino-2-hydroxy-6-(4-methoxyphenyl)-1,6-dihydropyrimidine-5-carbonitrile (SDU-8)
(9) 4-amino-2-hydroxy-6-(4-hydroxy-3-methoxyphenyl)-1,6-dihydropyrimidine-5-carbonitrile (SDU-9)
(10) 4-amino-6-furan-2-yl-2-hydroxy-1,6-dihydropyrimidine-5-carbonitrile (SDU-10)

These 1, 6-dihydropyrimidines have been synthesized by the condensation of equal molar amount of malononitrile, substituted aldehydes and urea. The mixture was refluxed for 5 hours in water bath, then poured on crushed ice, filtered and dried. The recrystallized samples were characterized by IR, NMR and Mass spectra.

Reaction Scheme



The physical data of these compounds are reported in Table 1.Following are the IR, NMR and Mass spectral data of the synthesized compounds.

SDU-1:
IR (KBr, cm^{-1}): C-H str. (asym.): 2931, C-H str. (sym.): 2837, C=C str.: 1509, C≡N str.: 2156, O-H str.: 3374, N-H str.: 3219; ^{1}H-NMR (δ,ppm): 7.11-8.10 (5H, m, Ar-H), 5.77 (1H, s, CH), 5.58 (1H, s, NH), 8.56 (1H, s, OH).; Mass: (m/z, rel. Int. %) 214m/z, (42%). 201m/z (27%) , 185m/z (38%), 174m/z (43%), 152m/z (54%), 77m/z (69%), 44m/z (98%).

SDU-2:
IR (KBr, cm^{-1}): C-H str. (asym.): 2956, C-H str. (sym.): 2831, C=C str.: 1559, C≡N str.: 2199, O-H str.: 3412, N-H str.: 3266; ^{1}H-NMR (δ,ppm): 7.20-7.96 (5H, m, Ar-H), 6.77 (1H, d, CH=C), 6.83 (1H, d, C=CH), 5.15 (1H, s, CH); Mass: (m/z, rel. Int. %) 242m/z, (63%), 191m/z (34%), 166m/z (38%), 151m/z (32%), 74m/z (44%), 60m/z (32%).

SDU-3:
IR (KBr, cm^{-1}): C-H str. (asym.): 2947, C-H str. (sym.): 2828, C=C str.: 1542, C≡N str.: 2212, O-H str.: 3411, N-H str.: 3226, C-Cl str: 751; ^{1}H-NMR (δ,ppm): 7.08-7.63 (4H, m, Ar-H), 5.74 (1H, s, CH), 5.51 (1H, s, NH); Mass: (m/z, rel. Int. %) 248m/z, (66%), 216m/z (27%) , 176m/z (33%), 151m/z (51%), 88m/z (42%), 74m/z (41%), 60m/z (55%).

SDU-4:
IR (KBr, cm^{-1}): C-H str. (asym.): 2981, C-H str. (sym.): 2817, C=C str.: 1522, C≡N str.: 2216, O-H str.: 3369, N-H str. 3223, C-Cl str: 623; ^{1}H-NMR (δ,ppm): 7.28-7.43 (4H, m, Ar-H), 5.77

(1H, s, CH), 5.61 (1H, s, NH); Mass: (m/z, rel. Int. %) 248m/z, (78%). 239m/z (32%) , 190m/z (38%), 164m/z (40%), 98m/z (29%), 58m/z (46%), 44m/z (98%).

SDU-5:
IR (KBr, cm^{-1}): C-H str. (asym.): 2955, C-H str. (sym.): 2842, C=C str.: 1524, C≡N str.: 2287, O-H str.: 3461, N-H str.: 3259, C-F str: 769; ^{1}H-NMR (δ,ppm): 6.68-7.63 (4H, m, Ar-H), 5.75 (1H, s, CH), 5.62 (1H, s, NH).; Mass: (m/z, rel. Int. %) 232m/z, (42%), 219m/z (35%), 194m/z (31%), 140m/z (41%), 126m/z (44%), 114m/z (69%), 74m/z (62%).

SDU-6:
IR (KBr, cm^{-1}): C-H str. (asym.): 2947, C-H str. (sym.): 2833, C=C str.: 1521, C≡N str.: 2203, O-H str.: 3511, N-H str.: 3254; ^{1}H-NMR (δ,ppm): 7.49-8.33 (4H, m, Ar-H), 6.19 (1H, s, CH), 5.62 (1H, s, NH); Mass: (m/z, rel. Int. %) 259m/z, (69%), 232m/z (45%), 207m/z (31%), 176m/z (29%), 165m/z (28%), 151m/z (49%), 75m/z (37%).

SDU-7:
IR (KBr, cm^{-1}): C-H str. (asym.): 2954, C-H str. (sym.): 2836, C=C str.: 1522, C≡N str.: 2298, O-H str.: 3611, N-H str.: 3244; ^{1}H-NMR (δ,ppm): 6.87-7.27 (4H, m, Ar-H), 5.77 (1H, s, CH), 5.72 (1H, s, NH) 5.75 (1H, s, OH); Mass: (m/z, rel. Int. %) 230m/z (28%), 185m/z (31%), 174m/z (24%), 112m/z (59%), 84m/z (48%).

SDU-8
IR (KBr, cm^{-1}): C-H str. (asym.): 2966, C-H str. (sym.): 2871, C=C str.: 1532, C≡N str.: 2288, O-H str.: 3594, N-H str.: 3221; ^{1}H-NMR (δ,ppm): 3.75 (3H, s, -OCH_3), 6.87-7.27 (4H, m, Ar-H), 5.76 (1H, s, CH), 5.62 (1H, s, NH).; Mass: (m/z, rel. Int. %) 244m/z (25%), 192m/z (34%), 176m/z (40%), 84m/z (37%), 77m/z (29%), 58m/z (67%).

SDU-9:
IR (KBr, cm^{-1}): C-H str. (asym.): 2931, C-H str. (sym.): 2837, C=C str.: 1502, C≡N str.: 2303, O-H str.: 3551, N-H str.: 3227, C-O-C str. (asym.): 1259, C-O-C str. (sym.): 1027; ^{1}H-NMR (δ,ppm): 3.80 (3H, s, -OCH_3), 6.83-6.99 (3H, m, Ar-H), 5.72 (1H, s, CH), 5.71 (1H, s, NH); Mass: (m/z, rel. Int. %) 260m/z, (68%), 195m/z (27%), 150m/z (45%), 138m/z (40%), 124m/z (24%), 97m/z (39%), 82m/z (42%).

SDU-10:
IR (KBr, cm^{-1}): C-H str. (asym.): 2952, C-H str. (sym.): 2820, C=C str.: 1544, C≡N str.: 2323, O-H str.: 3565, N-H str.: 3249; ^{1}H-NMR (δ,ppm): 6.31-7.32 (3H, m, furan ring), 5.33 (1H, s, CH), 5.61 (1H, s, NH); Mass: (m/z, rel. Int. %) 204m/z, (52%), 138m/z (14%), 112m/z (39%), 72m/z (48%).

Antimicrobial activity:
The following bacteria and fungal strains were taken for the study:

BC-Bacillus cereus ATCC11778, MF- Micrococcus flavus ATCC10240
KP-Klebsiella pnemoniae NCIM 2719, PM-Proteus mirabilis NCIM2241
CT- Candida tropicalis ATCC4563, CL- Cryptococcus luteolus ATCC32044

Preparation of test compound
Three different concentrations i.e., 2 mg/0.1ml, 0.2 mg / 0.1 ml and 0.02 mg / 0.1 ml were prepared for all the compounds in both DMF and DMSO.

Preparation of the plates and microbiological assays

A loop full of the given test strain was inoculated in 20ml of N-broth (Nutrient Broth). To activate the given bacterial strain, it was incubated for 24 hours in an incubator at 37°C.

The Agar well diffusion method [12] is used for antibacterial assay. 28-30 ml of molten agar (Mueller Hinton Agar No. 2) was added into the 100 mm diameter Petri plate. Care should be taken to avoid air bubbles during inoculation and pouring. To maintain sterile condition, all these procedures were done in the laminar air flow. The media was allowed to solidify. After solidification of the media, well was made in the plates with the help of cup-borer (0.85 cm) and then it was filled with the synthesized 1, 6-dihydropyrimidines solution (dissolved in DMF/DMSO).

The antibacterial activities of these synthesized bases were determined by the inhibition zone formed by these compounds against the particular test bacterial strain.

RESULTS AND DISCUSSION

Out of the three concentrations studied, zone of inhibition was not significant for 0.2 mg / 0.1 ml and 0.02 mg / 0.1 ml concentrations. Thus, results of only 2 mg/0.1ml are reported and discussed. The zone of inhibition against studied strains in both DMF and DMSO are reported in Table 2 and are also shown in Figures 1 and 2 respectively. Comparison of inhibition in two solvents shows that DMSO is better solvent than DMF.

Table 1: Physical constants of synthesized dihydropyrimidines

Sr. No.	Compound Code	R	Mol.Wt (g)	M.P. ^{0}C	Yield %
1	SDU-1	-C_6H_5	214	64	93.07
2	SDU-2	-CH=CH-C_6H_5	242	110	80.57
3	SDU-3	m-Cl-C_6H_4 -	248	146	94.25
4	SDU -4	p-Cl-C_6H_4 -	248	150	70.29
5	SDU -5	p-F-C_6H_4 -	232	134	59.85
6	SDU -6	m-NO_2-C_6H_4 -	259	154	60.73
7	SDU -7	p-OH-C_6H_4 -	230	184	77.59
8	SDU -8	p-OCH_3-C_6H_4 -	244	115	50.23
9	SDU -9	Vaniline	260	80	76.09
10	SDU-10	furan-2-carbaldehyde	204	70	85.05

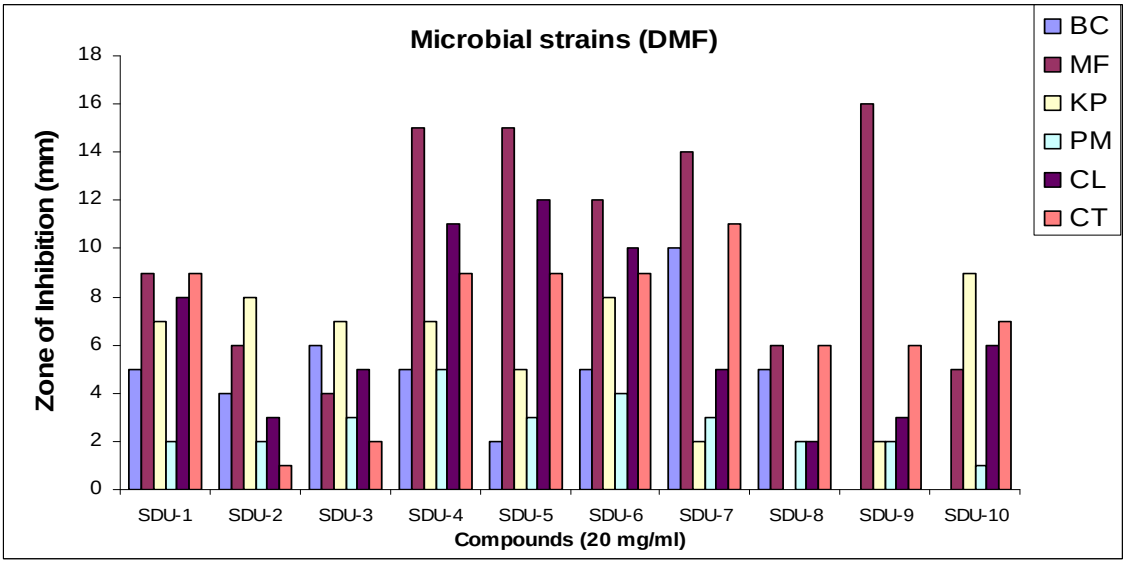
Against *Micrococcus flavus*, most of compounds exhibited maximum inhibition in DMF. Whereas in DMSO, overall inhibition is maximum against *Bacillus cereus*. In both the solvents, SDU-9 and SDU-7 showed maximum inhibition against *Micrococcus flavus* and *Bacillus cereus* respectively.

The inhibition depends upon three main factors: solvent, structure and strain [13]. All the derivatives have dihydropyrimidine as central moiety to which different aromatic aldehydes are attached. These different side chains affect differently in different solvents against different microbial strains.

Table 2: Zone of inhibition of dihydropyrimidines against microbial strains in DMF and DMSO

Compound Code	Test microorganisms					
	DMF					
	BC	MF	KP	PM	CL	CT
SDU-1	5.0	9.0	7.0	2.0	8.0	9.0
SDU-2	4.0	6.0	8.0	2.0	3.0	1.0
SDU-3	6.0	4.0	7.0	3.0	5.0	2.0
SDU-4	5.0	15.0	7.0	5.0	11.0	9.0
SDU-5	2.0	15.0	5.0	3.0	12.0	9.0
SDU-6	5.0	12.0	8.0	4.0	10.0	9.0
SDU-7	10.0	14.0	2.0	3.0	5.0	11.0
SDU-8	5.0	6.0	0.0	2.0	2.0	6.0
SDU-9	0.0	16.0	2.0	2.0	3.0	6.0
SDU-10	0.0	5.0	9.0	1.0	6.0	7.0
	DMSO					
SDU-1	19.0	16.0	13.0	2.0	8.0	2.0
SDU-2	14.0	16.0	11.0	4.0	1.0	4.0
SDU-3	17.0	10.0	10.0	4.0	4.0	4.0
SDU-4	17.0	13.0	12.0	3.0	9.0	3.0
SDU-5	14.0	12.0	8.0	1.0	7.0	1.0
SDU-6	19.0	15.0	10.0	4.0	10.0	4.0
SDU-7	25.0	19.0	10.0	10.0	4.0	10.0
SDU-8	10.0	0.0	7.0	2.0	2.0	1.0
SDU-9	12.0	24.0	5.0	1.0	4.0	1.0
SDU-10	15.0	15.0	13.0	1.0	11.0	1.0

Fig. 1: Comparative study of Dihydropyrimidines in DMF

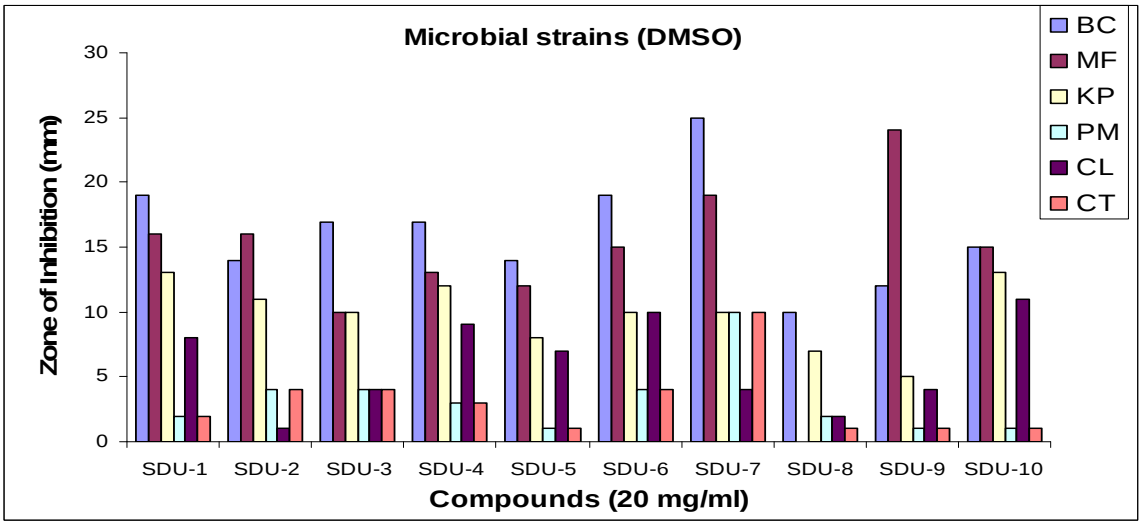


Thus, in both the solvents, vanillin is most effective side chain (in SDU-9) for *Micrococcus flavus* and salicyldehyde is most effective (in SDU-7) against *Bacillus cereus*.

In DMF, except, SDU-8, all compounds could inhibit *Klebsiella pnemoniae* and SDU-10 containing furan-2-carbaldehyde side chain exhibited maximum. Thus, p-methoxy benzaldehyde side chain (as in SDU-8) is not effective at all for *Klebsiella pnemoniae*. Against *Cryptococcus luteolus* and *Candida tropicalis*, SDU-5 (having p-flurobenzaldehyde) and SDU-7 (having salicydehyde) respectively, showed maximum inhibition.

In DMSO, SDU-8 containing p-methoxy benzaldehyde showed no inhibition against *Micrococcus flavus*. For *Klebsiella pnemoniae*, SDU-1 and SDU-10 containing benzaldehyde and furan-2-carbaldehyde side chains respectively, exhibited maximum inhibition. SDU-7 showed higher inhibition against *Proteus mirabilis* and *Candida tropicalis* in comparison to other compounds whereas SDU-10 exhibited maximum for *Cryptococcus luteolus*.

Fig. 2: Comparative study of Dihydropyrimidines in DMSO



CONCLUSION

DMSO is better solvent for the studied strains. Overall, Proteus mirabilis is most resistant bacterial strain in both the solvents. Candida tropicalis is found to be more resistant fungal strain in DMSO whereas in DMF2 mg/0.1ml, most of the compounds could inhibit this strain. Overall, SDU-7, SDU-9 and SDU-10 are most effective in inhibiting all the microbial strains in both solvents.

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