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Synthesis of New Dipyrimidine and Dialkyl Terephthalate Derivatives from 2,6-Diphenyl-sulphonyloxy-1H, 3H, 5H, 7H-pyrrolo [3,4-F] isoindole- 1, 3, 5, 7-tetrone

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THE TITLE compound 2 was obtained by treatment of 2,6-dihydroxypyromellitimide 1 with benzenesulphonyl chloride. Compound 2 was used as starting material for the synthesis of new dipyrimidine and dialkyl 2,5-di [(alkoxycarbonyl) amino] terephthalate derivatives. The reaction of 2 with different amines was intensively investigated with respect to the probability of isomerization.

Keywords: 2,5-Diaminoterephthalic acid diesters, 2,6-Dihydroxy-pyromellitic imide, Lossen degradation and Pyrimidinediones .

The considerable biological activities of pyrimidine and their annulated systems[(1-3)] as agrochemicals[(4,5)], sedatives[(6)], antibacterial[(6-11)], and as anti-inflammatory[(6,7,12)], anticonvulsant [(13)], antipyretic [(6)], antiparasitic [(9)], antifungal [(10,13,15)], antitoxic[(16)], anti-viral[(14,17-19)] and their DNA-binding activities [(20)] as well as their therapeutical uses[(21)] stimulated our interest in the synthesis of several new pyrimidine derivatives starting with 2,6-diphenylsulphonyloxy-1H, 3H, 5H, 7H-pyrrolo [3,4-f] isoindole- 1,3,5,7-tetrone (2).

Results and Discussion

As a part of our program aimed at developing the synthesis of new pyrimidine derivatives as potential pharmaceuticals and/or agrochemicals, we reported here the synthesis of new pyrimidine and dialkyl 2,5-di[(alkoxycarbonyl) amino] terephthalate derivatives. Thus, the reaction of pyromellitic dianhydride with hydroxylamine hydrochloride in pyridine gave the previously prepared 2,6-dihydroxypyromellitimide 1[(22)]. Treatment of 1 with benzene-sulphonyl chloride afforded 2,6-diphenylsulphonyloxy-1H,3H,5H,7H-pyrrolo[3,4-f]isoindole-1,3,5,7-tetrone (2)[(23)] as shown in Scheme 1.

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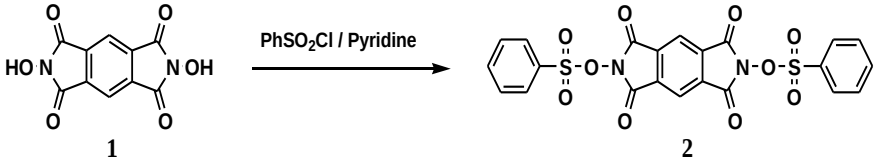


Scheme 1

Compound 2 was reacted with hydrazine hydrate giving a mixture of two isomers, namely 3,8-diaminopyrimidoquinazoline-2,4,7,9-tetrone (3a) and 3,7-diaminopyrimidoquinazoline-2,4,6,8-tetrone (4a) as indicated from TLC. Attempts to separate the two isomers using column chromatography and fractional crystallization were unsuccessful. The ^{1}H-NMR spectrum of 3a and 4a confirms their assigned structures as shown in Fig. 1.

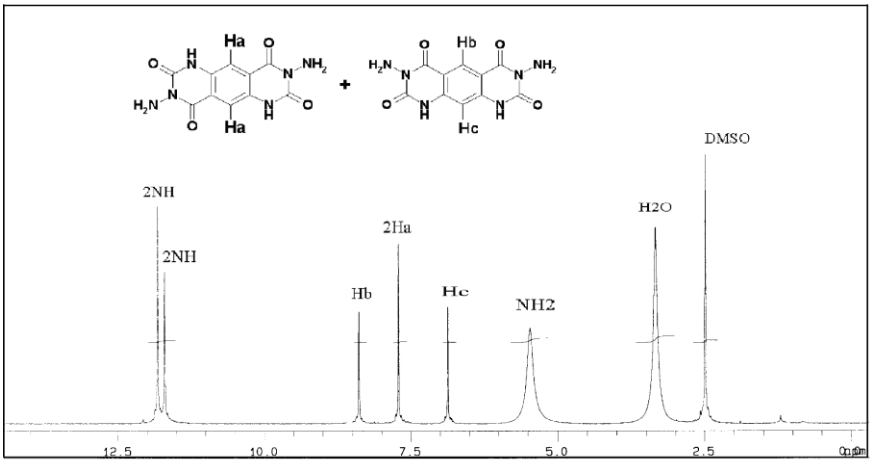


Fig. 1. The ^{1}H-NMR spectrum in (DMSO-d6) of the two isomeric structures 3a and 4a.

Refluxing of compound 2 with phenylhydrazine gave 3,8-dianilinopyrimidoquinazoline-2,4,7,9-tetrone (3b). When a mixture of compound 2 and hydroxylamine hydrochloride in pyridine was refluxed, 3,8-dihydroxypyrimidoquinazoline (3c) was obtained as the sole product as shown in Scheme 2.

The reaction of compound 2 with different aliphatic, aralkyl, aromatic and heterocyclic amines was intensively investigated with respect to the two competing processes going on, which leading to isomerization. So, when compound 2 was allowed to react with ethylamine and/or propylamine in acetic acid/ sodium acetate, a mixture of two isomers; 3d and 4b and/or 3e and 4c was obtained, respectively indicated by monitoring the reaction mixture using TLC. Separation of any mixture of them using column chromatography was unsuccessful owing to their comparable R_F values.

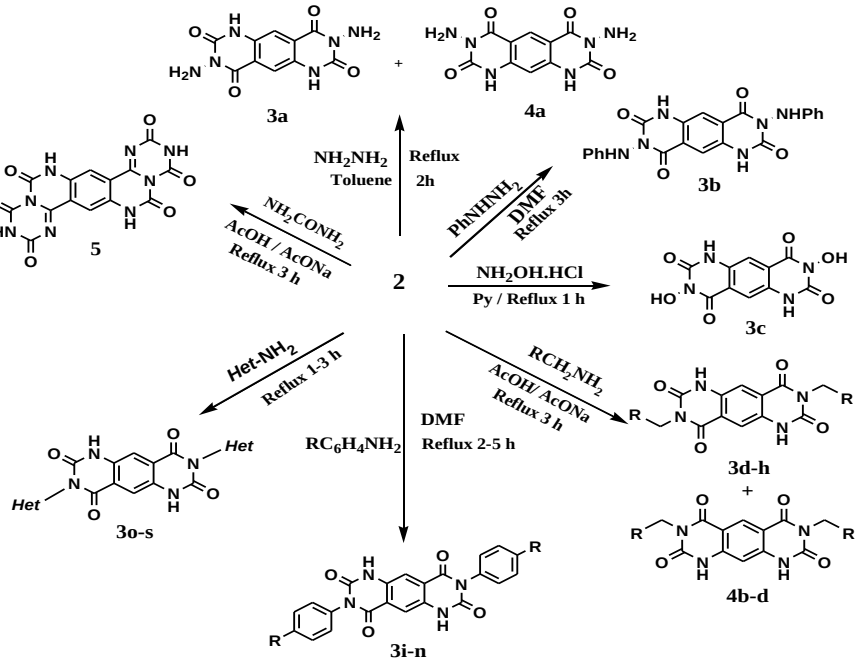
Using the fractional crystallization, 3d and 3e were separated in very pure state using hot acetic acid, both were found to be partially soluble, while 4b and 4c were completely soluble. Detection of the filtrate using TLC showed the presence of the two isomers in each case.

Structures 3d, 3e and "4b, 4c in the reaction mixtures" were established by their spectral data (*cf.* Experimental Part).

Monitoring the reaction of 2 with butylamine in refluxing acetic acid using TLC revealed the formation of the two isomers 3f and 4d, which are of comparable R_F values. All attempts to separate the two isomers using column chromatography, HPLC and fractional crystallization were unsuccessful.

Successively, we also investigated the behavior of compound 2 towards aralkylamines with respect to the probability of isomerization.

Refluxing of compound 2 with primary aralkylamine namely, benzylamine and/or 2-phenylethylamine in glacial acetic acid in presence of sodium acetate afforded only one product, 3g and/or 3h , respectively as shown in Scheme 2.

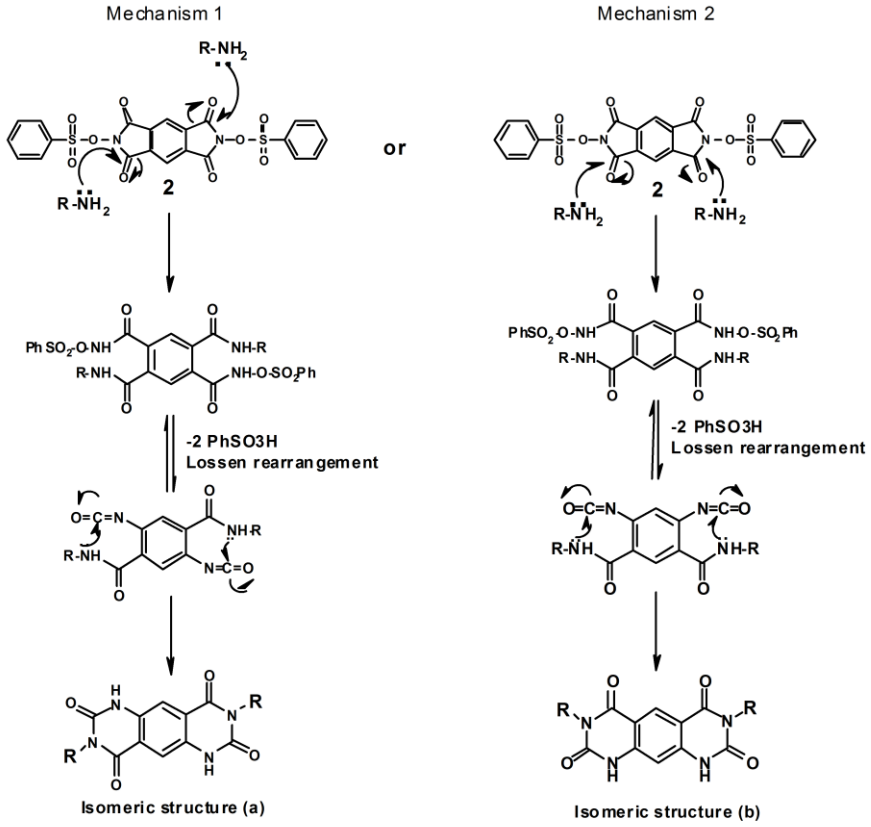


3d ; R = CH_3, 3e ; R = CH_3CH_2, 3f ; R = $CH_3CH_2CH_2$, 3g ; R = C_6H_5, 3h ; R = $CH_2C_6H_5$;
3i ; R = H, 3j ; R = OMe, 3k ; R = OH, 3L ; R = CH_3, 3m ; R = Br, 3n ; R = NO_2.
4b; R = CH_3, 4c ; CH_3CH_2, 4d ; $CH_3CH_2CH_2$.

3o ; *Het* =  **3p ; *Het* =**  **3q ; *Het* =**  **3r ; *Het* =**  **3s ; *Het* =** 

Scheme 2

The formation of the two isomeric structures (a) and (b) in case of reaction of 2 with different amines is related to the simultaneous attack of the amine used at the two carbonyl groups in position 1 and 5 to give pyrimido[4,5-g]quinazoline derivatives (a) as shown in "mechanism 1" in Scheme 3, or attacking of the amine used at the two carbonyl groups in position 1 and 7 to give pyrimido[5,4-g]quinazoline derivatives (b), according to "mechanism 2" in Scheme 3.



Scheme 3

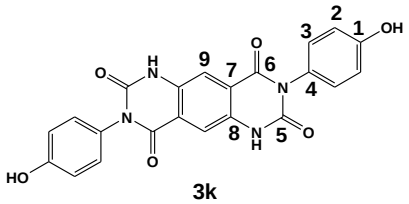
Obviously, the chemoselectivity outcome of the reaction of aralkylamine with compound 2 to give only one product takes place through the cross-attack at the carbons C1 and C5 which seems to be connected with the relative stability between the two isomeric structures (a) and (b) in addition to the steric factor.

In conjunction with our current research with the action of amine on compound 2, we studied the action of primary aromatic amines which have been found to be less basic than alkylamines and aralkylamines.

Due to the low solubility of compound 2 and the reaction mixture of the following reactions, compound 2 was refluxed in dimethylformamide with primary aromatic amine namely, aniline, p-anisidine, p-aminophenol, p-toluidine, p-bromoaniline and p-nitroaniline to give one product in each case assigned as 3,8-diaryl-1,6-dihydropyrimido[4,5-g]quinazoline-2,4,7,9(3H,8H)-tetrone 3i-n as shown in Scheme 2.

The configuration assigned to these proposed structures 3i-n was based on their spectroscopic evidence. ^{1}H NMR confirmed the cross-attack of the used aromatic amine in which two identical aromatic protons appeared as a singlet (*cf*. Experimental Part).

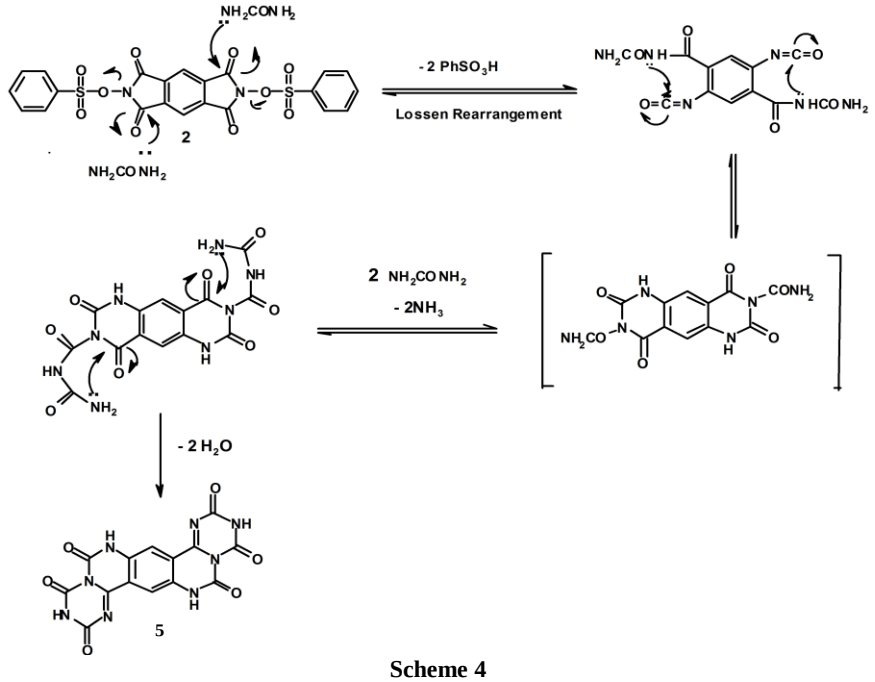
^{13}C NMR (DMSO) of compound 3k gave a convincing evidence to the cross-attack of the aromatic amine in which nine different signals for nine different carbon atoms were observed as follows: 150.02, s, C-1; 115.39, d, C-2; 129.85, d, C-3; 113.68, s, C-4; 157.23, s, C-5; 163.11, s, C-6; 134.12, s, C-7; 126.50, s, C-8; 120.21, d, C-9.



3k

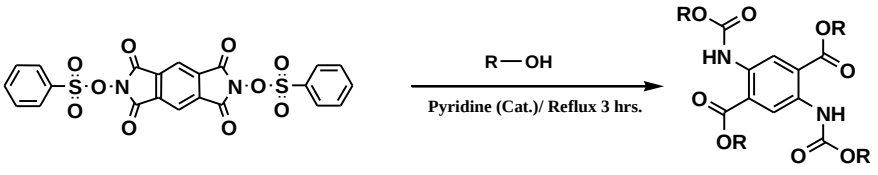
In continuation of the previous study, also the action of some heterocyclic amines on compound 2 was investigated. When compound 2 was allowed to react with different heterocyclic amines namely, 2-aminopyridine, 4-aminopyridine, 2-aminomethylpyridine, 2-amino-1,3,4-thiadiazole and/or 2-amino-1,3-thiazole in different media such as pyridine, acetic acid and/or DMF according to the solubility of the reaction mixture, 3,8-disubstituted-pyrimido[4,5-g]quinazoline-2,4,7,9-tetrones 3o-s were afforded respectively as shown in Scheme 2. Elucidation of the chemical structures of compounds 3o-s were based on their spectroscopic data (*cf*. Experimental Part).

Refluxing of compound 2 with urea in acetic acid/ sodium acetate for 3h gave compound 5 as shown in Scheme 2. The reaction of 2 with urea may proceed via a nucleophilic attack of urea to undergo ring enlargement to yield the pyrimidoquiazoline derivative as intermediate through "Lossen rearrangement" which reacts with urea followed by extra cyclization giving compound 5 as shown in Scheme 4.



Scheme 4

Boiling of compound 2 with alcohols such as methanol, ethanol, propanol, butanol, pentanol and/or isopropanol in presence of few drops of pyridine gave the corresponding dialkyl 2,5-di[(alkoxycarbonyl)amino]terephthalate derivatives 6a-f, respectively as shown in Scheme 5.



2 **6 a-f**

R : a = - CH_3 b = - CH_2CH_3 c = - $CH_2CH_2CH_3$

d = - $CH_2CH_2CH_2CH_3$ e = - $CH_2CH_2CH_2CH_2CH_3$ f = $(CH_3)_2CH$ -

Scheme 5

Identification of the chemical structure of compounds 6a-f were based on their spectroscopic data (*cf.* Experimental Part), in which the reaction was found to proceed under basic condition through cross-attack giving only the terephthalate derivative.

Conclusions

In summary, the action of aliphatic amines, aralkyl amines, aromatic amines and heterocyclic amines on 2,6-diphenylsulphonyloxypyromellitimide 2 was studied. We found that; the probability of isomerization is related to the relative stability between the two produced isomeric structures. Mainly one isomeric product takes place through the cross-attack at the carbonyl groups in position 1 and 5 of compound 2, which seems to be more stable than the other isomer produced through the other attacking of the amine used at the position 1 and 7 of compound 2.

Experimental

Melting points (uncorrected) were recorded on an Electrothermal melting apparatus. The IR spectra (KBr) were recorded on a Shimadzu 408 spectrometer. The ^{1}H NMR spectra were recorded by 400 MHz Varian EM 390 spectrometer. The ^{13}C NMR spectra were measured on Avance 600 spectrometer; Chemical shifts are reported in ppm with TMS as an internal standard and are given in δ units. Electron impact mass spectra were obtained at 70 eV using a GCMS sp.1000 Shimadzu. Elemental analyses and ^{13}C NMR spectra were carried out at Regensburg University.

3,8-Diaminopyrimido[4,5-g]quinazoline-2,4,7,9(1H,3H,6H,8H)-tetrone (3a) and 3,7-diamino-pyrimido[5,4-g]quinazoline-2,4,6,8(1H,3H,7H,9H)-tetrone (4a)

A mixture of compound 2 (0.6 g, 1 mmol) and hydrazine hydrate (0.29 g, 6 mmol) in toluene (30 ml) was heated under reflux for 2hr. After cooling, the solid formed was filtered off, washed with water and recrystallized from DMF to give a mixture of 3a and 4a (in 3:2 ratio, respectively) as yellow crystals in 61% yield. Attempts to separate the two isomers using fractional crystallization or column chromatography were unsuccessful. mp >360 ^{o}C; IR (KBr): ν 3450, 3350 cm^{-1} (NH_2), 3250 cm^{-1} (NH), 1700, 1670 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 5.46 (s, 8H, 4 NH_2), 6.87 (s, 1H, Hc) for 4a, 7.70 (s, 2H, 2Ha) for 3a, 8.38 (s, 1H, Hb) for 4a and two singlets one at 11.69 (2H, 2NH) for 4a and the other singlet at 11.82 (2H, 2NH) for 3a; MS: m/z 276. Anal. Calcd. For $C_{10}H_8N_6O_4$. C, 43.48; H, 2.92; N, 30.43. Found; C, 43.53; H, 2.96; N, 30.34%.

3,8-Dianilino-1,6- dihydropyrimido [4,5-g] quinazoline-2,4,7,9(3H,8H)-tetrone (3b)

Compound 2 (0.6 g, 1 mmol) and phenylhydrazine (0.42 g, 4 mmol) in dimethylformamide (15ml) were refluxed for 3 hr. After cooling, the solid crystals were filtered off, washed with water and recrystallized from DMF as yellow crystals in 66% yield, mp >360 ^{o}C; IR (KBr): ν 3300 cm^{-1} (NH), 1740, 1660 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 6.67- 7.17 (m, 10H, arom. H), 7.82 (s, 2H, 2Ha), 8.53 (s, 2H, 2NH (PhNH-)), 11.73(s, 2H, 2NH). Anal. Calcd. For $C_{22}H_{16}N_6O_4$. C, 61.68; H, 3.74; N, 19.63. Found; C, 61.60; H, 3.79; N, 19.66%.

3,8-Dihydroxypyrimido[4,5-g]quinazoline-2,4,7,9(3H,8H)-tetrone (3c)

A mixture of compound 2 (0.6 g, 1 mmol) and hydroxylamine hydrochloride (0.27 g, 4 mmol) in pyridine (10 ml) was heated under reflux for 1 hr. After cooling, the reaction mixture was poured on cold dilute HCl (1:1) and the solid formed was filtered off, dried and crystallized from DMF as yellow crystals in 72% yield, mp >360 ^{o}C; IR (KBr): ν 3300-2800 cm^{-1} (NH and OH), 1710-1660cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 7.72 (s, 2H, two identical benzene protons), 10.93 (s, 2H, 2OH), 11.48 (s, 2H, 2NH). Anal. Calcd. For $C_{10}H_6N_4O_6$. C, 43.17; H, 2.16; N, 20.14. Found; C, 43.20; H, 2.12; N, 20.15%.

3,8-Diethyl-1,6-dihydropyrimido [4,5-g] quinazoline-2,4,7,9(3H,8H)-tetrone (3d) and 3,7- diethyl-1,9-dihydropyrimido[5,4-g]quinazoline-2,4,6,8(3H,7H)-tetrone (4b)

A mixture of compound 2 (1.2 g, 2 mmol) and ethylamine (0.36 g, 4 mmol) in presence of anhydrous sodium acetate (0.12 g, 1.5 mmol) in glacial acetic acid (30 ml) was refluxed for 3 hr. A yellow precipitate was formed while hot, the reaction mixture was poured on ice-water and filtered off to give a mixture 3d and 4b indicated from TLC (0.44 g, 1.5 mmol 73% yield in ratio 1:1). Separation of this mixture using column chromatography was not possible owing to theIR comparable R_F values. Attempts to separate the two isomers using fractional crystallization, 3d was separated (0.15 g, 0.49 mmol) using acetic acid which was found to be partially soluble, while 4b was completely soluble. The filtrate was detected by TLC which showed the presence of the two isomers. mp >360 ^{o}C. IR (KBr): ν 3200 cm^{-1} (NH), 2980, 2860 (CH aliphatic), 1700, 1630 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 1.15 (t, 12H, 4CH_3) 3.89(q, 8H, 4CH_2), 6.86 (s, 1H, aromatic proton) for 4b, 7.73(s, 2H, two identical aromatic protons) for 3d, 8.46 (s, 1H, aromatic proton) for 4b, two singlets at 11.50 (2H, 2NH) and at 11.68 (2H, 2NH) for 3d and 4b. Anal. Calcd. For $C_{14}H_{14}N_4O_4$. C, 55.63; H, 4.67; N, 18.53. Found; C, 55.58; H, 4.70; N, 18.55%.

3,8-Diethyl-1,6-dihydropyrimido[4,5-g]quinazoline-2,4,7,9(3H,8H)-tetrone (3d)

Compound 3d was obtained in 34% yield, m.p > 360 ^{o}C; IR (KBr): ν 3400 cm^{-1} (NH), 2989 (CH aliphatic), 1726, 1645 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 1.20 (t, 6H, 2CH_3) 3.95(q, 4H, 2CH_2), 7.869(s, 2H, two identical aromatic protons) and broad singlets at 11.34 (2H, 2NH); MS: m/z 302. Anal. Calcd. For $C_{14}H_{14}N_4O_4$. C, 55.63; H, 4.67; N, 18.53. Found; C, 55.65; H, 4.64; N, 18.54%.

3,8-Dipropyl-1,6-dihydropyrimido [4,5-g] quinazoline- 2,4,7,9 (3H,8H)-tetrone (3e) and 3,7- dipropyl-1,9-dihydropyrimido [5,4-g] quinazoline-2,4,6,8- (3H,7H)-tetrone (4c)

Compound 2 (1.2 g, 2 mmol), propylamine (0.47 g, 4 mmol) and anhydrous sodium acetate (0.12 g, 1.5 mmol) were refluxed in glacial acetic acid (30 ml) for 3 hr. After cooling, the solid formed was filtered off to afford a mixture of 3e and 4c indicated from TLC (0.41 g, 1.3 mmol 62% yield in ratio 1:2, respectively) as yellow crystals. Attempt to isolate the two isomers using column chromatography

was unsuccessful. 3e was separated in very pure state (0.1 g, 0.3 mmol) using fractional crystallization from acetic acid , while 4c was always found to be contaminated with 3e detected by TLC. mp >360 ^{o}C; IR (KBr): ν 3350 cm^{-1} (NH), 1730 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 0.90 (t, 12H, 4CH_3), 1.59 (m, 8H, 4CH_2), 3.85 (t, 8H, 4CH_2), 6.86 (s, 1H, aromatic proton) for 4c, 7.73 (s, 2H, two identical aromatic protons) for 3e, 8.45 (s, 1H, aromatic proton) for 4c and two singlets one at 11.47 (2H, 2NH) for 3e and the other at 11.66 (2H, 2NH) for 4c. Anal. Calcd. For $C_{16}H_{18}N_4O_4$. C, 58.17; H, 5.49; N, 16.96. Found; C, 58.15; H, 5.50; N, 16.98%.

3,8-Dipropyl-1,6-dihydropyrimido[4,5-g]quinazoline-2,4,7,9(3H,8H)-tetrone (3e)

Compound 3e was obtained in 24% yield, mp >360 ^{o}C; IR (KBr): ν 3256 cm^{-1} (NH), 2965- 2875 cm^{-1} (CH aliphatic), 1722, 1626 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 0.89 (t, 6H, 2CH_3), 1.63 (m, 4H, 2CH_2), 3.87 (t, 4H, 2CH_2), 7.76 (s, 2H, arom. H, two identical aromatic protons) and broad singlet at 11.47 (2H, 2NH); MS: m/z 330. Anal. Calcd. For $C_{16}H_{18}N_4O_4$. C, 58.17; H, 5.49; N, 16.96. Found; C, 58.22; H, 5.51; N, 16.89%.

3,8-Dibutyl-1,6-dihydropyrimido [4,5-g] quinazoline-2,4,7,9(3H,8H)-tetrone (3f) and 3,7-dibutyl–1,9-dihydropyrimido[5,4-g]quinazoline-2,4,6,8(3H,7H)-tetrone (4d)

A mixture of compound 2 (1.2 g, 2 mmol) and butylamine (0.58 g, 4 mmol) in presence of anhydrous sodium acetate (0.12 g, 1.5 mmol) in glacial acetic acid (30 ml) was heated under and monitored using TLC. After 3 hr, the starting material had disappeared and the reaction mixture was poured onto ice- water and the solid formed was filtered off and crystallized from ethanol to give a mixture of 3f and 4d (0.46 mg, 1.28 mmol 64 % yield in 2: 1 ratio , respectively) as yellow crystals. mp >360 ^{o}C; IR (KBr): ν 3350 cm^{-1} (NH), 2950, 2900, 2850cm^{-1} (CH aliphatic), 1720, 1670, 1640 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 0.87 (t, 12H, 4CH_3), 1.32- 1.51 (m, 12H, 6CH_2), 3.03 (m, 4H, 2CH_2), 3.22 (t, 4H, 2 NCH_2), 3.58 (t, 4H, 2NCH_2), 7.57 (s, 1H, aromatic proton) for 4d, 8.19 (s, 2H, two identical aromatic protons) for 3f, 8.88 (s, 1H, aromatic proton) for 4d and two broad singlets one at 10.60 (2H, 2NH) for 3f and the other at 11.42 (2H, 2NH) for 4d. Anal. Calcd. For $C_{18}H_{22}N_4O_4$. C, 60.32; H, 6.19; N, 15.63. Found; C, 60.41; H, 6.22; N, 15.51%.

3,8-Dibenzyl-1,6- dihydropyrimido [4,5-g] quinazoline- 2,4,7,9(3H,8H)-tetrone (3g) and 3,8-di(2-phenylethyl)-1,6-dihydropyrimido [4,5-g] quinazoline-2,4,7,9(3H,8H)-tetrone (3h)

General procedure

A mixture containing compound 2 (0.6 g, 1 mmol), primary aralkylamine, namely, benzylamine and/ or 2-phenylethylamine (4 mmol) in glacial acetic acid (30 ml) in presence of anhydrous sodium acetate (0.12 g, 1.5 mmol) was refluxed for 3 hr. The solid formed while hot was filtered off and crystallized from DMF to give one component only 3g as greenish yellow crystals and/ or 3h as yellow crystals, respectively.

3,8-Dibenzyl-1,6-dihydropyrimido[4,5-g]quinazoline-2,4,7,9(3H,8H)-tetrone (3g)

Compound 3g was obtained in 78% yield, mp >360 ^{o}C; IR (KBr): ν 3250 cm^{-1} (NH), 1730, 1640 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 5.12(s, 4H, 2CH$_2$), 7.32 (m, 10H, arom.H), 7.83(s, 2H, two identical aromatic protons), 11.78(s, 2H, 2NH); MS: m/z 426. Anal. Calcd. For $C_{24}H_{18}N_4O_4$. C, 67.60; H, 4.25; N, 13.14. Found; C, 67.65; H, 4.22; N, 13.12%.

3,8- Di (2-phenyleth -1- yl)- 1,6- dihydropyrimido [4,5-g] quinazoline-2,4,7,9 (3H,8H)- tetrone (3h)

Compound 3h was obtained in 79% yield, mp >360 ^{o}C; IR (KBr): ν 3250 cm^{-1} (NH), 1730, 1650cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 2.86 (t, 4H, 2CH$_2$), 4.07 (t, 4H, 2CH$_2$), 7.22-7.28 (m, 10H, arom.H), 7.71 (s, 2H, two identical aromatic protons), 11.52 broad band (2H, 2NH); MS: m/z 454. Anal. Calcd. For $C_{26}H_{22}N_4O_4$. C, 68.71; H, 4.88; N, 12.33. Found; C, 68.75; H, 4.86; N, 12.31%.

Synthesis of 3,8-Diaryl-1,6-dihydropyrimido[4,5-g]quinazoline-2,4,7,9(3H,8H)-tetrone 3(i-n).

General procedure

A mixture of compound 2 (0.6 g, 1 mmol) and primary aromatic amine, namely, aniline, p-anisidine, p-aminophenol, p-toluidine, p-bromoaniline and p-nitroaniline (4.0 mmol) in DMF (15ml) was heated under reflux for 2-5 hr. After cooling, the solid crystals was filtered off, washed with water and recrystallized from appropriate solvent to give 3i-n.

3,8-Diphenyl-1,6-dihydropyrimido[4,5-g]quinazoline-2,4,7,9(3H,8H)-tetrone (3i)

Compound 3i was obtained in 81% yield, mp >360 ^{o}C; IR (KBr): ν 3400 cm^{-1} (NH), 1720, 1660cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 7.33-7.57(m, 10H, arom.H), 7.80(s, 2H, two identical aromatic protons), 11.62(s, 2H, 2NH). Anal. Calcd. For $C_{22}H_{14}N_4O_4$. C, 66.33; H, 3.54; N, 14.06. Found; C, 66.35; H, 3.51; N, 14.08%.

3,8-Di [4-methoxyphenyl] -1,6-dihydropyrimido [4,5-g] quinazoline -2,4,7,9 (3H,8H) - tetrone (3j)

Compound 3j was obtained in 76% yield, mp >360 ^{o}C; IR (KBr): ν 3250 cm^{-1} (NH), 2950, 2850 cm^{-1} (OCH$_3$), 1730, 1650 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 4.2(s, 6H, 2OCH$_3$), 7.2-7.4 (dd, A_2B_2 System, 8H, arom.H), 7.9(s, 2H, two identical aromatic protons), 11.6 (s, 2H, 2NH); MS: m/z 458. Anal. Calcd. For $C_{24}H_{18}N_4O_6$. C, 62.88; H, 3.96; N, 12.22. Found; C, 62.84; H, 3.98; N, 12.24%.

3,8-Di [4-hydroxyphenyl] -1,6- dihydropyrimido [4,5-g] quinazoline -2,4,7,9 (3H,8H)- tetrone (3k)

Compound 3k was obtained in 58% yield, mp >360 ^{o}C; IR (KBr): ν 3400 cm^{-1} (NH), 1730, 1650 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 6.8-7.8 (dd, A_2B_2 system, 8H, arom.H), 7.8 (s, 2H, two identical aromatic protons), 9.7 (s, 2H, 2OH) 11.6 (s, 2H, 2NH); ^{13}C NMR (DMSO): 150.02, s, C-1; 115.39, d, C-2; 129.85, d, C-3; 113.68, s, C-4; 157.23, s, C-5; 163.11, s, C-6; 134.12, s, C-7; 126.50, s, C-8; 120.21, d, C-9. Anal. Calcd. For $C_{22}H_{14}N_4O_6$. C, 61.40; H, 3.28; N, 13.02. Found; C, 61.38; H, 3.30; N, 13.01%.

3,8-Di [4-methylphenyl] -1,6- dihydropyrimido [4,5-g]quinazoline 2,4,7,9 (3H,8H) - tetrone (3L)

Compound 3L was obtained in 70% yield, mp >360 ^{o}C; IR (KBr): ν 3230 cm^{-1} (NH), 2950, 2800 cm^{-1} (CH_3), 1730, 1670 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 2.37 (s, 6H, $2CH_3$), 7.22-7.27 (dd, A_2B_2 System, 8H, arom.H), 7.79(s, 2H, two identical aromatic protons), 11.57 (s, 2H, 2NH). Anal. Calcd. For $C_{24}H_{18}N_4O_4$. C, 67.60; H, 4.25; N, 13.14. Found; C, 67.63; H, 4.27; N, 13.09%.

3,8-Di [4-bromophenyl] -1,6- dihydropyrimido [4,5-g] quinazoline-2,4,7,9 (3H,8H)-tetrone (3m)

Compound 3m was obtained in 66% yield, mp >360 ^{o}C; IR (KBr): ν 3250 cm^{-1} (NH), 1730, 1650 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 7.32-7.72 (dd, A_2B_2 System, 8H, arom.H), 7.85(s, 2H, two identical aromatic protons), 11.51 (s, 2H, 2NH). Anal. Calcd. For $C_{22}H_{12}Br_2N_4O_4$. C, 47.51; H, 2.17; N, 10.07; Br, 28.73. Found; C, 47.49; H, 2.14; N, 10.11; Br, 28.75%.

3,8-Di[4-nitrophenyl]-1,6-dihydropyrimido [4,5-g] quinazoline-2,4,7,9 (3H,8H)-tetrone (3n)

Compound 3n was obtained in 68% yield, mp >360 ^{o}C; IR (KBr): ν 3250 cm^{-1} (NH), 1720, 1670 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 7.68-7.83 (dd, 8H, arom.H), 8.33(d, 2H, 2Ha [Long rang zigzag coupling aromatic protons, NH, J=0.5 Hz]), 11.75 (s, 2H, 2NH). Anal. Calcd. For $C_{22}H_{12}N_6O_8$. C, 54.11; H, 2.48; N, 17.21. Found; C, 54.14; H, 2.40; N, 17.25%.

3,8-Di(pyridin-2-yl)-1,6-dihydropyrimido [4,5-g] quinazoline-2,4,7,9(3H,8H)-tetrone (3o) and 3,8-Di(pyridin-4-yl)-1,6-dihydropyrimido [4,5-g] quinazoline-2,4, 7,9 (3H,8H)-tetrone (3p)

A mixture of compound 2 (0.6 g, 1 mmol) and 2-aminopyridine and/ or 4-aminopyridine (0.37 g, 4 mmol) in pyridine (15 ml) was heated under reflux for 1 hr. After cooling, the solid crystals was filtered off, washed with water and recrystallized from DMF to give 3o and/ or 3p as yellow crystals.

3,8-Di (pyridin-2-yl)- 1,6-dihydropyrimido [4,5-g] quinazoline-2,4,7,9 (3H,8H)-tetrone (3o)

Compound 3o was obtained in 81% yield, mp >360 ^{o}C; IR (KBr): ν 3250 cm^{-1} (NH), 1720, 1650 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 7.53-8.62 (m, 10H, Py.H), 8.02(s, 2H, two identical aromatic protons), 11.67(s, 2H, 2NH). Anal. Calcd. For $C_{20}H_{12}N_6O_4$. C, 60.00; H, 3.02; N, 20.99. Found; C, 60.10; H, 2.90; N, 21.01%.

3,8-Di(pyridin-4-yl)- 1,6-dihydropyrimido [4,5-g] quinazoline-2,4,7,9 (3H,8H)-tetrone (3p)

Compound 3p was obtained in 78% yield, mp >360 ^{o}C; IR (KBr): ν 3400 cm^{-1} (NH), 1730, 1680 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 7.4 (dd, 4H, Py.H-2,6), 7..88 (s, 2H, two identical aromatic protons), 8.75(dd, 4H, Py.H-3,5), broad singlet at 11.62 (2H, 2NH). Anal. Calcd. For $C_{20}H_{12}N_6O_4$. C, 60.00; H, 3.02; N, 20.99. Found; C, 60.07; H, 2.99; N, 20.95%.

3,8-Di(pyridin- 2-ylmethyl)- 1,6-dihydropyrimido [4,5-g] quinazoline- 2,4,7,9 (3H,8H)-tetrone (3q)

When compound 2 (0.6 g, 1 mmol) was added to a solution of 2-aminomethylpyridine (0.42 g, 4 mmol) in acetic acid (20 ml) in presence of anhydrous sodium acetate (0.21 g, 1.5 mmol), the reaction mixture turns to green colour. Heating the reaction mixture under reflux for 3hr, needles crystals were formed after cooling which were crystallized from acetic acid to give 3q as green crystals.

3,8-Di(pyridin-2- ylmethyl)-1,6-dihydropyrimido [4,5-g] quinazoline- 2,4,7,9 (3H,8H)- tetrone (3q)

Compound 3q was obtained in 92% yield, mp >360 ^{o}C; IR (KBr): ν 3200 cm^{-1} (NH), 1710, 1650 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 5,25 (s, 4H, $2CH_2$), 7.28 (dd, 4H, Py H-3,5), 7.72 (dd, 2H, Py H-4), 8.40 (dd, 2H, Py H-6), 7.84 (s, 2H, two identical aromatic protons), 11.62(s, 2H, 2NH) and disappearance of NH in DMSO. Anal. Calcd. For $C_{22}H_{16}N_6O_4$. C, 61.68; H, 3.76; N, 19.62. Found; C, 61.70; H, 3.71; N, 19.65%.

Synthesis of pyrimido[4,5-g]quinazoline 3r and 3s.

General procedure

2-amino-1,3,4-thiadiazole and/or 2-amino-1,3-thiazole (0.4 g, 4 mmol) was heated under reflux with compound 2 (0.6 g, 1 mmol) in DMF (15 ml) for 2 hr. After cooling, the solid formed was filtered off, washed with water and recrystallized from DMF to give 3r and/or 3s as yellow crystals, respectively.

3,8-Di(1,3,4-thiadiazol-2-yl)-1,6-dihydropyrimido [4,5-g] quinazoline-2,4,7,9 (3H,8H)- tetrone (3r)

Compound 3r was obtained in 83% yield, mp >360 ^{o}C; IR (KBr): ν 3350 cm^{-1} (NH), 1730, 1650 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 7.87(s, 2H, two identical aromatic protons), 9.79 (s, 2H, thiadiazole H-5) 11.90 (s, 2H, 2NH). Anal. Calcd. For $C_{14}H_6N_8O_4S_2$. C, 40.58; H, 1.46; N, 27.07; S, 15.48. Found; C, 40.63; H, 1.40; N, 27.05; S, 15.51%.

3,8-Di(1,3-thiazol-2-yl)-1,6-dihydropyrimido [4,5-g] quinazoline-2,4,7,9 (3H,8H) tetrone (3s)

Compound 3s was obtained in 75% yield, mp >360 ^{o}C; IR (KBr): ν 3350 cm^{-1} (NH), 1730, 1650 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 7.83 (s, 2H, two identical aromatic protons), 7.88(d, 2H, thiazole H-5), 7.95 (d, 2H, thiazole H-4) 11.83 (s, 2H, 2NH). Anal. Calcd. For $C_{16}H_8N_6O_4S_2$. C, 46.60; H, 1.96; N, 20.38; S, 15.55. Found; C, 46.63; H, 1.95; N, 20.36; S, 15.54%.

Pyrimidino[3`,4`-a]s-triazino [9`,8`-j]-quinazolino [3,4-a]s-triazine-2,3,4,6,7,10, 11,12,14,15-decahydro-2,4,6,10, 12,14-hexone (5)

A mixture of compound 2 (0.6 g, 1 mmol) and urea (0.35 g, 6 mmol) in glacial acetic acid (20 ml) in presence of anhydrous sodium acetate (0.12 g, 1.5 mmol) was refluxed for 3 hrs. After cooling, the solid formed was filtered off, washed with water and crystallized from DMSO as yellow crystals in 73% yield,

mp >360 ^{o}C; IR (KBr): ν 3150 cm^{-1} (NH), 1730-1660 cm^{-1} (C=O's); ^{1}H NMR (DMSO): δ 7.75 (s, 2H, two identical aromatic protons) and two broad bands at 10.96 and at 11.20 (4H, 4NH). Anal. Calcd. For $C_{14}H_6N_8O_6$. C, 43.99; H, 1.58; N, 29.31. Found; C, 43.94; H, 1.55; N, 29.39%.

Synthesis of dialkyl 2,5-di[(alkoxycarbonyl)amino]terephthalate (6a-f).

General procedure

When compound 2 (0.6 g, 1 mmol) was boilied in alcohol, namely, methanol, ethanol, propanol, butanol, pentanol and isopropanol (30 ml) in presence of few drops of pyridine under reflux for 1-3 hr, solid crystals were formed after cooling. The precipitate was filtered off, washed with water and recrystallized from appropriate solvent to give 6a-f.

Dimethyl 2,5-di[(methoxycarbonyl)amino]terephthalate (6a)

Compound 6a was obtained in 68 % yield, mp 278-79 ^{o}C; IR (KBr): ν 3350 cm^{-1} (NH), 1740, 1700 cm^{-1} (C=O's); ^{1}H NMR ($CDCl_3$): δ 3.77 (s, 6H, $2CH_3$), 3.92 (s, 6H, $2CH_3$), 9.05 (s, 2H, two identical aromatic protons), 10.19 (s, 2H, 2NH). Anal. Calcd. For $C_{14}H_{16}N_2O_8$. C, 49.41; H, 4.74; N, 8.23. Found; C, 49.45; H, 4.70; N, 8.24%.

Diethyl 2,5-di[(ethoxycarbonyl)amino]terephthalate (6b)

Compound 6b was obtained in 73 % yield, mp= 202-4 ^{o}C; IR (KBr): ν 3300 cm^{-1} (NH), 1730, 1690 cm^{-1} (C=O's); ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 6H, $2CH_3$), 1.40 (t, 6H, $2CH_3$), 4.18 (q, 4H, $2CH_2$), 4.35 (q, 4H, $2CH_2$), 9.05 (s, 2H, two identical aromatic protons), 10.19 (s, 2H, 2NH); MS: m/z 396. Anal. Calcd. For $C_{18}H_{24}N_2O_8$. C, 54.54; H, 6.10; N, 7.07. Found; C, 54.57; H, 6.08; N, 7.06%.

Dipropyl 2,5-di[(propoxycarbonyl)amino]terephthalate (6c)

Compound 6c was obtained in 58 % yield, mp= 162-64 ^{o}C; IR (KBr): ν 3300 cm^{-1} (NH), 1730, 1690 cm^{-1} (C=O's); ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 6H, $2CH_3$), 1.00 (t, 6H, $2CH_3$), 1.65 (m, 4H, $2CH_2$), 1.79 (m, 4H, $2CH_2$), 4.08 (t, 4H, $2CH_2$), 4.26 (t, 4H, $2CH_2$), 9.07 (s, 2H, two identical aromatic protons), 10.17 (s, 2H, 2NH). Anal. Calcd. For $C_{22}H_{32}N_2O_8$. C, 58.39; H, 7.13; N, 6.19. Found; C, 58.42; H, 7.15; N, 6.14%.

Dibutyl 2,5-di[(butoxycarbonyl)amino]terephthalate (6d)

Compound 6d was obtained in 72 % yield, mp= 115-17 ^{o}C; IR (KBr): ν 3300 cm^{-1} (NH), 1730, 1690 cm^{-1} (C=O's); ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 6H, $2CH_3$), 0.95 (t, 6H, $2CH_3$), 1.37 (m, 8H, $4CH_2$), 1.60 (m, 4H, $2CH_2$), 1.73 (m, 4H, $2CH_2$), 4.13 (t, 4H, $2CH_2$), 4.30 (t, 4H, $2CH_2$), 9.05 (s, 2H, two identical aromatic protons), 10.16 (s, 2H, 2NH). Anal. Calcd. For $C_{26}H_{40}N_2O_8$. C, 61.40; H, 7.93; N, 5.51. Found; C, 61.43; H, 7.91; N, 5.49%.

Dipentyl 2,5-di[(pentoxycarbonyl)amino]terephthalate (6e)

Compound 6e as obtained in 79 % yield, mp= 129-31 ^{o}C; IR (KBr): ν 3300 cm^{-1} (NH), 1730, 1690 cm^{-1} (C=O's); ^{1}H NMR ($CDCl_3$): δ 0.89 (t, 6H, $2CH_3$),

0.90 (t, 6H, $2CH_3$), 1.32 (m, 16H, $8CH_2$), 1.63 (m, 4H, $2CH_2$), 1.75 (m, 4H, $2CH_2$), 4.12 (t, 4H, $2CH_2$), 4.29 (t, 4H, $2CH_2$), 9.06 (s, 2H, two identical aromatic protons), 10.16 (s, 2H, 2NH). Anal. Calcd. For $C_{30}H_{48}N_2O_8$. C, 63.81; H, 8.57; N, 4.96. Found; 63.85; H, 8.55; N, 4.93%.

Diisopropyl 2,5-di[(isopropoxycarbonyl)amino]terephthalate (6f)

Compound 6f was obtained in 75% yield, mp= 180-82 ^oC; IR (KBr): ν 3300 cm^{-1} (NH), 1730, 1690 cm^{-1} (C=O's); ^1H NMR ($CDCl_3$): δ 0.93 (t, 6H, $2CH_3$), 1.00 (t, 6H, $2CH_3$), 1.65 (m, 4H, $2CH_2$), 1.79 (m, 4H, $2CH_2$), 4.08 (t, 4H, $2CH_2$), 4.26 (t, 4H, $2CH_2$), 9.07 (s, 2H, two identical aromatic protons), 10.17 (s, 2H, 2NH). Anal. Calcd. For $C_{22}H_{32}N_2O_8$. C, 58.39; H, 7.13; N, 6.19. Found; C, 58.41; H, 7.15; N, 6.14%.

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تخليق مشتقات جديدة للبيريميدين و الثنائى ألكيل تيريفيثلات من 6،2- ثنائى فنيل سلفونيلوكسى- بيرولو أيزواندول- تترون

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فى هذا البحث تم تحضير مركب 6،2- ثنائى فنيل سلفونيلوكسى- بيرولو أيزواندول- تترون واستخدم كمركب بداية لتحضير بعض المركبات الغير متجانسة الحلقة الجديدة لمشتقات الثنائى بيريميدين بتفاعله مع الامينات المختلفة. كذلك بتفاعله مع الكحولات المختلفة تم تحضير مشتقات جديدة من الثنائى ألكيل تيريفثلات. وتم دراسة تأثير الثباتية النسبية من ناحية تكون الايزوميرات.