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Research Paper

Chemistry

KEYWORDS : pyrimidinedione, pyrimidinethione, antimicrobial, anticancer, anti-inflammatory, reflux.

Synthesis and Characterization of Some New Substituted Pyrimidine Derivatives

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ABSTRACT

Pyrimidindiones are associated with the broad spectrum of biological activities including antimicrobial, anticancer, anti-inflammatory, etc. These findings prompted us to synthesize compounds containing pyrimidine moiety and to evaluate for anti-inflammatory activity. A series of new substituted pyrimidine derivatives have been synthesized by condensing substituted phenyl cyano ester with urea and thiourea. All these pyrimidine derivatives are characterized by IR, 1H, 13C NMR and Mass spectral studies. These compounds are found to possess anti-bacterial activity.

INTRODUCTION:

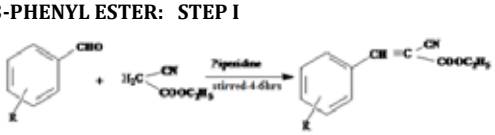
Pyrimidindiones are associated with the broad spectrum of biological activities including antimicrobial [1-2], anticancer [3], anti-inflammatory [4-8], etc. In spite of remarkable growth in human medicines, infectious diseases caused by bacteria, fungi, viruses and parasites are still a major threat to public health. There impact is particularly large in developing countries due to relative unavailability of medicines and the emergence of widespread drug resistance [9]. During the last two decades, the development of drug resistance as well as the appearance of undesirable side effect of certain antibiotics [10] has lead to the search of new antimicrobial agents with the goal to discover new chemical structures, which overcome the above disadvantage[11]. Pyrimidine-2, 4-dione is a six-membered heterocyclic ring system having two nitrogen atoms at 1-and 3- position of the ring.

The small and simple pyrimidine nucleus is present in compounds involved in research aimed at evaluating new products that possess biological activities, such as anti-viral, anti- malarial agents, adenosine receptor ligands, anti-cancer agents, compounds targeting delayed type hypersensivity and anticonvulsant agents. After that pyrimidine-2,4-dione derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity [12-15]. In the last few years pyrimidine derivatives substituted either at the C-5 and C-6 position have emerged in the field of chemotherapy[16]. Among the important 6-substituted uralic derivative HEPT and its analogues [17]. Emivirine (EMV) [18] has been chosen as a candidate for clinical trials, and DABOs [19] a potent and selective activity against HIV-1 [20-22]Structure.

MATERIAL AND METHODS

All the chemicals and the reagents used in the study were of synthesis grade purity. Ethyl cyano acetate, substituted benzaldehde, urea and thiourea are purchased from Qualigents Fine Chemicals Company. Solvents used were purified by distillation. All substance prepared for studies were purified by crystallization using appropriate solvents and established procedures. Melting points were measured on a sigma melting point apparatus using capillary tubes. Analytical TLC was performed on precoated sheets of silica gel to monitor the process of the reaction as well as to check the purity. The spots were visualized by using iodine vapour.IR spectra were recorded on FTIR-8300 shimadzu spectrometer. 1H&13C NMR spectra were recorded on Jeol-FXQ (90MHz), Jeol GSX (400 MHz) and DPX 200 (200MHz). Mass spectra were recorded on Jeo-JMS-DX 30hf.

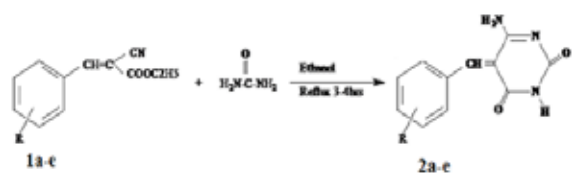
SCHEME I : SYNTHESIS OF SUBSTITUTED ETHYL-2-CYANO-3-PHENYL ESTER: STEP I



1a-e

R= H, (p-OH, m-OCH3), p-chloro, p-hydroxy, p-OCH3.

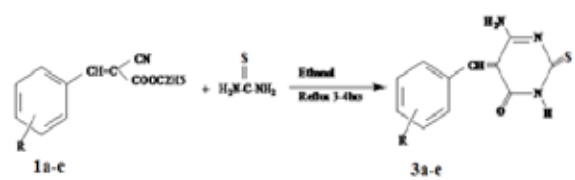
STEP II
SYNTHESIS OF SUBSTITUTED 6–AMINO-5–BENZYLIC PYRIMIDINE–2, 4–DIONE



1a-e 2a-e

R= H, (p-OH, m-OCH3), p-chloro , p-hydroxy, p-OCH3.

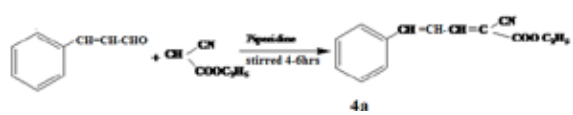
SCHEME II
SYNTHESIS OF SUBSTITUTED 6–AMINO-5–BENZYLIC PYRIMIDINE–2-THIO-4-ONE



1a-e 3a-e

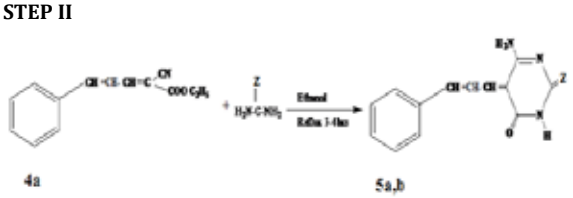
R= H, (p-OH, m-OCH3), p-chloro, p-hydroxy, p-OCH3.

SCHEME III
SYNTHESIS OF 6-AMINO-5-(ALLYL PHENYL)-2-THIO-4-ONE
STEP I



4a

STEP II



4a 5a,b

Z= O, S

RESULT AND DISCUSSION:
EXPERIMENTAL:
SYNTHESIS OF SUBSTITUTED ETHYL-2-CYANO-3-PHENYL ESTER: 1a-e

Benzaldehyde (2.21g, 0.05mol)and ethylcyanoacetate (2.26g, 0.05mol) and two drops of piperidine were added in 10ml of rectified spirit. The mixture was stirred for 4 to 6 hours at room

temperature. The resulting yellow colour liquid was added to ice water. The separated solid was filtered washed with water and crystallized from ethanol. The substituted ethyl-2-cyano-3-phenyl ester 1a-e was prepared.

6–AMINO-5–BENZYLIC PYRIMIDINE–2, 4–DIONE: 2a

A mixture of ethyl-2-cyano-3-phenyl ester 1a (1.21g, 0.01mol) with urea (1.26g, 0.02mol) in ethanol was refluxed on water bath for 3 hours. The reaction mixture was concentrated in vacuo and added to crush ice. Crystalline masses that deposited from the solution during ice cooling were purified by recrystallization from ethanol. The substituted 6 – amino 5 – benzylic pyrimidine – 2, 4-dione 2a was prepared. M.P: 51-53 ^{o}C. 1H NMR: δ 1.44 (s, NH_2), 4.31 (s, NH), 7.55-8.21 (m, Ar-H), 8.42 (s, CH). 13C NMR: δ 13.07 (C), 62.32 (CH), 102-133 (Ar CH, C), 154.7, 162.2 (C=O). IR: 1715-1725cm^{-1} (keto carbonyls); 1560cm^{-1}(olefinicbond); 3000-3100 cm^{-1} (aromatic C-H carbons); 1600cm $^{-1}$ (aromatic carbons); 1620cm^{-1}(NH_2); 1550-1650 cm^{-1}(N-H). Mass: (m/z): 215.

6–AMINO-5-(3-METHOXY-4-HYDROXY)-BENZYLIC PYRIMIDINE–2,4–DIONE: 2b

A mixture of ethyl-2-cyano-3-(3-methoxy-4-hydroxy)-phenyl ester 1b (1.47g, 0.01mol) with urea (1.2g, 0.02mol) in ethanol by the usual workup afforded 6–amino 5-(3-methoxy-4-hydroxy) – benzylic pyrimidine – 2, 4-dione 2b. M.P: 100-105 oC. ^{1}H NMR: δ 1.40 (s, NH_2), 3.32(s, OCH3), 4.35 (s, NH), 7.46-7.82 (m, Ar-H), 8.18 (s, OH), 8.41 (s, CH). ^{13}C NMR: δ 13.04 (C), 53.6 (O-CH3), 62.34 (=CH), 101-132 (Ar-CH, C), 154.6, 162.0 (C=O). IR 1700-1730cm^{-1} (keto carbonyls); 1559cm^{-1} (olefinicbond); 2810cm^{-1} (OCH3); 3000-3110cm^{-1} (aromatic C-H corbons); 1600cm $^{-1}$ (aromatic carbons); 1630cm^{-1}(NH_2); 1560-1660 cm^{-1}(N-H); 1330cm^{-1}(OH). Mass: (m/z): 245.

6–AMINO–5-(4-CHLORO)–BENZYLIC PYRIMIDINE–2,4–DIONE: 2c

A mixture of ethyl-2-cyano-3-(4-chloro) phenyl ester 1c (2.35g, 0.01mol) with urea (1.2g, 0.02mol) in ethanol by the usual workup afforded 6 – amino- 5-(4-chloro)–benzylic pyrimidine – 2,4-dione 2c. M.P: 120-123 oC. 1H NMR: δ 1.42 (s, NH_2), 4.37 (s, NH), 7.51-8.20 (m, Ar-H), 8.43 (s, CH). 13C NMR: δ 13.06 (C), 62.35 (=CH), 102-136 (Ar-CH,C),153.6,162.3(C=O). IR: 1720-1740cm^{-1} (keto carbonyls); 1560cm^{-1} (olefinicbond); 3010-3120cm^{-1} (aromatic C-H carbons); 1630cm –1 (aromatic carbons); 1650cm^{-1} (NH_2); 1545cm^{-1} (N-H): Mass: (m/z): 249,251

6–AMINO-5-(4-HYDROXY)-BENZYLIC PYRIMIDINE–2,4–DIONE: 2d

A mixture of ethyl-2-cyano-3-(4- hydroxy) phenyl ester 1d (2.17g, 0.01mol) with urea (1.2g, 0.02mol) in ethanol by the usual workup afforded 6–amino-5-(4- hydroxy) –benzylic pyrimidine–2,4-dione 2d. M.P: 170 oC. 1H NMR: δ 1.43 (s, NH_2), 4.34 (s, NH), 7.45-7.79 (m, Ar-H), 7.89 (s, OH), 8.45(s, CH). 13CNMR: δ13.09(C), 62.29 (=CH), 102-123 (Ar-CH, C), 154.9, 162.0 (C=O). IR: 1725-1745cm^{-1} (keto carbonyls); 1559cm (olefinicbond); 3000-3115cm^{-1} (aromatic C-H carbons); 1635cm –1 (aromatic carbons); 1660cm^{-1}(NH_2); 1570cm^{-1} (N-H); 1350cm^{-1} (OH). Mass: (m/z): 231

6–AMINO-5-(4-METHOXY)-BENZYLIC PYRIMIDINE–2,4–DIONE: 2e

A mixture of ethyl-2-cyano-3-(4- methoxy) phenyl ester 1e (2.31g, 0.01mol) with urea (1.2g, 0.02mol) in ethanol by the usual workup afforded 6–amino-5-(4-methoxy) –benzylic pyrimidine–2,4-dione 2e. M.P:163-165 oC. 1H NMR: δ 1.48 (s, NH_2), 3.22 (S, OCH3), 4.35 (s, NH), 7.43-7.85 (m, Ar-H), 8.43 (s, CH). 13C NMR: δ 13.08(C), 54.9(O-CH3), 62.30 (=CH), 102-135 (Ar-CH, C), 154.6, 162.2 (C=O). IR: 1640-1880cm^{-1} (keto carbonyls); 1559cm^{-1} (olefinicbond); 2830cm^{-1}(OCH3); 3000-3125cm^{-1} (aromatic C-H carbons); 1640cm –1 (aromatic carbons); 1655cm^{-1} (NH_2); 1565cm^{-1}(N-H). Mass: (m/z): 245.

6–AMINO-5–BENZYLIC PYRIMIDINE–2-THIO-4-ONE: 3a

A mixture of ethyl-2-cyano-3-phenyl ester 1a (1.21g, 0.01mol) with thiourea (1.26g, 0.02mol) in ethanol was refluxed on water bath for 3 hours. The reaction mixture was concentrated in vacuo and added to crush ice. Crystalline masses that deposited from the solution during ice cooling were purified by recrystallization from ethanol. The substituted 6–amino-5 – benzylic pyrimidine –2-thio-4-one 3a was prepared. M.P: 45-47 oC. 1H NMR: δ 1.41 (s, NH_2), 4.32 (s, NH), 7.55-8.23 (m, Ar-H), 8.46(s, CH).13C NMR: δ 13.06 (C), 62.36(=CH), 103-133 (Ar-CH, C), 154.8, 162.3(C=O), 137.13, 181.72 (C=S). IR: 1735, 1050cm^{-1} (keto, thiocarbonyls); 1560 cm^{-1} (olefinicbond); 3000-3123 cm^{-1} (aromatic CH carbons); 1635cm^{-1} (aromatic carbons); 1675 cm^{-1}(NH_2); 1570cm^{-1}(NH). Mass: (m/z): 231.

6-AMINO-5-(3-METHOXY-4-HYDROXY)-BENZYLIC PYRIMIDINE–2-THIO-4–ONE: 3b

A mixture of ethyl-2-cyano-3-(3-methoxy-4-hydroxy) phenyl ester 1b (1.47g, 0.01mol) with thiourea (1.52g, 0.02mol) in ethanol by the usual workup afforded 6–amino 5-(3-methoxy-4-hydroxy)–benzylic pyrimidine–2-thio-4-one 3b. M.P: 90-91oC. 1H NMR: δ 1.41 (s, NH_2), 3.34 (S, OCH3), 4.35 (s, NH), 7.46-7.82 (m, Ar-H), 8.18 (s, OH), 8.40 (s, CH). 13C NMR: δ 13.07 (C), 62.32 (=CH), 101-134 (Ar-CH, C), 162.2 (C=O), 190.69 (C=S). IR: 1730,1060 cm^{-1}(keto, thio carbonyls); 1559 cm^{-1} (olefinicbond); 2840 cm^{-1} (OCH3); 3015-3130 cm^{-1} (aromatic C-H carbons); 1670cm^{-1} (NH_2); 1590cm^{-1} (N-H); 1350cm^{-1} (OH). Mass: (m/z): 261

6–AMINO–5-(4-CHLORO)–BENZYLIC PYRIMIDINE –2-THIO-4–ONE: 3c

A mixture of ethyl-2-cyano-3-(4-chloro) phenyl ester 1c (2.35g, 0.01mol) with thiourea (1.52g, 0.02mol) in ethanol by the usual workup afforded 6–amino-5-(4-chloro) –benzylic pyrimidine – 2-thio-4-one 3c. M.P: 75-77 oC. 1H NMR: δ 1.40-141 (s, NH_2), 4.33 (s, NH), 7.5-8.2 (m, Ar-H), 8.42 (s, CH). 13C NMR: δ 13.09 (C), 62.38 (=CH), 102-133 (Ar-CH,C), 162.5 (C=O), 189.92 (C=S). IR: 1710, 1080cm^{-1} (keto, thiocarbonyls); 1560cm^{-1} (olefinicbond); 3000-3150cm^{-1} (aromatic C-H carbons); 3365cm –1 (aromatic carbons); 1660cm^{-1} (NH_2); 1585cm^{-1} (N-H):. Mass: (m/z): 265, 267.

6–AMINO-5-(4-HYDROXY)-BENZYLIC PYRIMIDINE –2-THIO-4–ONE: 3d

A mixture of ethyl-2-cyano-3-(4- hydroxy) phenyl ester 1d (2.17g, 0.01mol) with thiourea (1.52g, 0.02mol) in ethanol by the usual workup afforded 6 – amino 5-(4- hydroxy) –benzylic pyrimidine – 2-thio-4-one 3d. M.p:82-83 oC. 1H NMR: δ 1.43 (s,NH_2), 4.36 (s,NH), 7.46-7.91 (m, Ar-H), 8.18(s,OH), 8.43 (s,CH). 13C NMR : δ 13.10(C),62.32(=CH),102-136(Ar-CH,C), 154.7(C=O), 200.8(C=S).IR 1735,1100cm^{-1}(keto,thio carbonyls) 1559cm^{-1}(olefinicbond):3000-3160cm^{-1} (aromatic C-H carbons): 1655cm –1 (aromatic carbons); 1600cm^{-1}(NH_2); 1595cm^{-1}(N-H): 1360cm^{-1}(OH). Mass: (m/z): 247.

6–AMINO-5-(4-METHOXY)- PYRIMIDINE–2-THIO-4–ONE: 3e

A mixture of ethyl-2-cyano-3-(4- methoxy) phenyl ester 1e (2.31g, 0.01mol) with thiourea (1.52g, 0.02mol) in ethanol by the usual workup afforded 6 – amino 5-(4- methoxy) –benzylic pyrimidine – 2-thio-4-one 3e. M.p:95-97 oC. 1H NMR: δ 1.45 (s, NH_2), 3.42 (s, OCH3), 4.34 (s, NH), 7.46-7.82 (m, Ar-H), 8.48 (s, CH). 13C NMR: δ 13.04(C), 62.24 (=CH), 108-133 (Ar-CH, C), 162.3 (C=O), 195.7 (C=S). IR: 1680, 1898cm^{-1} (keto, thio carbonyls); 1559 cm^{-1}(olefinicbond); 2840 cm^{-1} (OCH3); 3030-3140 cm^{-1} (aromatic C-H carbons); 1640 cm $^{-1}$ (aromatic carbons); 1610cm^{-1}(NH_2); 1577cm^{-1}(N-H). Mass: (m/z): 261.

SYNTHESIS OF ETHYL-2-CYANO-3-(ALLYL PHENYL)-ESTER: 4a

Cinnamaldehyde (2.21g, 0.05mol) and ethylcyano acetate (2.26g, 0.05mol) and two drops of piperidine were added in 10ml of rectified spirit. The mixture was stirred for 4 to 6 hours at room temperature. The resulting yellow colour liquid was added to ice water. The separated solid was filtered washed with water and crystallized from ethanol. The ethyl-2-cyano-3-(allyl phenyl) ester 4a was prepared

6-AMINO-5–(ALLYL PHENYL)-PYRIMIDINE–2, 4–DIONE: 5a

A mixture of ethyl-2-cyano-3-(allyl phenyl ester) 4a (1.21g, 0.01mol) with urea (1.26g, 0.02mol) in ethanol was refluxed on

water bath for 3 hours. The reaction mixture was concentrated in vacuo and added to crushed ice. Crystalline masses that deposited from the solution during ice cooling were purified by recrystallization from ethanol. The substituted 6 – amino 5–(allyl phenyl) -pyrimidine – 2, 4-dione 5a was prepared. M.P: 100-102 oC. 1H NMR: δ 1.42 (s, NH_2), 4.2 (s, CH), 4.34 (s,NH), 7.52-8.20 (m, Ar-H),6.20-8.41 (d,CH). 13C NMR: δ 13.06(C), 62.30(CH), 120.8(CH), 152.7(CH), 102-134(Ar-CH, C), 154.8, 162.4 (C=O). IR: 1715-1720cm^{-1} (keto carbonyls); 1560 cm^{-1} (olefinicbond); 3030-3137cm^{-1}(aromatic C-H carbons); 1617cm^{-1} (aromatic carbons); 1628cm^{-1}(NH_2); 1598cm^{-1}(N-H). Mass: (m/z): 241.

6–AMINO-5–(ALLYL PHENYL)-PYRIMIDINE–2-THIO-4-ONE: 5b

A mixture of ethyl-2-cyano-3-(allyl phenyl ester) 4a (1.21g, 0.01mol) with thiourea (1.26g, 0.02mol) in ethanol by the above method afforded 6 – amino 5–(allyl phenyl) pyrimidine – 2-thio-4-one 5b. M.P: 95 oC. 1H NMR: δ 1.42 (s, NH_2), 4.23 (s, CH), 4.34 (s, NH), 7.52-8.20 (m, Ar-H), 6.20-8.41 (d, CH). 13C NMR: δ 13.06 (C), 61.30 (CH), 125.8 (CH), 157.7 (CH), 103135 (Ar-CH, C), 162.4 (C=O), 200.10 (C=S). IR: 1730-1200cm^{-1} (keto, thiocarbonyls); 1570cm^{-1}(olefinicbond); 3060-3150cm^{-1} (aromatic C-H carbons); 1612cm^{-1} (aromatic carbons). 1632 cm^{-1} (NH_2); 1594 cm^{-1} (N-H). Mass: (m/z): 257

ANTI-BACTERIAL ACTIVITY

The chloroform dye extract were used for antibacterial study (Ozkan et al., 2004; Janarthanam and Sumathi 2010). Different concentrations (10 mg, 20mg and 30mg /ml) of the concentrated chloroform extract was tested for its antimicrobial activity against pathogenic bacterial strains such as Staphylococcus aureus, Bacillus cereus, Bacillus subtilis, Pseudomonas aeruginosa and Escherichia coli. The bacterial cultures were grown in Muller Hinton Agar and Muller Hinton Broth (Himedia) (Lopez et al., 2001).

ANTIBACTERIAL ACTIVITY ASSAYS

Antibacterial activity was measured using the standard method of diffusion disc plates on agar (Erturk et al., 2003). Then 0.1ml of each culture of bacteria was spread on agar plate surfaces. For antimicrobial assay, all bacterial strains were grown in Muller Hinton Broth Medium (Himedia) for 24h at 37°C and plated on Muller Hinton Agar (Himedia) for agar diffusion experiments. Paper disc (6mm in diameter) were placed on the agar medium to load 20µl of different concentration (10 -30mg /ml) of dye chloroform extracts were tested. Inhibition diameters were measured after incubation for 24hrs at 37°C. Blanks of solvent only (processed in the same way), were also tested for antibacterial activity.

Table-1: Antimicrobial activity of the synthesized pyrimidine dione and thione compounds

compound	Conc. (µg/well) In DMF	Zone of Inhibition in nm* Antibacterial activity				
		Basillus subtilis	Basillu scereus	Psesdomonas aerugenosa	Staphylococcus aureus	Eschaerichia coli
1a	600	16	18	12	-	16
1b	600	15	17	11	-	17
1c	600	12	12	12	-	16
1d	600	14	16	14	-	12
1e	600	15	13	12	-	16
1f	600	17	10	13	-	17
2a	600	14	15	15	6	15
2b	600	13	14	13	5	14
2c	600	14	15	16	8	17
2d	600	13	14	15	6	16
2e	600	11	11	14	7	16
2f	600	12	15	16	8	15
Gentamycin	600	15	16	18	17	17
ketaconzole	600	-	-	-	-	-

REFERENCE

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