Synthesis and Application of Thiobarbituric Acid Derivatives as Antifungal Agents

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to the carbonyl group followed by dehydration. Malonic ester synthesis is a reaction where an ester of malonic acid is alkylated at the carbon alpha to both carbonyl groups, and then converted to a substituted acetic acid. TBA derivatives have been reported to possess a broad spectrum of biological activities namely antifungal, antimicrobial, and anti-tubercular, herbicides, antioxidants, antiviral & anticonvulsant activities [14-17]. Due to their wide range of biological activity thiobarbituric ring constitutes a relevant synthetic target in pharmaceutical industry [18].

Materials and Methods

e chemicals used for the experimental work were commercially procured from various chemical units: Haryana Scienti c Engineering Corporation Ltd., E. Merck India Ltd. Melting points were determined by open tube capillary method and were uncorrected. e purity of the compounds was checked on thin layer chromatography (TLC) plates (silica gel G) in benzene-acetone (9:1), benzene-acetone (8:2), benzene-acetone (6:4) solvent systems; the spots were located under iodine vapors and UV light. e IR spectra were recorded by using BIO-RAD FT-IR spectrometer by making KBr pellets.^{1}H-NMR spectra were recorded on Bruker 300 MHz and 400 MHz instrument in solvent (DMSO-d_6, $CDCl_3$). e chemical shi s are given in δ (ppm) down eld from tetramethylsilane (TMS) as internal standard.

Common method of synthesis of (1, 2, 3, 4, 5, 6-Hexa Hydro-4, 6-Dioxo- 2- ioxopyrimidine) (Scheme 1(3))

A mixture of aniline (20 g, 19.6 mL, and 0.215 mol) and carbon disul de (25 g, 19.7 mL, 0.329 mole) in absolute alcohol (50 mL) was re uxed on water bath for 12 hr or until the reaction mixture solidi ed. e separated product ltered and washed with excess of dilute HCL (1:1) to remove unreacted aniline and nally with cold alcohol. e 1, 3- diphenylthiourea thus obtained is crystallized from ethanol as white shinning crystals [19]. A mixture of 1, 3-diphenylthiourea (2.28g, 0.01mol), dry malonic acid (1.1 g, 0.01 mol) and acetyl chloride (10 mL) was stirred at 40-50°C (oil bath) for 4-6 hrs. e progress of the reaction was followed by TLC. e reaction was stopped when all the thiourea has been consumed. e mixture was stirred with crushed ice and the separated product is ltered, washed with water and crystallized with acetic acid [20].

General procedure for the synthesis of carboxaldehyde derivatives of substituted thiobarbituric acids (Scheme 1(4-12)).

5-(Indol-3-yl) barbituric acid was prepared by Knoevenagel condensation of indol-3-carboxaldehyde and barbituric acid in ethanol using piperidine as a base. Barbituric acid (5.5 g, 0.039 mol) and indole-3-carboxaldehyde (5.66 g, 0.039 mol) in ethanol (75 mL) was heated under re ux for 15 minutes. Piperidine (1 mL) was added in one portion and the re ux was continued for further 5-10 hrs. e reaction mixture was cooled to room temperature and the solid formed was ltered, washed with ethanol (2 × 20 mL) and dried 5-(Indol-3-yl) barbituric acid was recrystallized from ethanol as dark yellow powder [21].

5-(1H-Indol-3-yl-methylidene)-1, 3-diphenyl-2-thioxo dihydropyrimidine-4, 6(1H, 5H)-dione (Scheme 1(4))

Pale yellow; IR (KBr) cm^{-1}: 3244 (NH str.), 2923, 2835 (C-H), 1656 (C=O), 1522 (C=C), 1275 (C-N), 1039 (C=S). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.13-7.21 (m, 4H, H_{Indole}), 7.39-7.57 (m, 10H, H_{Phenyl}), 7.82 (s, 1H, C_2-H_{indole}), 8.51 (s, 1H, =CH-), 11.23 (s, 1H, NH_{Indole}). C, H, N % analysis calculated: C, 70.90; H, 4.05; N, 9.92; Found: C, 70.96; H, 4.08; N, 9.88.

5-(1H-Indol-3-yl-methylidene)-1, 3-di-o-tolyl-2-thioxo dihydropyrimidine-4, 6(1H, 5H)-dione (Scheme 1(5))

Lemon yellow; IR (KBr) cm^{-1}: 3256 (NH str.), 2914, 2839 (C-H), 1662 (C=O), 1519 (C=C), 1278 (C-N), 1044 (C=S). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 6H, 2×CH_3), 7.15-7.24 (m, 4H, H_{Indole}), 7.34-7.50 (m, 8H, H_{Phenyl}), 7.79 (s, 1H, C_2-H_{indole}), 8.53 (s, 1H, =CH-), 11.17 (s, 1H, NH_{Indole}).

5-(1H-Indol-3-yl-methylidene)-1, 3-di-p-tolyl-2-thioxo dihydropyrimidine-4, 6(1H, 5H)-dione (Scheme 1(6)).

Pale yellow; IR (KBr) cm^{-1}: 3252 (NH str.), 2919, 2833 (C-H), 1667 (C=O), 1522 (C=C), 1270 (C-N), 1049 (C=S). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.34 (s, 6H, 2×CH_3), 7.17-7.26 (m, 4H, H_{Indole}), 7.31-7.47 (m, 8H, H_{Phenyl}), 7.72 (s, 1H, C_2-H_{indole}), 8.48 (s, 1H, =CH-), 11.24 (s, 1H, NH_{Indole}).

5-[(5-chloro-3-methyl-1H-pyrazol-4-yl) methylidene]-1, 3-diphenyl-2-thioxodihydro pyrimidine-4, 6(1H, 5H)-dione (Scheme 1(7)).

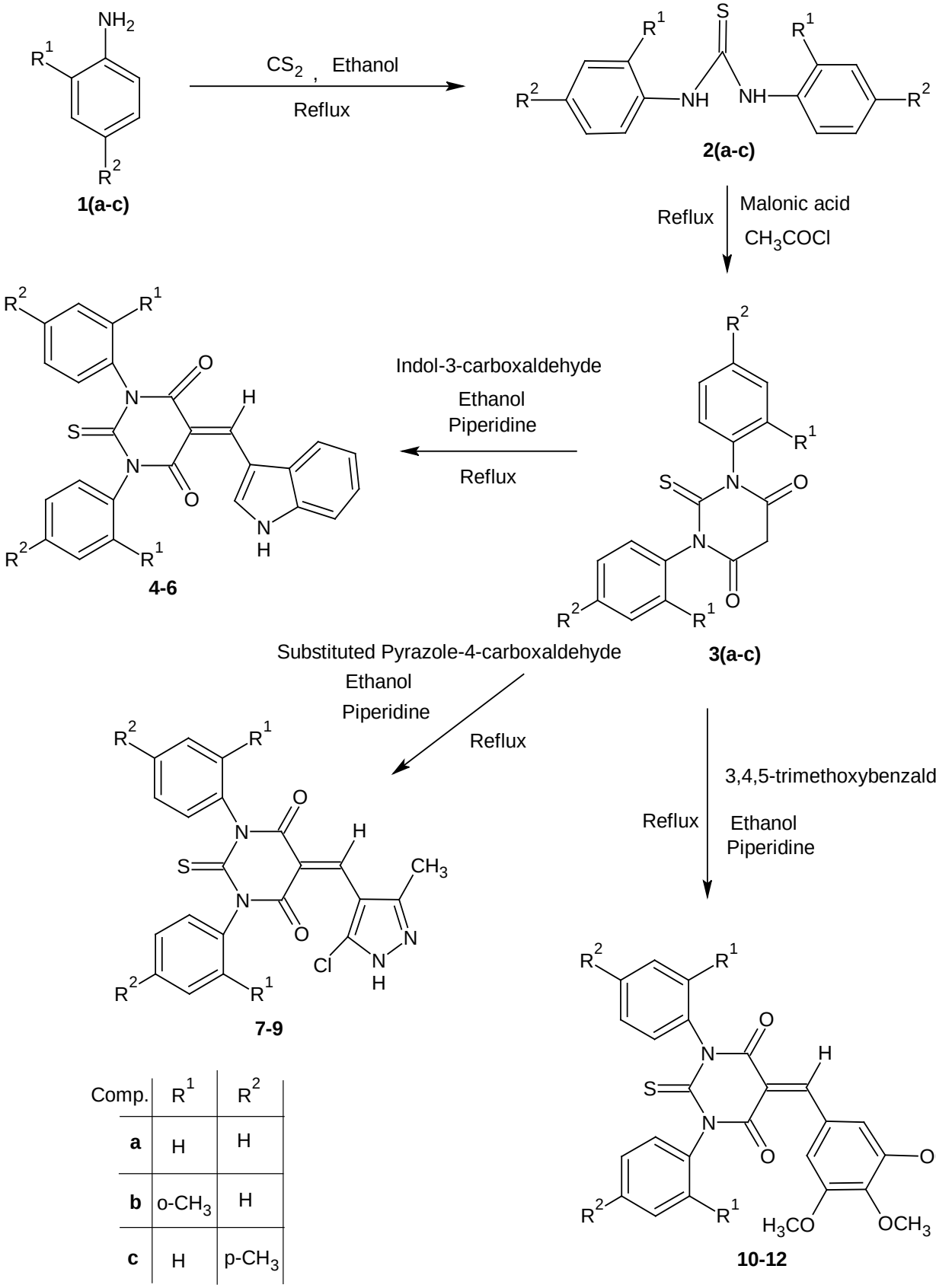
Dark yellow; IR (KBr) cm^{-1}: 3258 (NH str.), 2932, 2839 (C-H), 1664 (C=O), 1526 (C=C), 1270 (C-N), 1043 (C=S), 736 (C-Cl). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.31 (s, 3H, CH_3), 7.41-7.59 (m, 10H, H_{Phenyl}), 8.45 (s, 1H, =CH-), 11.23 (s, 1H, $NH_{pyrazole}$). C, H, N % analysis calculated: C, 59.64; H, 3.58; N, 13.25; Found: C, 59.58; H, 3.57; N, 13.23.

5-[(5-chloro-3-methyl-1H-pyrazol-4-yl) methylidene]-1, 3-bis (2-methylphenyl)-2-thioxodihydro pyrimidine-4, 6(1H, 5H)-dione (Scheme 1(8)).

Reddish yellow; IR (KBr) cm^{-1}: 3258 (NH str.), 2937, 2841 (C-H), 1669 (C=O), 1532 (C=C), 1268 (C-N), 1037 (C=S), 732 (C-Cl). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.31 (s, 3H, CH_3), 2.36 (s, 6H, 2×CH_3), 7.32-7.54 (m, 8H, H_{Phenyl}), 8.39 (s, 1H, =CH-), 11.26 (s, 1H, $NH_{pyrazole}$).

5-[(5-chloro-3-methyl-1H-pyrazol-4-yl) methylidene]-1, 3-bis (4-methylphenyl)-2-thioxodihydro pyrimidine-4, 6(1H, 5H)-dione (Scheme 1(9)).

Creamish yellow; IR (KBr) cm^{-1}: 3244 (NH str.), 2933, 2846 (C-H), 1666 (C=O), 1529 (C=C), 1262 (C-N), 1033 (C=S), 746 (C-Cl). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.29 (s, 3H, CH_3), 2.41 (s, 6H, 2×CH_3), 7.36-7.58 (m, 8H, H_{Phenyl}), 8.34 (s, 1H, =CH-), 11.20 (s, 1H, $NH_{pyrazole}$).



Comp.	R^1	R^2
a	H	H
b	o-CH_3	H
c	H	p-CH_3

Scheme 1: Synthesis of the intermediate and target compounds [1(a-c), 2(a-c), 3(a-c), and 4-6, 7-9 & 10-12].

5-(3,4,5-trimethoxybenzylidine)-2-thioxo-1,3-di-p-tolyl--dihydropyrimidine-4,6(1H,5H)-dione (Scheme 1(12)).

Pale yellow; IR (KBr) cm^{-1}: 3245 (NH str.), 2923, 2839 (C-H), 1669 (C=O), 1541 (C=C), 1247 (C-N), 1049 (C=S). ^{1}H NMR (300 MHz, $CDCl_3$

Citation: