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2,4-DIAMINO-5,10-DIOXO-1,5,10,10A-TETRAHYDROBENZO[G]QUINOLINE-3-CARBONITRILE FOR THE SYNTHESIS OF NEW AZOLES AND AZINES COMPOUNDS

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Abstract: A series of new fused pyrazoles (**4a-c,5a-c**), isoxazoles (**6a-c**), pyrimidines (**7a-c**), pyrimidinethiones (**8a-c**) have been synthesized from 2,4-diamino-5,10-dioxo-1,5,10,10a-tetrahydrobenzo[*g*]quinoline-3-carbonitrile (**1**), these compounds expected to have biological activity .

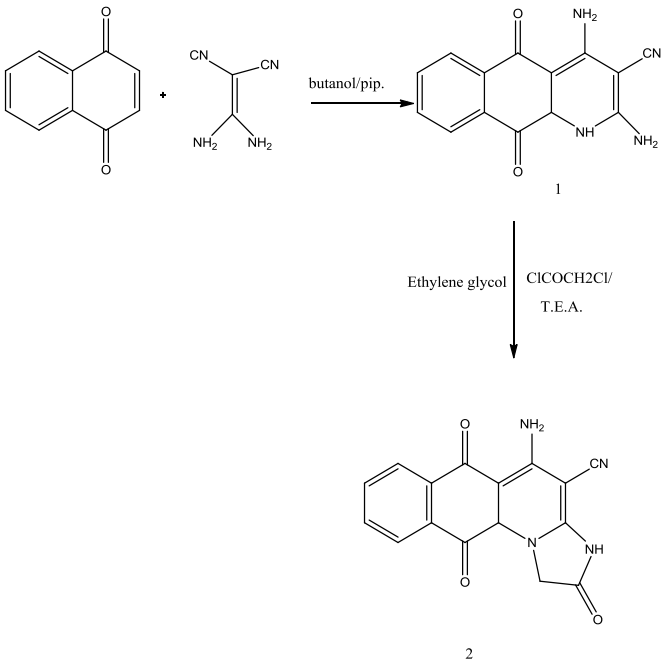
Keywords: pyrimidine, pyrimidine thione, pyrazoles, isoxazoles,anticancer agents.

Introduction

pyrimidine derivativeshave wide applications asanti-inflammatory [I]ant malarial[II],anticancer agents [III],antihypertensive [IV],antibacterial[V],and as antiviral[VI],The pyrazole derivatives are very important in the developmentof pesticides and medicines and are found to exhibitbioactivities such as anti-inflammatory [VII], anti-cancer activity [VIII],anti-viral [IX], antimicrobial [X] anti-tumor [XI], and anti-depressant, anti-convulsant [XII].,Alsosomepyrazole derivatives are widely used as analgesic agents, fungicides, , insecticides and herbicides , antiviral agents [XIII].Isoxazole derivatives are an important class of heterocyclicpharmaceuticals and bioactive natural products due to their significant and wide spectrum ofbiological activities, including potent and selective antagonism of the NMDA receptor [XIV] and anti-HIVactivity [XV].Naphthoquinoneexhibit interesting range of pharmacological properties such as antibacterial[XVI,XVII]Antiviral[XVIII], trypanocidal[XIX], anticancer[XX], antimalarial[XXI,XXII]and antifungal[XXIII]activities so my research project aim to synthesis triazin ring related to naphthoquinone, these compounds expected to exhibit biological activities

Results and Discussion

Our initial strategy was to synthesize fused heterocycles from compound **(1)**. In an attempt propose compound **(1)** through three component reaction of 1,4-naphthoquinone, urea and malononitriel in equimolar amount afford compound **(1)** scheme 1.



1

2

Scheme1

Structure of the compound **(1)** was determined by its spectroscopic data and elemental analysis.

IR spectrum showed an intense peak for CN group characteristic peak at 2212 cm^{-1}. ^{1}HNMR of the compound showed three broad singlet corresponding to $2NH_2$ and one NH at δ 6.79, 4.23 and 10.45 ppm respectively. Most spectrum of the compound was found in agreement with the assigned structure.

The suggested mechanism for compound 1 as follow (Fig.1)

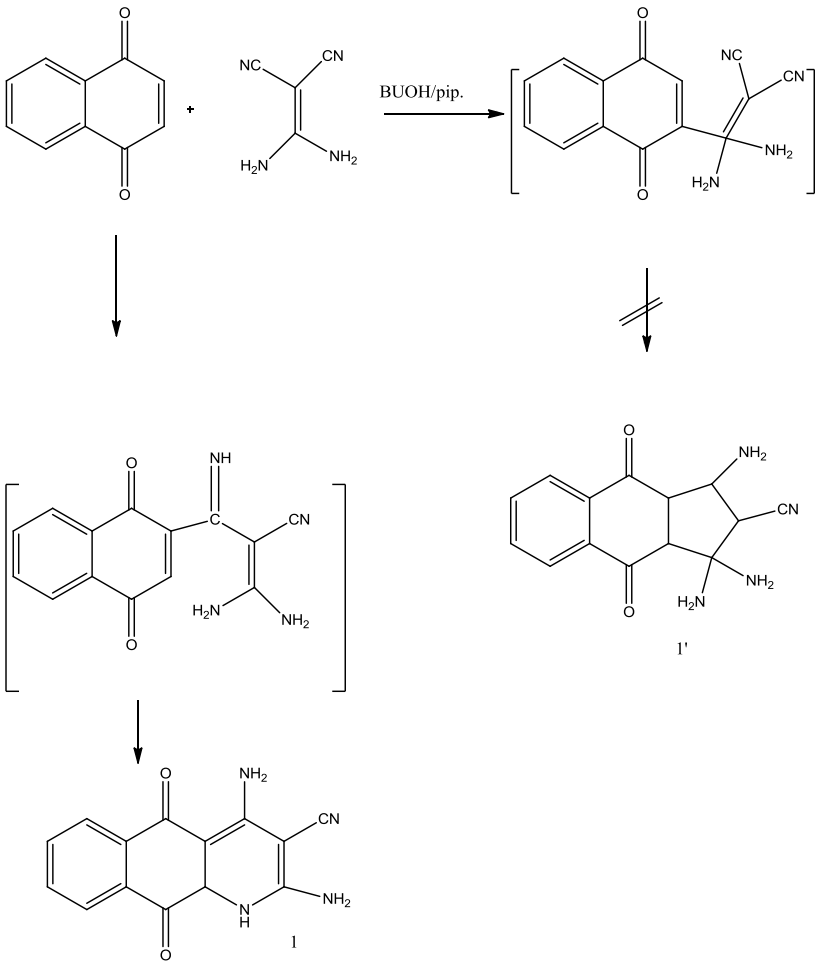
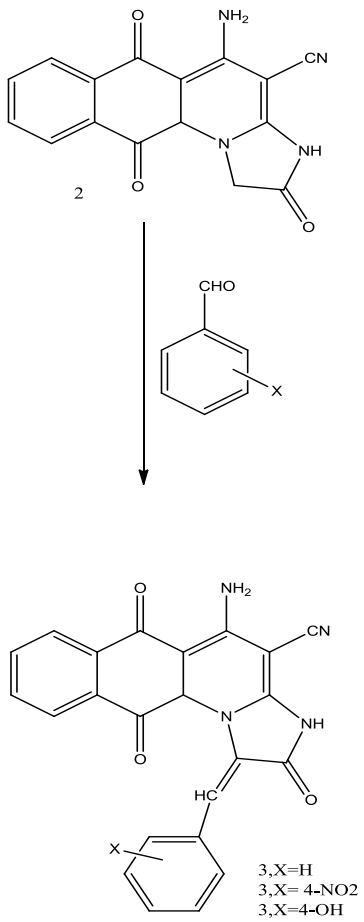


Fig.1

In this study, some new fused pyrazolines, isoxazolines, pyrimidines, have been prepared one of the rings of compound (**1)** endowed with electron donating group amino and electron withdrawing group cyano make it an opportune subtracted for cyclocondensation reaction with suitable reagent. Compound**(1)** on reaction with chloroacetyl chloride in ethylene glycol and triethylamine catalyst, under reflux condition afford compound (**2)** (scheme 2).

In order to synthesize some of new fused heterocyclic quinone compounds which may be of certain interest compound **(2)**was condensed with different aromatic aldehydes to give the corresponding α,β-unsaturated ketones **(3)**scheme2.

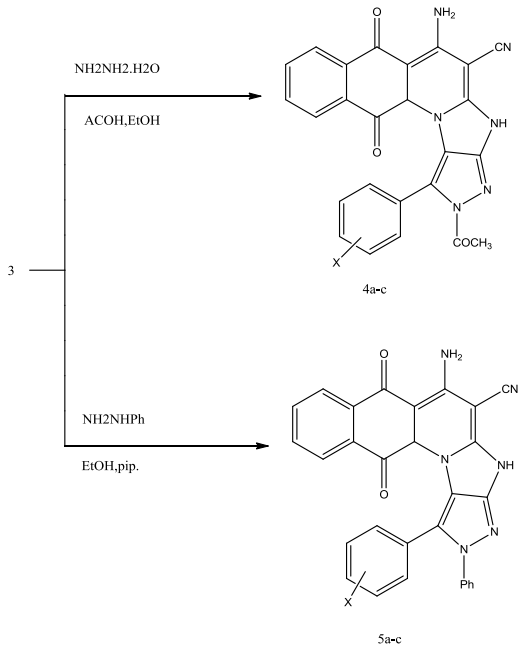


Scheme2

The compound 3 undergo cyclic condensed reaction with hydrazines, hydroxylamine hydrochloride, urea and thiourea to yield fused heterocyclic compound **(4a-c, 8a-c)**. Structure of the compounds gave us the arguments that the reaction is carried out by condensation addition reaction throughα,β-unsaturated ketonic system.

Thus, the chemical work covers the implementation of the following fused heterocyclic compounds and the details are as follows:

N-acetyl (phenyl) derivatives of compounds **4a-c** and **5a-c** were synthesized by the interaction of **3a-c** with equimolecular ratios of hydrazine hydrate or phenyl hydrazine in the presence of glacial acetic acid or in the presence of piper dine as catalyst respectively[XXIV].

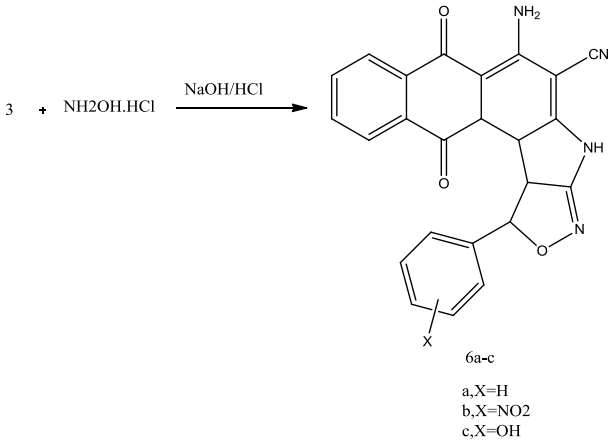


Scheme3

The structures of (**4a-c)**, (**5a-c)** were confirmed by elemental analysis, IR, ^{1}HNMR and mass spectra

Compounds (**4a-c)**; (**5a-c)** proved to be stable on boiling with mixture of acetic acidand dilute sulphuric acid or on heating above their melting points which are theconditionthat bringout the cyclisation of hydrazine hydrate or phenyl hydrazine to pyrazolines.

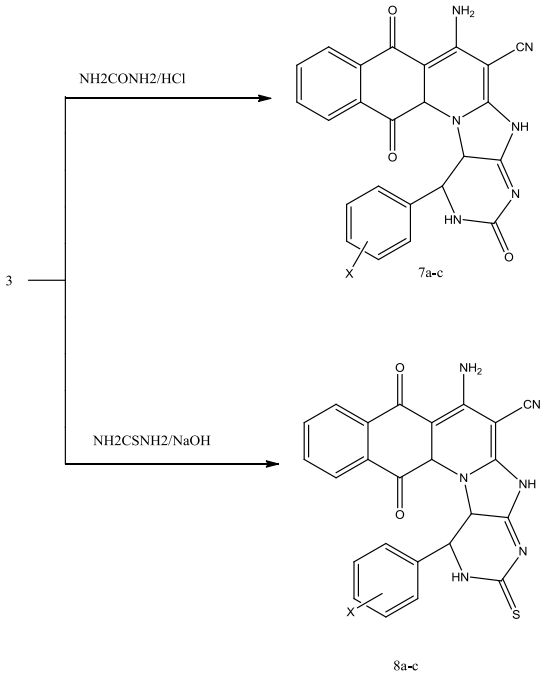
Isoxazoline derivatives of compounds (**6a-c**)were synthesized by the reaction of (**3a-c)** with equimolecular ratios of hydroxylamine hydrochloride in the presence of sodium hydroxide. The structures of (**6a-c)** were confirmed by elemental analysis, IR, ^{1}HNMR and mass spectra .



Scheme4

Pyrimidino and pyrimidine thiono derivatives of compounds (**7a-c)**, (**8a-c)** were synthesized by the reaction of (**3a-c)** with equimolecular ratios of urea and/or thiourea in ethanol containing 20 mL hydrochloric acid and or in the presence of sodium hydroxide respectively. The

structures of compounds (**7a-c)** and (**8a-c)** were confirmed by elemental analysis, IR, ^{1}HNMR and mass spectra.



Conclusion:we synthesis the new pyrazoles and Isoxazoles via the cyclocondensation reaction between compound **(3a-c)**with hydrazine hydrate ,phenylhydrazine and hydroxyle amine hydrochloride to afford **(4a-c,5a-c,6a-c)**respectively, Also pyrimidine and pyrimidine thiones derivatives were prepared by the reaction of urea and or thiourea with **(3a-c)** in presence of hydrochloric acid or sodium hydroxide to afford the corresponding **(7a-c)**and **(8a-c)**.

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EXPERIMENTAL

All melting points are uncorrected,the reactions were monitored and the purity of products was controlled by Thin Layer Chromatography (TLC) using silica gel aluminum sheets $60F_{254}$ (Merck, Germany). The IR spectra were obtained from KBr disks using Perkin Elmer 1650 ET-IR Spectrophotometer (USA). ^{1}H NMR spectra were recorded on Bruker AMX-250 spectrometer (Germany) at 250 MHz Mass spectra were recorded on Hewlett Packard Ms 5988 Spectrometer (USA). Elemental microanalyses were carried out on CE 440 Elemental Analyzer-Automatic Injector (Exeter Analytical, Inc., USA) at CairoUniversity, Cairo, Egypt

Synthesis of 2,4-diamino-5,10-dioxo-1,5,10,10a-tetrahydrobenz[*g*]quinoline-3-carbonitrile (1) :

A mixture of 1,4-naphthoquinone (1.58 g, 10 mmol), urea (0.60 g, 10 mmol) and malononitrile (0.66 g, 10 mmol) in butanol (30 mL) in presence of piperidine catalyst was refluxed for 10-15 h; Butanol was evaporated under reduced pressure product thus obtained washed with ether and finally crystallized from DMF.

yield 70%; Mp:295°C;IR(KBr,Cm^{-1}): ν˜, 3350(NH), 3200($2NH_2$), 2212(CN), 1652(CO);^{1}H-NMR ð(ppm): ð6.79(s, NH_2), 4.23(s, NH_2), 8.1-7.2(m, 5H), 10.25(s, NH).;MS (266) ; analysis calculated for:$C_{14}H_{10}O_2N_4$;C, 63,15 , H, 3.79;N, 21.04 , Found; C, 63.12;H,3.75;N,21.01

Synthesis of 5-amino-2,6,11-trioxo-1,2,3,6,11,11a-hexahydrobenzo[*g*]-imidazo[1,2-*a*]quinoline-4-carbonitrile (2) :

A mixture of 1 (2.66 g, 10 mmol) and chloroacetyl chloride (1.13 g, 10 mmol) was refluxed for 14-16 h. in ethylene glycol (5 mL) in presence of piperidine catalyst. The solvent was evaporated under reduced pressure and crude product crystallized from DMF.Yield66%,MP>300°C;IR(KBr,Cm^{-1}): ν˜2210(CN), 3390(NH), 3180(NH_2), 1645(CO).;^{1}H-NMRð (ppm):ð2.01-2.85(s, 2H), 6.77(s, NH_2), 8.02-7.1(m, 5H), 10.36(s, NH).
;MS [307(M^{+1})] ; analysis calculated for:$C_{16}H_{10}O_3N_4$;C,62.74;H,3.29 ;N,18.29; Found;C, 62.68; H,3.24;N,18.21.

Synthesis of 5-amino-1-phenylmethylene-2,6,11-trioxo-1,2,3,6,11,11a-hexa-hydrobenzo[*g*]imidazo[1,2-*a*]quinoline-4-carbonitrile (3a-c) :

A mixture of compound 2 (2.90 g, 10 mmol), aromatic aldehydes (10 mmol) and piperidine (0.5 mL) in absolte ethanol (40 mL) and DMF (5 mL) was refluxed for 15-17 h. The reaction mixture was cooled to room temperature, evaporated to dryness, residue redissolved in cold water (55 mL) containing dilute ammountHCl (in necessary) and left over night. the solid product formed was filtered and crystallized from DMF.

3a:Yield 67%;Mp>300°C;IR(KBr,Cm^{-1}): ν˜2216(CN), 3380(NH), 3150(NH_2), 1624(NHCO), 1614(C=C), 1643(CO).
;^{1}H-NMRð (ppm):ð6.56(s, NH_2), 8.02-7.1(m, 11H), 10.62(s, NH).;MS (394); analysis calculated for:$C_{23}H_{14}O_3N_4$;C, 70.06; H, 3.58;N, 14.21; Found; C,70.03; H, 3.54; N,14.17 .

3b: Yield 65%;Mp>300°C;IR(KBr,Cm^{-1}): ν˜;2215(CN), 3420(NH), 3170(NH_2), 1666(CO), 1595, 1625(NHCO);^{1}H-NMRð (ppm): ð6.55(s, NH_2), 8.02-7.1(m, 10H), 10.67(s, NH).;
MS(439); analysis calculated for:$C_{23}H_{13}O_5N_5$; C,62.87; H, 2.98; N,15.94 ;Found;C,62.84;H,2.95;N,15.90

3c: Yield 68%;Mp>300°C;IR(KBr,Cm^{-1}): ν˜;2213(CN), 3360(NH), 3210(NH_2), 3400(OH), 1665(CO), 1590(C=C), 1620(NHCO).;^{1}H-NMRð(ppm):ð6.53(s, NH_2), 8.02-7.1(m, 10H), 9.21(brs,OH), 10.69(s,NH).; MS(410);analysis calculated for:$C_{23}H_{14}O_4N_4$;C, 67.32; H,3.44;
N, 13.65; Found; C, 67.30; H, 3.41; N, 13.62 .

Synthesis of fused pyrazoles (4a-c) :

A solution of **3** (10 mmol) in absolute ethanol (50 mL) was refluxed with hydrazine hydrate (10 mmol) in presence of catalytic amount glacial acetic for 13-14 h. The reaction mixture was filtered in hot condition, solvent was then evaporated under reduced pressure the petroleum ether (60-80°) and filtred a gain it was treated with ice/water and finally crystallized from DMF.

4a: Yield77%Mp>300°C;IR(KBr,Cm^{-1}): ν˜;2220(CN), 3380(NH), 3200(NH_2), 1630(C=N), 1680(C=O), 1645(CO).;^{1}H-NMR ð(ppm):ð2.93(s, 3H), 6.71(s, NH_2), 8.02-7.1(m, 12H), 10.66(s,NH).; MS[451(M^{+1})];analysis calculated for:$C_{25}H_{18}O_3N_6$, C,66.66; H,4.03;
N, 18.67; Found: C, 66.62; H, 4.01;N, 18.63.

4b: Yield66%Mp>300°C;IR(KBr,Cm^{-1}): ν˜;2214(CN), 3410(NH), 3880(NH_2), 1635(C=N), 1680(CO), 1655(C=O).
H-NMRð (ppm):ð2.91(s, 3H), 6.78(s, NH_2), 8.02-7.1(m, 11H), 10.68(s, NH).; MS(495) ;
analysis calculated for:$C_{25}H_{17}O_5N_7$; C, 60.61;H,3.46; N,19.79; Found: C, 60.58; H,3.42;
N, 19.75 .

4c: Yield69%Mp>300°C;IR(KBr,Cm^{-1}): ν˜;2219(CN), 1635(C=N), 3350(NH), 3280 (NH_2), 3415(OH), 1685(CO), 1650(CO).;^{1}H-NMR ð(ppm): ð2.89(s, 3H), 6.75(s, NH_2), 8.02-7.1(m, 11H), 9.32(brs, OH), 10.67(s, NH).; MS(466) ;
analysis calculated for:$C_{25}H_{18}O_4N_6$; C, 64.37; H,3.89; N, 18.02; Found: C,64.33; H,3.85; N, 18.00 .

Synthesis of fused pyrazoles (5a-c) :

A solution of **3** (10 mmol) in dimethylformamide (40 mL) was refluxed with phenylhydrazine (10 mmol) in the presence of catalytic amount of piperidine (0.5 mL) for 13-15h. The reaction mixture was concentrated to half its volume, poured into crushed ice containing dilute HCl (if necessary). The solid product thus formed was filtred and crystallized from DMF.

5a: Yield70%Mp>300°C;IR(KBr,Cm^{-1}): ν˜;3360(NH), 3250(NH_2), 2217(C≡N), 1616(C=N), 1675(C=O).;^{1}H-NMR ð(ppm):ð6.65(s, NH_2), 8.02-7.1(m, 17H), 10.75(s, NH).;MS (484) ;analysis calculated for:$C_{29}H_{20}O_2N_6$;C,71.89;H,4.16;N.17.35;Found;C,71.85;H,4.13;N,17.13.

5b: Yield73 %Mp>300°C;IR(KBr,Cm^{-1}): ν˜;3400-3100(NH, NH_2), 2215(C≡N), 1689(C=O), 1619(C=N).;^{1}H-NMRð (ppm):ð 6.68(s, NH_2), 8.02-7.1(m, 16H), 10.78(s, NH).;MS(529) ;analysis calculated for:$C_{29}H_{19}O_4N_7$;C,65.78;H,3.62;N,18.52;Found;C,65.73;H,3.55;N,18.46.

5c: Yield71%Mp>300°C;IR(KBr,Cm^{-1}): ν˜3400-3100(NH,NH_2,OH), 2218(C≡N), 1690(C=O).;^{1}H-NMRð (ppm): ð6.66(s, NH_2), 8.02-7.1(m, 16H), 9.42(brs, OH), 10.74(s, NH).; MS(500); analysis calculated for:$C_{29}H_{19}O_3N_6$; C,69.59;H,4.03; N,16.79; Found;C,69.70;H,3.79;N,16.81.

Synthesis of fused isoxazoles (6a-c) :

A solution of **3** (10 mmol) in absolute ethanol (40 mL) was refluxed for 15-17 h. with hydroxylamine hydrochloride (0.69g, 10 mmol) in the presence of sodium hydroxide (0.5 g) as catalyst. The reaction mixture was filtered at hot, and evaporated under reduced pressure and residue boiled with petroleum ether (60-80°) filtred. The residue was again treated with ice water and crystallized from DMF.

6a: Yield74 %Mp>300°C;IR(KBr,Cm^{-1}): ν˜3370(NH), 3295(NH_2), 222(C≡N), 1617(NHCO), 1695(C=O).;^{1}H-NMRð (ppm): ð6.73(s, NH_2), 8.02-7.1(m, 12H), 10.58(s, NH).; MS(409) ;analysis calculated for:$C_{23}H_{15}O_3N_5$;C,67.48;H,3.69;N,17.12;Found;C,67.44;H,3.66;N,17.09.

6b: Yield70%Mp>300°C;IR(KBr,Cm^{-1}): ν˜3400-3100(NH, NH_2), 2225(C≡N), 1615(NHCO), 1668(C=O).;^{1}H-NMRð(ppm):ð6.75(s,NH_2), 8.02-7.1(m,11H), 10.55(s,NH).; MS(454);analysis calculated for:$C_{23}H_{14}O_5N_6$;C,60.80;H,3.11;N,18.50;Found;C,60.77;H,4.08;N,18.4

6c: Yield65%Mp>300°C;IR(KBr,Cm^{-1}): ν˜3450-3150(NH, NH_2, OH), 2227(C≡N) 1617(NHCO), 1675(C=O).;^{1}H-NMRð (ppm):ð 6.71(s, NH_2), 8.02-7.1(m, 11H), 9.51(brs, OH), 10.61(s,NH).;MS(425)
analysis calculated for:$C_{23}H_{15}O_4N_5$;C,64.94;H,3.55;N,16.46;Found;C,64.90;H,3.52;N,16.44.

Synthesis of fused pyrimidines (7a-c) :

A solution of **3** (10 mmol) in ethanol (30 mL) was refluxed for 18-19 h. with urea (0.60g, 10 mmol) in presence of conc. Hcl (5 mmol). The reaction mixture was filtred at hot, evaporated under reduced pressure, residue dissolved ice cold water neutrallized with 5N NaOH. The solid precipitate was filtred and crystallized from DMF.

7a: Yield63 %Mp>300°C;IR(KBr,Cm^{-1}): ν˜3385(NH), 3230(NH_2), 2223(C≡N), 1634(NHCO), 1650(C=O).;^{1}H-NMRð(ppm):ð6.55(s, NH_2), 8.02-7.1(m, 12H),10.34(s, 2NH).;MS [435(M^{-1})] ;
analysis calculated for:$C_{24}H_{16}O_3N_6$;C,66.05;H,3.70;N,19.26;Found;C,66.02;H,3.66;N,19.23.

7b: Yield66%Mp>300°C;IR(KBr,Cm^{-1}): ν˜3360(NH), 3180(NH_2), 2220(C≡N), 1630(NHCO), 1640(C=O).;^{1}H-NMRð (ppm):6.57(s, NH_2), 8.02-7.1(m, 11H), 10.36(s, 2NH)..;MS (481) ;analysis calculated for:$C_{24}H_{15}O_5N_7$;C,59.89;H,3.14;N,20.37;Found;C,59.86;H,3.10;N,20.33.

7c: Yield 75%Mp>300°C;IR(KBr,Cm^{-1}): ν˜3425(OH), 3370(NH), 3220(NH_2), 2225(C≡N), 1645(C=O), 1626(NHCO).;^{1}H-NMRð (ppm):ð6.54(s, NH_2), 8.02-7.1(m, 11H), 9.26(brs, OH), 10.38(s, 2NH).; MS(452);analysis calculated for:$C_{24}H_{16}O_4N_6$;C,63.72;H,3.56;N,18.58; Found;C,63.68;H,3.52;N,18.54.

Synthesis of fused pyrimidinethione (8a-c) :

A solution of **3** (10 mmol) in ethanol (30 mL) was refluxed with thiourea (10 mmol) for 15-17 h. in presence of sodium hydroxide (5 mmol). The reaction mixture was then filtred at hot, evaporated under reduced pressure, residue treated with petroleum ether (60-80°), and with cold water. The solid product was filtred and crystallized from DMF.

8a: Yield73 %Mp>300°C;IR(KBr,Cm^{-1}): ν˜3355(NH), 3215(NH_2), 2220(C≡N), 1625(C=N), 1650(C=O).˜;^{1}H-NMRð (ppm): ð6.53(s, NH_2), 8.02-7.1(m, 12H), 10.25(s, 2NH).;MS (452) ;analysis calculated for:$C_{24}H_{16}O_2N_6S$;C,63.71;H,3.56;N,18.57;S,7.09;Found;C,63.67;H,3.53;N,18.55;S,7.05.

8b: Yield69%Mp>300°C;IR(KBr,Cm^{-1}): ν˜3375(NH), 3220(NH_2), 2224(C≡N), 1623(C=N), 1655(C=O).;^{1}H-NMR ð(ppm): ð6.56(s, NH_2), 8.02-7.1(m, 11H), 10.23(s, 2NH).; MS(497);analysis calculated for:$C_{24}H_{15}O_4N_7S$; C,57.94;H,3.04;N,19.71;S,6.44;Found;C,57.91;H,3.00;N,19.68;S,6.41.

8c: Yield63%Mp>300°C;IR(KBr,Cm^{-1}): ν˜3415(OH), 3380(NH), 3190(NH_2), 2226(C≡N), 1627(C=N), 1645(C=O).;^{1}H-NMRð (ppm): ð6.58(s, NH_2), 8.02-7.1(m, 11H), 9.22(brs, OH), 10.22(s, 2NH).;MS (468);analysis calculated for:$C_{24}H_{16}O_3N_6S$;C,61.53;H,3.44;N,17.94;S,6.84;Found;C,61.50;H,3.42;N,17.90;S,6.81 .

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