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Synthesis and Antimicrobial Activity of 1-Substituted Phenyl-3-substituted Phenyl-4-[(3,4,5-trimethoxy)-5-benzyl]-4-aminopyrimidine Formazans

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A series of 15 novel 1-substituted phenyl-3-substituted phenyl-4-[(3,4,5-trimethoxy)-5-benzyl]-4-amino pyrimidine formazans [**2a-2o**] were synthesized from trimethoprim. All the compounds were characterized by analytical and spectral analysis. The antibacterial and antifungal activities were screened for all the compounds. The synthesized compounds were found to have significant effect against the tested organisms.

Key Words: Synthesis, Pyrimidine formazans, Antibacterial, Antifungal.

INTRODUCTION

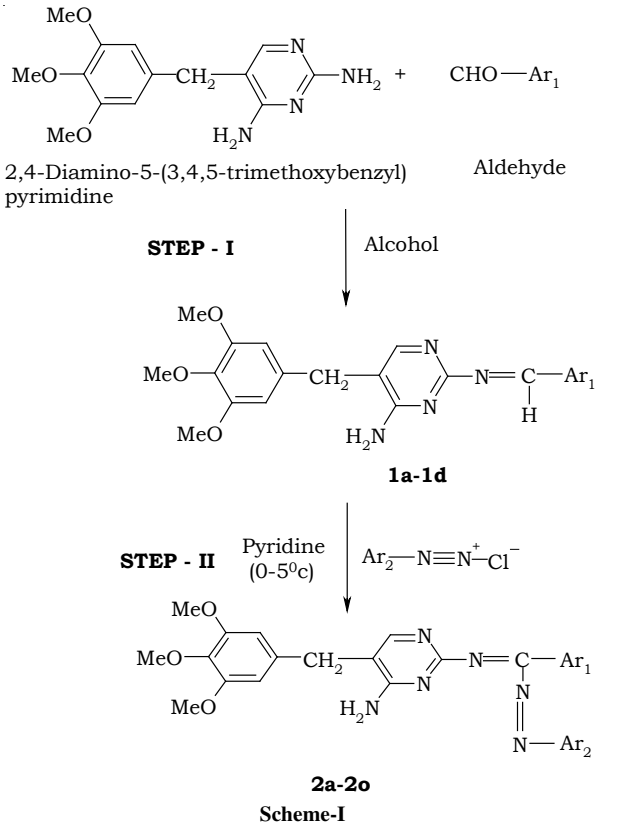
Pyrimidine nucleus has wide range of importance in medicinal chemistry, due to wide spectrum of biological activities exhibited by them. Pyrimidines and formazans have exhibited a variety of biological activities. Literature survey revealed that various substituted pyrimidines are known to possess antimicrobial[1,2], antiinflammatory[3], herbicidal[4], anticancer[5], antiviral[6], antimalarial[7] and other miscellaneous activities while formazans show promising antifertility[8], antiparkinsonian[9], anticancer[10], antibacterial[11-13], antifungal[11-13], antiviral[14], antidepressant[15], MAO inhibitory[15], antiinflammatory[16] activities.

All these valid observations led us to synthesize some new pyrimidine formazan derivatives to explore their possible biological activities.

EXPERIMENTAL

Melting points of the newly synthesized compounds were determined by open capillary method and uncorrected. Purity of the compound was checked by TLC using silica gel-G plate, chloroform:benzene (8.5:1.5) as mobile phase and iodine vapours as detecting agent. IR spectra (KBr, ν_{max}, cm^{-1}) were recorded on Perkin Elmer FTIR spectrophotometer. ^1H NMR spectra were recorded on Brucker AMX 400 MHz instrument using TMS as internal standard. Mass spectra were recorded on Agilent LC-MSD spectrometer.

The synthesis of 1-substituted phenyl-3-substituted phenyl-4-[(3,4,5-trimethoxy)-5-benzyl]-4-amino pyrimidine formazans is given in the **Scheme-I**. The physical data are given in Table-1.



Scheme-I

Synthesis of N-substituted phenyl-4-[(3,4,5-trimethoxy)-5-benzyl]-4-aminopyrimidine azomethines (1): A mixture of 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine

TABLE-1
PHYSICAL DATA OF SYNTHESIZED COMPOUNDS

Compound	Ar_1	Ar_2	Physical state	m.f. (m.w.)	m.p. (ºC)	Yield (%)
2a	C_6H_5	C_6H_4Cl	Yellow amorphous	$C_{27}H_{25}N_6O_3Cl$ (517)	144	63.3
2b	C_6H_5	C_6H_4Br	Brown amorphous	$C_{27}H_{25}N_6O_3Br$ (561.4)	218	58.5
2c	C_6H_5	$C_6H_4NO_2$	Brown amorphous	$C_{27}H_{25}N_7O_5$ (527.5)	280	61.2
2d	C_6H_5	C_6H_3FCl	Black amorphous	$C_{27}H_{24}N_6O_3FCl$ (535)	198	58.0
2e	C_6H_4Cl	C_6H_4Cl	Pale yellow amorphous	$C_{27}H_{24}N_6O_3Cl_2$ (551.4)	138	67.2
2f	C_6H_4Cl	C_6H_4Br	Pale yellow amorphous	$C_{27}H_{24}N_6O_3ClBr$ (596)	226	66.3
2g	C_6H_4Cl	$C_6H_4NO_2$	Pale brown amorphous	$C_{27}H_{24}N_7O_5Cl$ (562)	292	65.1
2h	C_6H_4Cl	C_6H_3FCl	Pale brown amorphous	$C_{27}H_{23}N_6O_3FCl$ (534)	214	70.0
2i	$C_6H_4NO_2$	C_6H_4Br	Yellow amorphous	$C_{27}H_{24}N_7O_5Br$ (606.4)	162	62.3
2j	$C_6H_4NO_2$	$C_6H_4NO_2$	Brown amorphous	$C_{27}H_{24}N_8O_7$ (572.5)	258	58.9
2k	$C_6H_4NO_2$	C_6H_3FCl	Black crystalline	$C_{27}H_{23}N_7O_5FCl$ (580)	190	61.0
2l	$C_6H_4N(CH_3)_2$	C_6H_4Cl	Pale yellow amorphous	$C_{29}H_{30}N_7O_3Cl$ (560)	186	59.3
2m	$C_6H_4N(CH_3)_2$	C_6H_4Br	Brown amorphous	$C_{29}H_{30}N_7O_3Br$ (604.5)	260	60.4
2n	$C_6H_4N(CH_3)_2$	$C_6H_4NO_2$	Brown amorphous	$C_{29}H_{30}N_8O_5$ (570.6)	310	66.2
2o	$C_6H_4N(CH_3)_2$	C_6H_3FCl	Black crystalline	$C_{29}H_{29}N_7O_3FCl$ (578)	272	56.9

(trimethoprim) (0.1 mol) and aldehyde or substituted aldehyde (0.1 mol) in alcohol were refluxed for 6 h and poured into ice-cold water. The resulting mass was washed with water for several times and crystallized from DMSO.

Synthesis of 1-substituted phenyl-3-substituted phenyl-4-[(3,4,5-trimethoxy)-5-benzyl]-4-amino pyrimidine formazans (2a-2o): The diazonium salts obtained from the respective amines (0.01 mol) were added with stirring to N-substituted phenyl-4-[(3,4,5-trimethoxy)-5-benzyl]-4-amino pyrimidine azomethines (0.01 mol) in pyridine at 0-5 ºC for 0.5 h. The mixture was poured into cold water. The resulting product was filtered, dried and crystallized from DMSO.

2b: IR (KBr, ν_{max}, cm^{-1}): 1596 (C=N), 1512 (N=N), 3438 (N-H), 1485 (aromatic C=C), 1196 (C-O, -OCH_3), 3193 (C-H, -CH_2), 825 (C-Cl). ^{1}H NMR (δ ppm): 7.443-7.528 (m, 12H, Ar-H), 3.322 (s, 2H, -NH_2), 3.322 (s, 3H, -OCH_3), 2.507-2.511 (s, 2H, -CH_2).

2c: IR (KBr, ν_{max}, cm-1): 1595 (C=N), 1515 (N=N), 3442 (N-H), 1167 (C-O, -OCH_3), 1342 (N-O, -NO_2), 3278 (C-H, -CH_2). ^{1}H NMR (δ ppm): 7.694-8.459 (m, 12H, Ar-H), 3.325 (s, 2H, -NH_2), 3.752 (s, 3H, -OCH_3), 2.512 (s, 2H, -CH_2). MS: m/z (M^+) 529.

2e: IR (KBr, ν_{max}, cm^{-1}): 1595 (C=N), 1507 (N=N), 3437 (N-H), 1462 (aromatic C=C), 1195 (C-O, -OCH_3), 3158 (-C-H,-CH_2), 827 (C-Cl). ^{1}H NMR (δ ppm): 6.067-8.588 (m, 11H, Ar-H), 3.333 (s, 2H, -NH_2), 3.534-3.730 (s, 3H, -OCH_3), 2.511 (s, 2H, -CH_2).

2f: IR (KBr, ν_{max}, cm^{-1}): 1593 (C=N), 1506 (N=N), (aromatic C=C), 1195 (C-O, -OCH_3), 3323 (N-H), 3157 (C-H, -CH_2), 824 (C-Cl), 706 (C-Br). ^{1}H NMR (δ ppm): 6.062-8.591 (m, 11H, Ar-H), 3.328 (s, 2H, -NH_2), 3.532-3.728 (s, 3H, -OCH_3), 2.506-2.514 (s, 2H, -CH_2).

2g: IR (KBr, ν_{max}, cm^{-1}): 1594 (C=N), 1513 (N=N), 3472 (N-H, primay amine), 1165 (C-O, -OCH_3), 1340 (N-O, -NO_2), 1474.86 (aromatic, C=C), 3281 (C-H, -CH_2), 857 (C-Cl). ^{1}H NMR (δ ppm): 7.373-8.588 (m, 11H, Ar-H), 3.326 (s, 2H, -NH_2), 3.535-3.730 (s, 3H, -OCH_3), 2.506-2.510 (s, 2H, -CH_2).

2i: IR (KBr, ν_{max}, cm^{-1}): 1597 (C=N), 1511 (N=N), 3436 (N-H, primay amine), 1196 (C-O, -OCH_3), 1346 (N-O, -NO_2), 1482 (aromatic, C=C), 3195 (C-H, -CH_2), 735.39 (C-Br). ^{1}H NMR (δ ppm): 7.567-8.439 (m, 11H, Ar-H), 3.321 (s, 2H, -NH_2), 3.643-3.753 (s, 3H, -OCH_3), 2.505-2.514 (s, 2H, -CH_2). MS: m/z (M^+) 602.7.

2j: IR (KBr, ν_{max}, cm^{-1}): 1600 (C=N), 1520 (N=N), 3271 (N-H), 1194 (C-O, -OCH_3), 1344 (N-O, -NO_2), 3104 (C-H, -CH_2). ^{1}H NMR (δ ppm): 6.617-8.453 (m, 11H, Ar-H), 3.335 (s, 2H, -NH_2), 3.752 (s, 3H, -OCH_3), 2.510-2.512 (s, 2H, -CH_2). MS: m/z (M^+) 575.1.

2k: IR (KBr, ν_{max}, cm^{-1}): 1598 (C=N), 1498 (N=N), 3387 (N-H), 1196 (C-O, -OCH_3), 3103 (C-H, -CH_2), 1344 (N-O, -NO_2), 1196 (C-F), 815 (C-Cl). ^{1}H NMR (δ ppm): 6.577-8.427 (m, 11H, Ar-H), 3.337 (s, 2H, -NH_2), 3.757 (s, 3H, -OCH_3), 2.475-2.511 (s, 2H, -CH_2). MS: m/z (M^+) 562.

2n: IR (KBr, ν_{max}, cm^{-1}): 1594 (C=N), 1516 (N=N), 3369 (N-H), 1164 (C-O, -OCH_3), 1447 (aromatic C-C), 3071 (C-H, -CH_2), 1340 (N-O, -NO_2). ^{1}H NMR (δ ppm): 6.780-8.457 (m, 11H, Ar-H), 3.332 (s, 2H, -NH_2), 3.701-3.751 (s, 3H, -OCH_3), 2.505 -2.514 (s, 2H, -CH_2), 1.932 (s, 3H, -CH_3).

2o: IR (KBr, ν_{max}, cm^{-1}): 1599.82 (C=N), 1524.84 (N=N), 3388 (N-H), 1195 (C-O, -OCH_3), 1499 (aromatic C=C), 3103 (C-H, -CH_2), 1122 (C-F, aryl flouride), 815 (C-Cl). ^{1}H NMR (δ ppm): 6.604-8.855 (s, 11H, Ar-H), 3.344 (s, 2H, -NH_2), 3.748 (s, 3H, -OCH_3), 2.511 (s, 2H, -CH_2), 1.918-1.920 (s, 3H, CH_3).

Antimicrobial screening: Antibacterial activity of synthesized compounds were screened against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus* and *Staphylococcus epidermidis* using paper disc diffusion method. The compounds were tested at 10 mg/mL level. The results were compared with ciprofloxacin (100 µg/disc). All the compound showed moderate to significant antibacterial activity (Table-2).

Antifungal activity of the synthesized compounds were screened against *Aspergillus niger*, *Saccharomyces cerevisiae*, *Candida albicans*, *Candida glabrata* using paper disc diffusion method at 10 mg/mL level. Fluconazole (100 µg/disc) was used as standard for comparison. All the compounds showed moderate to significant activity (Table-2).

RESULTS AND DISCUSSION

Various 1-substituted phenyl-3-substituted phenyl-4-[(3,4,5-trimethoxy)-5-benzyl]-4-amino pyrimidine formazan

TABLE-2
ANTIMICROBIAL SCREENING-ZONE OF INHIBITION (mm)

Microorganism (bacteria)	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**	**2i**	**2j**	**2k**	**2l**	**2m**	**2n**	**2o**	Std.*
E. coli	19	18	20	17	17	15	16	20	19	21	20	9	5	15	12	22
P. aeruginosa	5	–	12	9	11	13	11	5	21	20	18	6	5	13	17	21
B. subtilis	25	24	22	25	15	16	13	–	25	25	15	–	5	24	14	21
B. cereus	–	8	13	8	13	13	15	8	19	17	15	–	6	14	13	17
S. aureus	–	9	15	10	12	18	20	22	22	21	21	20	15	13	18	20
S. epidermidis	25	19	25	24	17	17	16	24	24	26	14	–	11	14	18	20
Microorganism (fungi)																
A. niger	–	–	21	–	9	13	18	14	23	21	26	10	14	16	–	17
S. cerevisiae	–	8	23	8	11	12	14	–	16	22	19	10	13	22	–	18
C. albicans	–	6	18	10	15	7	10	14	20	20	17	9	10	12	8	19
C. glabrata	10	7	24	16	9	19	18	20	22	24	20	8	10	23	10	22

derivatives were synthesized from trimethoprim. The structures of the synthesized compounds were confirmed by IR, ^{1}H NMR and mass spectral analysis. The compounds having aryl nitro, fluorine and chlorine at 4th position of one phenyl ring along with formazan nucleus enhances biological activity. The compounds **2c, 2i, 2j, 2k, 2n** and **2o** have exhibited significant antibacterial activity where as compounds **2e, 2f** and **2g** shown good antibacterial activity when compared with standard drug ciprofloxacin. The compounds **2c, 2i, 2j, 2k** and **2n** exhibited significant antifungal activity when compared with the standard drug fluconazole.

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