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Synthesis and Anti Bacterial and Anti-ulcer Evaluation of New S-mannich Bases of 4,6-diaryl-3,4-dihydropyrimidin-2(1*H*)-thiones

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ABSTRACT. The synthesis of title compounds were accomplished by synthetic sequence shown in *Scheme* 1. Chalcones on cyclocondensation with thiourea in ethanol and potassium hydroxide under reflux yielded the respective dihydropyramidin-2(1*H*)-thiones. Each of the dihydropyrimidin thiones was, then subjected to the Mannich condensation in alkaline medium using three different secondary amines, viz., dimethylamine, diethylamine and morpholine to obtain a new series of S-Mannich bases. All the synthesised compounds **(C_1–C_{15})** were evaluated for their antiulcer and antibacterial activities. Compounds **C_4**, **C_5**, **C_6**, **C_{14}** and **C_{15}** exhibited relatively more potent antiulcer activity but not comparable to the standard; Omeprazole, while **C_1**, **C_2**, **C_3** and **C_{13}** were moderate in activity at 100 mg/kg p.o. All the compounds **(C_1–C_{15})** showed mild to moderate activity against both Gram-positive (*S.aureus, L.delbrueckii*) and Gram-negative (*P.vulgaris, E.coli*) bacteria. Amongst the compounds tested, only **C_6**, **C_9**, **C_{12}** and **C_{15}** were found to be potent.

Key words: 4, 6-diaryl-3,4-dihydropyramidin-2(1*H*)-thiones, Anti-ulcer activity, Antibacterial activity

INTRODUCTION

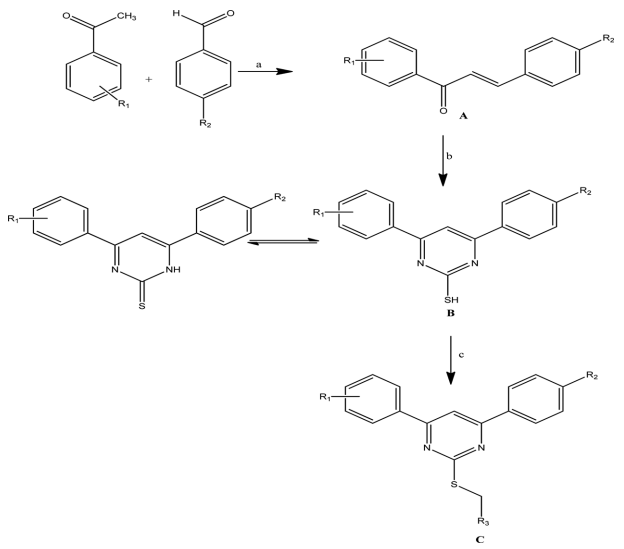
Pyrimidines are of considerable chemical and biological significance. Many pyrimidine derivatives have displayed diverse pharmacological activities such as anti-inflammatory,[1–3] antimicrobial,[4] analgesic,[5] antiplatelet,[6] antithrombotic,[6] antineoplastic,[7] antianginal,[8] antiulcer[9] activities, etc., keeping in view the importance of these dihydropyrimidines in the field of medicine and biology and in continuation of our work on new dihydropyrimidine derivatives, an attempt has now been made to synthesize novel S-Mannich bases and to investigate their antiulcer and antibacterial activities.

The present work describes the synthesis of S-Mannich bases of dihydropyrimidin-2(1*H*)-thiones and evalution of antiulcer activity using aspirin-induced model and antibacterial activity against Gram-(+ve) (*S.aureus*, *L.delbrueckii*) and Gram-(–ve) (*P.vulgaris, E.coli*) bacteria. A new series of S-Mannich bases of dihydropyrimidin-2(1*H*)-thiones **(C_1–C_{15})** were synthesized by the Mannich reaction on five different 3,4-dihyropyrimidine 2(1*H*)-thiones **(B1–B5)** using aqueous formaldehyde, potassium carbonate and three different secondary amines, viz., dimetylamine, diethylamine and morpholine. All the compounds prepared were characterized by their physical and spectral (IR, NMR, Mass) data. Results of biological activities showed that some of these new S-Mannich bases possess antiulcer and antibacterial activities, with a variation in potencies.

RESULTS AND DISCUSSION

Chemistry

A novel series of [4,6-substituted diaryl-3,4-dihyropyramidine-2-yl-thiomethyl]-amines were synthesized on the lines of a synthetic route presented in *Scheme* 1. The desired compounds were synthesized as follows: initially, an equimolar quantities of differently substituted acetophenones and substituted benzaldehydes in the presence of sodium hydroxide, through a mixed aldol condensation yielded the corresponding chalcones **(A_1–A_5)**. Each of these chalcones **(A_1–A_5)** was heated under reflux with thiourea in the presence of sodium hydroxide to yield the respective 4,6-diaryl dihydropyrimidine-2(1*H*)-thione **(B_1–B_5)**. The Mannich condensation of thiones, **B_1–B_5** with three secondary amines (dimethylamine, diethylamine and morpholine) and formaldehyde, in dimethyl sulfoxide (DMSO) afforded the corresponding Mannich bases **(C_1–C_{15})**. These compounds have been characterized by their IR, ^{1}HNMR and Mass spectral data and elemental analyses. The physical data of the chalcones and dihydropyrimidin-2(1*H*)-thiones are presented in *Table* 1 and that of their S-



***Scheme* 1. Substituents:** R_1 = *p*-Cl, *p*-OH, *m*-NO_2; R_2 = *p*-Cl, *p*-OCH_3, *p*-$N(CH_3)_2$; R_3 = dimethylamino, diethylamino & 4-morpholino. **Reaction conditions:** a = aq. NaOH, ethanol; b = thiourea, KOH, ethanol; c = secondary amines (dimethylamine, diethylamine or morpholine), aq.formaldehyde (37%), K_2CO_3 and DMSO.

Mannich bases in *Table* 2, respectively.

Spectral Analyses

A sharp singlet peak at δ 3.40 ppm indicates the presence of **CH** proton (C_5 of pyrimidine), a characteristic signal at δ 3.62 ppm as a singlet is assigned to **CH_2** proton (S-**CH_2–N**), a multiplet at δ 7.2–7.8 ppm indicates the presence of aromatic protons (Ar–H) The mass spectra of all the synthesized compounds (**C_1–C_{15}**) showed molecular ion peak at M+1 and M+2, characteristic of the presence of sulphur.

BIOLOGICAL EVALUATION

Antiulcer Activity[13–16]

Antiulcer activity of all the synthesized compounds was evaluated by using aspirin induced ulcer model in Albino rats. Albino rats weighing 150–200 g were divided into different groups consisting of six animals per group and starved for 24 hrs. The test compounds were administered orally 30 min prior to aspirin administration (100 mg/kg). Control group received only vehicle (1% sodium carboxy methyl cellulose), whereas the standard group received omeprazole 20 mg/kg. After 5 hr of drug treatment all the animals were sacrificed according to the CPCSEA guidelines and stomach was cut open in the greater curvature, washed with ice cold saline and cleaned. The gastric mucosa was examined for ulcer scoring by using 4x binocular magnifier .The ulcer score is according to its severity in comparison with that of the standard. Ulcer scores were recorded as follows:

0: Normal, no ulcer
1: Isolated haemorrhagic spot
2: Dense haemorrhagic spot
3: Small ulcer
4: Large ulcer
5: Perforation

The severity of the mucosal damage was assessed by Ulcer Index (UI) and it was calculated by using the formula:

$UI = U_N + U_S + U_P \times 10^{-1}$
U_N = average of number of ulcers per animal,
U_S = average of severity score, and
U_P = percentage of animals with ulcers.

The mean ulcer index and percentage protection produced

***Table* 1.** Physical data of chalcones and dihydropyrimidin-2(1*H*)-thiones

Code	R_1	R_2	Mol. formula	Mol. Weight	M.P	% Yield	R_f*
A_1	p-Cl	p-Cl	$C_{15}H_{10}Cl_2O$	276	95–100	67	0.71
A_2	p-Cl	p-OCH_3	$C_{15}H_{13}ClO_2$	260	79–82	62	0.68
A_3	p-Cl	p-$N(CH_3)_2$	$C_{17}H_{16}ClNO$	285	87–91	67	0.67
A_4	p-OH	p-Cl	$C_{15}H_{11}ClO_2$	258	85–87	69	0.54
A_5	m-NO_2	p-Cl	$C_{15}H_{10}ClNO_3$	287	92–96	65	0.63
B_1	P-Cl	p-Cl	$C_{16}H_{11}Cl_2N_2O$	317	155–160	59	0.49
B_2	P-Cl	p-OCH_3	$C_{16}H_{14}ClN_2O_2$	301	174–178	49	0.52
B_3	P-Cl	p-$N(CH_3)_2$	$C_{18}H_{17}ClN_3O$	326	163–165	45	0.47
B_4	P-OH	p-Cl	$C_{16}H_{13}ClN_2O_2$	300	168–170	43	0.55
B_5	m-NO_2	p-Cl	$C_{16}H_{11}ClN_3O_3$	329	182–185	59	0.47

*n-hexane–ethyl acetate (1:1) on silica gel.

***Table* 2.** Physical data of S-Mannich bases of dihydropyrimidin-2(1*H*)-thiones

Code	R_1	R_2	R_3	Mol. formula	Mol. weight	M.P (°C)	% Yield	R_f*
C_1	p-Cl	p-Cl	dimethylamino	$C_{17}H_{14}Cl_2N_3S$	390	268–270	56	0.50
C_2	p-Cl	p-Cl	diethylamino	$CH_{21}Cl_2N_3S$	417	248–252	60	0.44
C_3	p-Cl	p-Cl	4-morpholino	$CH_{19}Cl_2N_3OS$	431	264–268	64	0.48
C_4	p-Cl	p-OCH_3	dimethylamino	$C_{20}H_{20}ClN_3OS$	385	254–256	56	0.42
C_5	p-Cl	p-OCH_3	diethylamino	$C_{24}H_{22}ClN_3OS$	413	264–266	60	0.40
C_6	p-Cl	p-OCH_3	4-morpholino	$C_{22}H_{22}ClN_3O_2S$	427	250–254	54	0.50
C_7	p-Cl	p-$N(CH_3)_2$	dimethylamino	$C_{21}H_{23}ClN_4S$	398	268–270	56	0.51
C_8	p-Cl	p-$N(CH_3)_2$	diethylamino	$C_{23}H_{27}ClN_4S$	426	276–278	60	0.57
C_9	p-Cl	p-$N(CH_3)_2$	4-morpholine	$C_{23}H_{25}ClN_4OS$	440	284–286	64	0.59
C_{10}	p-OH	p-Cl	dimethylamino	$C_{19}H_{18}ClN_3OS$	310	279–282	56	0.50
C_{11}	p-OH	p-Cl	diethylamino	$C_{21}H_{22}ClN_3OS$	399	285–288	60	0.54
C_{12}	p-OH	p-Cl	4-morpholino	$C_{21}H_{20}ClN_3O_2S$	413	274–276	64	0.58
C_{13}	m-NO_2	p-Cl	dimethylamino	$C_{19}H_{17}ClN_4O_2S$	400	268–270	56	0.47
C_{14}	m-NO_2	p-Cl	diethylamino	$C_{21}H_{19}ClN_4O_3S$	428	275–278	60	0.50
C_{15}	m-NO_2	p-Cl	4-morpholino	$C_{21}H_{19}ClN_4O_3S$	442	281–284	71	0.48

*n-hexane–ethyl acetate (1:2) on silica gel.

***Table* 3.** Results of antiulcer activity of different compounds

Code	R_1	R_2	R_3	Ulcer index (UI)*	% protection
C_1	p-Cl	p-Cl	dimethylamino	$19.23\pm4.2^{*}$	30.73
C_2	p-Cl	p-Cl	diethylamino	$19.56\pm3.8^{*}$	29.54
C_3	p-Cl	p-Cl	4-morpholino	$17.96\pm4.2^{**}$	35.30
C_4	p-Cl	p-OCH_3	dimethylamino	$12.50\pm0.52^{***}$	54.97
C_5	p-Cl	p-OCH_3	diethylamino	$11.66\pm0.23^{***}$	58.00
C_6	p-Cl	p-OCH_3	4-morpholino	$11.33\pm0.09^{***}$	59.19
C_7	p-Cl	p-$N(CH_3)_2$	dimethylamino	22.66 ± 5.3^{ns}	18.37
C_8	p-Cl	p-$N(CH_3)_2$	diethylamino	23.58 ± 6.1^{ns}	15.06
C_9	p-Cl	p-$N(CH_3)_2$	4-morpholine	$18.16\pm4.2^{**}$	34.58
C_{10}	p-OH	p-Cl	dimethylamino	27.36 ± 6.2^{ns}	1.44
C_{11}	p-OH	p-Cl	diethylamino	27.00 ± 6.4^{ns}	2.74
C_{12}	p-OH	p-Cl	4-morpholino	26.50 ± 7.8^{ns}	4.54
C_{13}	m-NO_2	p-Cl	dimethylamino	$17.98\pm5.3^{**}$	35.23
C_{14}	m-NO_2	p-Cl	diethylamino	$12.50\pm0.98^{***}$	54.97
C_{15}	m-NO_2	p-Cl	4-morpholino	$12.80\pm0.68^{***}$	53.89
Control	–	–	–	27.76±7.3	–
Standard	–	–	–	$0.25\pm0.06^{***}$	99.10

*Ulcer index expressed in Mean±S.D.

Test dose for control, standard and test compounds: 100 mg/kg.

n=6, values expressed as Mean ± SD, statistical comparison was performed using One-Way ANOVA followed by Dunnett's post-test, $*p\leq 0.05$, $**p\leq0.01$, $***p\leq0.001$, ^{ns}– non significant, compared to control.

by different test compounds are presented in *Table* 3 along with their statistical significance.

In vivo antiulcer activity of the synthesized compounds **(C_1–C_{15})** was evaluated by aspirin-induced ulcer model using Omeprazole as the standard drug. Ulcer index and percentage protection of test compounds was calculated. From the results, it could be inferred that the compunds **C_4, C_5, C_6, C_{14}** and **C_{15}** possess more antiulcer activity while compounds **C_1, C_2, C_3, C_9** and **C_{13}** were moderate in their activity when compared with the control group. The compounds **C_7, C_8, C_{10}, C_{11}** and **C_{12}** were lacking significant activity. However, the antiulcer activity of the present series of compounds is not at all comparable with that of the standard Omeprazole.

***Table* 4.** Antibacterial activity of synthesised compounds (C_1–C_{15}) and their MIC (μg/ml)

Code	*S.aureus*	*L.delbrueckii*	*P.vulgaris*	*E.coli*
Ciprofloxacin	10	10	10	10
C_1	50	25	50	75
C_2	60	75	60	100
C_3	50	25	60	50
C_4	75	100	100	50
C_5	100	100	50	50
C_6	30	25	25	35
C_7	25	50	100	25
C_8	100	100	25	25
C_9	25	55	45	35
C_{10}	50	125	50	25
C_{11}	25	50	100	125
C_{12}	50	35	60	75
C_{13}	125	25	50	50
C_{14}	100	100	125	50
C_{15}	25	50	35	25

Antibacterial Activity[17]

The antibacterial activity of the test compounds was assayed, against four different strains of bacteria, i.e., *Staphylococcus aureus* and *Lactobacillus delbrueckii* (Gram positive) *Proteus vulgaris* and *Escherichia coli* (Gram negative) by the agar diffusion method. Generally, the antibacterial activity of a compound is expressed in terms of its ability to inhibit the growth of bacteria in nutrient broth or agar. Ciproflaxacin was used as the standard drug. The compounds and their minimum inhibitory concentrations (MIC) in μg/ml are presented in *Table* 4.

In vitro antibacterial activity of all the synthesized compounds **(C_1–C_{15})** showed to be mild to moderate against both the Gram-positive (*S.aureus, L.delbrueckii*) and Gram-negative (*P.vulgaris, E.coli*) bacteria. Amongst them, the compounds **C_6, C_9, C_{12}** and **C_{15}** were found to be relatively more potent.

EXPERIMENTAL SECTION

All the chemicals were of synthetic grade and commercially procured from Sigma Aldrich, Mumbai, India. Melting points were determined by open capillary method and were uncorrected. IR spectra were recorded on FTIR (Bruker Alpha-E) by KBr disc method. The ^{1}H NMR spectra were recorded at 400MHz in DMSO-d_6 as solvent and TMS as an internal standard using BRUKER ADVANCE 400 instrument. Mass spectra were recorded on PEP-SCIUX-APIQ pulsar mass spectrophotometer. Elemental analyses were performed on Perkin-Elmer EAL240 elemental analyzer.

General Procedure for Synthesis of Chalcones (A)

A mixture of 22gm of sodium hydroxide in 200 ml of water and 100gm of rectified spirit in a 500 ml bolt head flask was provided with a mechanical stirrer. The flask was immersed in a bath of crushed ice; 52 gm (0.43 mol) of freshly distilled acetophenone was added while stirring and then followed by 46gm (44 ml, 0.43 mol) of pure benzaldehyde. The temperature of the reaction mixture was maintained at about 25 °C (limits are: 15–30 °C) and stirred vigorously until the reaction mass was so thick that stirring was no longer possible (2–3 hr). Stirrer was removed and the reaction mixture was kept in an ice chest or refrigerator, overnight. The product was filtered and washed with cold water until the washings were neutral to litmus followed with 20 ml of ice cold, rectified spirit and dried. It was purified by recrystallization from ethanol to give a pure compound.[10]

General Procedure for Synthesis of 4,6-diaryl-pyrimidin-2-thiol (B)

A mixture of 0.01 moles of chalcone, 0.01 moles of thiourea and potassium hydroxide (1gm) in 20 ml ethanol was heated under reflux for 6 hr. The reaction was monitored by TLC. After completion of the reaction, the contents were cooled to room temperature and poured into ice cold water (50 ml) while stirring. The solid thus resulted was filtered, washed with portions of cold water and dried. It was purified by recrystallization from ethanol to give a pure compound.[11]

General Procedure for the Synthesis of S-Mannich Bases of 4,6-diaryl-dihydropyrimidin-2(1H) Thione (C)

Dihydropyrimidine thione (0.005 moles) was dissolved in dimethyl sulfoxide (25 ml) in a conical flask and stirred with 37% formaldehyde (0.01 moles) then added anhydrous potassium carbonate (1.0gm), appropriate secondary amine (0.005 mol) and continued the stirring magnetically for about 2 hrs. The reaction mixture was then heated under reflux for about 5 hrs. Completion of reaction was confirmed by TLC and then kept in refrigerator for 48 hr, filtered the product, washed with small portions of cold water and dried. The crude product was purified by recrystallization from petroleum ether-chloroform (1:1) mixture.[12]

Characterization Data of Synthesised S-Mannich Bases (C_1–C_{15})

1-((4,6-bis(4-chlorophenyl)pyrimidin-2-yl)thio)-N,N-dimethylmethanamine (C_1):

IR(KBr, cm^{-1}): 3050 (=C–H str, aromatic), 1648 (C=N str, pyrimidine), 1602 and 1425 (C=C str, aromatic), 770 (C–Cl str), 620 (C–S–C str); **^{1}H NMR** (400Hz, DMSO-d_6) δ ppm: 2.26(s, 6H, $2CH_3$), 4.00 (s, 2H, CH_2), 7.21 (s, 1H, CH), 7.28–8.00 (m, 8H, Ar–H); **EI-MS**: 389; Ana. Calcd. for $C_{19}H_{17}Cl_2N_3S$: C, 58.06; H, 4.39; N, 10.77. Found: C, 58.03; H, 4.35; N, 10.71%.

N-(((4,6-bis(4-chlorophenyl)pyrimidin-yl)thio)methyl)-N-ethylethanamine (C_2):

IR(KBr, cm^{-1}): 3048 (=C-H str, aromatic), 1648(C=N str, pyrimidine) 1605 and 1428 (C=C str, aromatic), 750 (C–Cl str), 618 (C–S–C str); **^{1}H NMR** (400 Hz, DMSO-d_6) δ ppm: 1.04 (t, 6H, $2CH_3$), 2.65 (q, 4H, $2CH_2$), 3.99 (s, 2H, CH_2), 7.20 (s, 1H, CH) 7.26–8.01 (m, 8H, Ar–H); **EI-MS**: 417; Ana. Calcd. for $C_{21}H_{21}Cl_2N_3S$: C, 60.29; H, 5.06; N, 10.04. Found: C, 60.27; H, 5.02; N, 10.01%.

4-(((4,6-bis(4-chlorophenyl)pyrimidin-2-yl)thio)methyl)morpholine (C_3):

IR(KBr, cm^{-1}): 3052 (=C–H str, aromatic), 1645 (C=N str, pyrimidine) 1601 and 1426 (C=C str, aromatic), 755 (C–Cl str), 619 (C–S–C str); **^{1}H NMR** (400 Hz, DMSO-d_6) δ ppm: 2.98 (t, 4H, $2CH_2$), 3.68 (t, 4H, $2CH_2$) 3.97 (s, 2H, CH_2), 7.20 (s, 1H, CH), 7.27–8.00 (m, 8H, Ar–H); **EI-MS**: 431; Ana. Calcd. for $C_{21}H_{19}Cl_2N_3OS$: C, 58.34; H, 4.43; N, 9.72. Found C, 58.36; H, 4.41; N, 9.69%.

1-((4-(4-chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl)thio)-N,N-dimthyimethanamine (C_4):

IR (KBr, cm^{-1}): 3049 (=C–H str, aromatic), 1650 (C=N str, pyrimidine) 1602 and 1429 (C=C str, aromatic), 758 (C–Cl str), 622 (C–S–C str); **^{1}H NMR** (400 Hz, DMSO-d_6) δ ppm: 2.28 (s, 6H, $2CH_3$), 3.85 (s, 3H, CH_2), 4.00 (s, 2H, CH_2), 7.22 (s, 1H, CH), 7.28–8.02 (m, 8H, Ar–H); **EI-MS**: 385; Ana. Calcd. for $C_{20}H_{20}ClN_3OS$: C, 62.25; H, 5.22; N, 10.89. Found C, 62.21; H, 5.19; N, 10.85%.

N-(((4-(4-chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl)thio)methyl)-N-ethylethanamine (C_5):

IR (KBr, cm^{-1}) 3052 (=C–H str, aromatic), 1645 (C=N str, pyrimidine) 1605 and 1430 (C=C str, aromatic), 760 (C–Cl str), 625(C–S–C str); **^{1}H NMR** (400 Hz, DMSO-d_6) δ ppm: 1.02 (t, 6H, $2CH_3$), 2.64 (q, 4H, $2CH_2$), 3.83 (s, 3H, OCH_3), 3.99 (s, 2H, CH_2), 7.25 (s, 1H, CH), 7.29–8.00 (m, 8H, Ar-H); **EI-MS**: 413; Ana. Calcd. for $C_{24}H_{22}ClN_3OS$: C, 63.83; H, 5.84; N, 10.15. Found C, 63.81; H, 5.80; N, 10.11%.

4-(((4-(4-chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl)thio)methyl)morphine (C_6):

IR (KBr, cm^{-1}): 3054 (=C–H str, aromatic), 1651 (C=N str, pyrimidine) 1600 and 1429 (C=C str, aromatic), 761 (C–Cl str), 621(C–S–C str); **^{1}H NMR** (400 Hz, DMSO-d_6) δ ppm: 2.96 (t, 4H, $2CH_2$), 3.70 (t, 4H2CH_2), 3.84 (s, 3H, OCH_3), 4.02 (s, 2H, CH_2), 7.23 (s, 1H, CH), 7.28–8.02 (m, 8H, Ar–H); **EI-MS**: 427; Ana.Calcd.for $C_{22}H_{22}ClN_3O_2S$: C, 61.74; H, 5.18; N, 9.82. Found C, 61.71; H, 5.12; N, 9.79%.

4-(6-(4-chlorophenyl)-2-(((dimethylamino)methyl)thio)pyrimidin-4-yl)-N,N-dimethylaniline (C_7):

IR (KBr, cm^{-1}): 3049 (=C–H str, aromatic), 1649 (C=N str, pyrimidine) 1604 and 1427 (C=C str, aromatic), 754 (C–Cl str), 617 (C–S–C str); **^{1}H NMR** (400 Hz, DMSO-d_6) δ ppm: 2.28 (s, 6H, $2CH_3$), 3.06 (s, 6H, Ar–N$(CH_3)_2$), 3.99 (s, 2H, CH_2), 7.22 (s, 1H, CH), 7.26–8.00 (m, 8H, Ar–H); **EI-MS**: 398; Ana. Calcd. for $C_{21}H_{23}ClN_4S$: C, 63.22; H, 5.81; N, 14.04. Found C, 63.19; H, 5.79; N, 14.01%.

4-(6-(4-chlorophenyl)-2-(((diethylamino)methyl)thio)pyrimidin-4-yl)-N,N-dimethylaniline (C_8):

IR (KBr, cm^{-1}): 3047 (=C–H str, aromatic), 1647 (C=N str, pyrimidine) 1605 and 1428 (C=C str, aromatic), 757 (C–Cl str), 621 (C–S–C str); **^{1}H NMR** (400 Hz, DMSO-d_6) δ ppm: 1.03 (t, 6H, $2CH_3$), 2.64 (q, 4H, $2CH_2$), 3.04 (s, 6H, Ar–N$(CH_3)_2$), 4.02 (s, 2H, CH_2), 7.20 (s, 1H, CH), 7.26–8.00 (m, 8H, Ar–H); **EI-MS**: 426; Ana. Calcd. for $C_{23}H_{27}ClN_4S$: C, 64.69; H, 6.37; N, 13.12. Found C, 64.65; H, 6.32; N, 13.11%.

4-(6-(4-chlorophenyl)-2-((morpholinomethyl)thio)pyrimidin-4-yl)-N,N-dimethylaniline (C_9):

IR (KBr, cm^{-1}): 3055 (=C–H str, aromatic), 1645 (C=N str, pyrimidine) 1601 and 1430 (C=C str, aromatic), 761 (C–Cl str), 619 (C–S–C str); **^{1}H NMR** (400 Hz, DMSO-d_6) δ ppm: 2.96 (t, 4H, $2CH_2$), 3.06 (s, 6H, Ar–N $(CH_3)_2$), 3.66 (t, 4H, $2CH_2$), 4.01 (s, 2H, CH_2), 7.21 (s, 1H, CH), 7.25–8.00 (m, 8H, Ar–H); **EI-MS**: 440; Ana. Calcd. for $C_{23}H_{25}ClN_4$ OS: C, 62.64; H, 5.71; N, 12.70. Found C, 62.61; H, 5.69; N, 12.68%.

4-(6-(4-chlorophenyl)-2-(((dimethylamino)methyl)thio)pyrimidin-4-yl)phenol (C_{10}):

IR (KBr, cm^{-1}): 3320 (O–H str), 3055 (=C–H str, aro-

matic), 1645 (C=N str, pyrimidine) 1601 and 1430 (C=C str, aromatic), 755 (C–Cl str), 619 (C–S–C str); **^{1}H NMR** (400 Hz, DMSO-d_6) δ ppm: 2.27 (s, 6H, $2CH_3$), 3.98 (s, 2H, CH_2), 5.35 (s, 1H, Ar–OH), 7.23 (s, 1H, CH), 7.27–8.02 (m, 8H, Ar–H); **EI-MS**: 371; Ana. Calcd. for $C_{19}H_{18}ClN_3OS$: C, 61.36; H, 4.88; N, 11.30. Found C, 61.32; H, 4.82; N, 11.29%.

***4-(6-(4-chlorophenyl)-2-(((diethylamino)methyl)thio)pyrimidin-4-yl)phenol (C_{11})*:**

IR (KBr, cm^{-1}): 3325 (O–H str), 3055 (=C–H str, aromatic), 1645 (C=N str, pyrimidine) 1601 and 1430 (C=C str, aromatic), 765 (C–Cl str), 619 (C–S–C str); **^{1}H NMR** (400 Hz, DMSO-d_6) δ ppm: 1.02 (t, 6H, $2CH_3$), 2.66 (q, 4H, $2CH_2$), 3.99 (s, 2H, CH_2), 5.33 (s, 1H, Ar–OH), 7.20 (s, 1H, CH), 7.26–8.01 (m, 8H, Ar–H); **EI-MS**: 399; Ana. Calcd. for $C_{21}H_{22}ClN_3OS$: C, 63.36; H, 5.54; N, 10.51. Found C, 63.32; H, 5.52; N, 10.49%.

***4-(6-(4-chlorophenyl)-2-(morpholinomethyl)thio)pyrimidin-4-yl)phenol (C_{12})*:**

IR (KBr, cm^{-1}): 3329 (O–H str), 3055 (=C–H str, aromatic), 1645 (C=N str, pyrimidine) 1601 and 1430 (C=C str, aromatic), 769 (C–Cl str), 619 (C–S–C str); **^{1}H NMR** (400 Hz, DMSO-d_6) δ ppm: 2.96 (t, 4H, $2CH_2$), 3.69 (t, 4H, $2CH_2$), 3.97 (s, 2H, CH_2), 5.31 (s, 1H, Ar–OH), 7.21 (s, 1H, CH), 7.27–8.01 (m, 8H, Ar–H); **EI-MS**: 413; Ana. Calcd. for $C_{21}H_{20}ClN_3O_2S$: C, 60.94; H, 4.87; N, 10.15. Found C, 60.91; H, 4.85; N, 10.12%.

***1-((4-(4-chlorophenyl)-6-(3-nitrophenyl)pyrimidin-2-yl)thio)-N,N-dimethylmethanamine (C_{13})*:**

IR (KBr, cm^{-1}): 3061 (=C–H str, aromatic), 1650 (C=N str, pyrimidine) 1606 and 1428 (C=C str, aromatic), 1525 and 1350 (N=O str, aromatic), 760 (C–Cl str), 619 (C–S–C str); **^{1}H NMR** (400 Hz, DMSO-d_6) δ ppm: 2.26 (s, 6H, $2CH_3$), 4.00 (s, 2H, CH_2), 7.25 (s, 1H, CH), 7.29–8.0 5(m, 8H, Ar–H); **EI-MS**: 400; Ana. Calcd. for $C_{19}H_{17}ClN_4O_2S$: C, 56.93; H, 4.27; N, 13.98. Found C, 56.92; H, 4.25; N, 13.95%.

***N-(((4-(4-chlorophenyl)-6-(3-nitrophenyl)pyrimidin-2-yl)thio)methyl)-N-ethylethanamine (C_{14})*:**

IR (KBr, cm^{-1}): 3052 (=C–H str, aromatic), 1647 (C=N str, pyrimidine) 1601 and 1429 (C=C str, aromatic), 1528 and 1352 (N=O str, aromatic), 751 (C–Cl str), 618 (C–S–C str); **^{1}H NMR** (400 Hz, DMSO-d_6) δ ppm: 1.05 (s, 6H, $2CH_3$), 2.64 (q, 4H, $2CH_2$), 3.99 (s, 2H, CH_2), 7.23 (s, 1H, CH), 7.26–8.01 (m, 8H, Ar–H); **EI-MS**: 428; Ana. Calcd. for $C_{21}H_{21}ClN_4O_2S$: C, 58.80; H, 4.93; N, 13.06. Found C, 58.79; H, 4.91; N, 13.02%.

***N-(((4-(4-chlorophenyl)-6-(3-nitrophenyl)pyrimidin-2-yl)thio)methyl)morpholine (C_{15})*:**

IR (KBr, cm^{-1}): 3058 (=C–H str, aromatic), 1645 (C=N str, pyrimidine) 1606 and 1429 (C=C str, aromatic), 1530 and 1354 (N=O str, aromatic), 762 (C–Cl str), 616 (C–S–C str); **^{1}H NMR** (400 Hz, DMSO-d_6) δ ppm: 2.95 (t, 4H, $2CH_2$), 3.67 (t, 4H, $2CH_2$), 4.01 (s, 2H, CH_2), 7.23 (s, 1H, CH), 7.28–8.05 (m, 8H, Ar–H); **EI-MS**: 442; Ana. Calcd. for $C_{21}H_{19}ClN_4O_3S$: C, 56.95; H, 4.32; N, 12.65. Found C, 56.93; H, 4.31; N, 12.63%.

CONCLUSION

The S-Mannich bases of 4,6-diaryl-3,4-dihydropyrimidin-2(1*H*)-thiones were synthesised by a facile method. All the synthesised compounds **(C_1–C_{15})** were evaluated for their anti-ulcer and antibacterial activities. Compounds **C_4**, **C_5**, **C_6**, **C_{14}** and **C_{15}** exhibited more potent anti-ulcer activity; compounds **C_6**, **C_9**, **C_{12}** and **C_{15}** have more potent antibacterial activity.

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REFERENCES

1. Sushil kumar, B. S.; Devanand, S. B. *Acta Pharm.* **2003**, *53*, 223.
2. Sham, M.; Sondhi, N. S.; Monika, J.; Ashok Kumar, B. *Med. Chem.* **2005**, *13*, 6158.
3. Dravyakar, B. R.; Kawade, D. P.; Bhusari, K. P. *Ind. J. Heterocycl. Chem.* **2007**, *16*, 301.
4. Nagaraj, A.; Sanjeev Reddy, C. *Iran. Chem. Soc.* **2008**, *5*, 262.
5. Rathod, I. S.; Baheta, K. G. *Indian J. Pharm. Sci.* **2005**, *67*, 593.
6. Brun, O.; Ballabeni, V.; Barocellin, E. *Biorg. Med. Chem.* **2004**, *12*, 553.
7. Sinythises, J. R. *Psychoneuroendocrinology.* **1979**, *4*, 177.
8. Lavilla, R. J. *Chem. Soc.* **2002**, *1*, 1141.
9. Patil, P. A.; Bhole, R. P.; Chikhale, R. V.; Bhusari, K. P. *Inter. J. Chem Tech Res.* **2009**, *1*, 373.
10. Vogle, A. I.; Tachell, A. R.; Furnis, B. S.; Hannaford, A. J.; Smith, P. W. G. *Vogel's Book of Practical Organic Chem-*

istry, 5th ed.; Prentice Hall: 1996, p 1034.
11. Amit, R. T.; Dipti, K. D; Naresh, R. R.; Viresh, H. S. *ARKIVOC* **2008**, *11*, 131.
12. Shah, T. B.; Gupte, A.; Patel, M. R.; Chaudhari, V. S.; Patel, H.; Patel, V. C. *Ind. J. Chem.* **2009**, *48B*, 88.
13. Barrett, W. E.; Rutledge, R.; Plummer, A. J.; Yonkman, F. F. *J. Pharmacol. Exp. Ther.* **1953**, *108*, 305.
14. Hemmati, M.; Razvani, A.; Diahanguini, B. *Pharmacology* **1973**, *9*, 374.
15. Shay, H.; Komarow, S. A.; Fels, S. S.; Meranze, D.; Gruenstein, M.; Siplet, H. *Gastroenterol.* **1973**, *5*, 43.
16. Gerhard Vogel, H. *Drug Discovery and Evaluation,* 2nd ed.; Springers: 2002.
17. Fung,T. J. C.; Minassian, B. *Antimicrob Agents Chemother* **2000**, *44*, 3351.