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Synthesis of Novel cyanopyridine Derivatives Containing s-Triazine via Chalcones and Evaluation of their Antimicrobial Activity

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Abstract : 6-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-4-(substituted phenyl)-2-methoxypyridine -3-carbonitrile**(7a-7h)** have been synthesized by treatment of (E)-1-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-3-(substituted phenyl)prop-2-en-1-one**.(6a-6h)** chalcones. With malono nitrile and sodium methoxide in DMF.All the prepared compounds were evaluated for anti-fungal and anti-bacterial activity. Most of the compound showed potent activity.

Keywords :
Cyanuricchloride,MalonoNitrile,SodiumMethoxide,Chalcones,Triazine,cyanopyridine.

Introduction:

Pyridine moieties are very common in many Natural Products, pharmaceuticals, and functional materials [1-3].Polysubstituted pyridine having good Biological and Pharmacological activity. It could be used as a Agrochemical also for example Herbisides[4]Cyanopyridine derivatives attracted considerable attraction because of their wide Activity,anticonvulsant[5],antibacterial[6-7],antitumor[8] ,antihypertensive[9],cardiovascular[10] and antisoriasis[11]etc. due to such wide Activity of Cyanopyridine derivatives researchers are more interesting in synthesis of such compound.

A literature survey reveals that majority of Cyanopiridine derivatives were synthesized by treatment of chalcones with ammonium acetate and malono nitrile via condensation reaction.

In view of the above and in continuation of our work[12-13].we have synthesized new series of cyanopyridine derivatives. In present work,6-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-4-(substituted phenyl)-2-methoxypyridine-3-carbonitrile have been synthesized **(7a-7h)**by treatment of (E)-1-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-3-(substituted phenyl)prop-2-en-1-one.**(6a-6h)**chalcones with Malono Nitrile and Sodium Methoxide. In DMF **(Scheme I).**The structures of all synthesized compounds were assigned on the basis of IR, Mass, 1H NMR spectral data and elemental analysis and synthesized compounds were screened for their antimicrobial activity.

Materials and Methods

Experimental

Melting points were determined in open capillaries and are uncorrected.IR spectra were recorded using Perkin –Elmer spectrometer.1H NMR spectra were recorded on Brucker Advance II 400 spectrometer in DMSO by using TMS as internal standard. Thin layer chromatography was performed with E. Merkprecoated TLC plates, silica gel 60F254 with thickness of 0.25mm and spots were visualized by irradiation with ultraviolet light (254 nm).

General procedure for the synthesis of 1-(4-(4,6-dichloro-1,3,5-triazin-2-yl amino) phenyl)ethanone (3)[14]

4-Amine acetophenone (0.01 mole) was added slowly to cyanuric chloride (0.01 mole) in acetone (30 ml) with constant stirring over a period of 4 hr at 0 to 50 C. Then, sodium carbonate (0.005 mole) dissolved in water (10 ml) was added drop wise to neutralize HCl evolved during the reaction. Finally, the contents were poured into crushed ice. The solid was separated out by filtration and washed with water. The product is dried, recrystallized from alcohol to give the product **(3).**

General procedure for the synthesis of 1-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino) phenyl)ethanone (4)

1-(4-(4,6-dichloro-1,3,5-triazin-2-yl amino)phenyl)ethanone**(3)** (0.01 mole) was added slowly to sodiumethoxide (0.02 mole) with constant stirring in DMF: H2O (9: 1 ml) over a period of 4 hrs. at room temperature and refluxed for 4 hrs. at 80 0C. The contents were poured onto ice cold water and filtered. The product 4 was obtained and recrystallized from DMF.

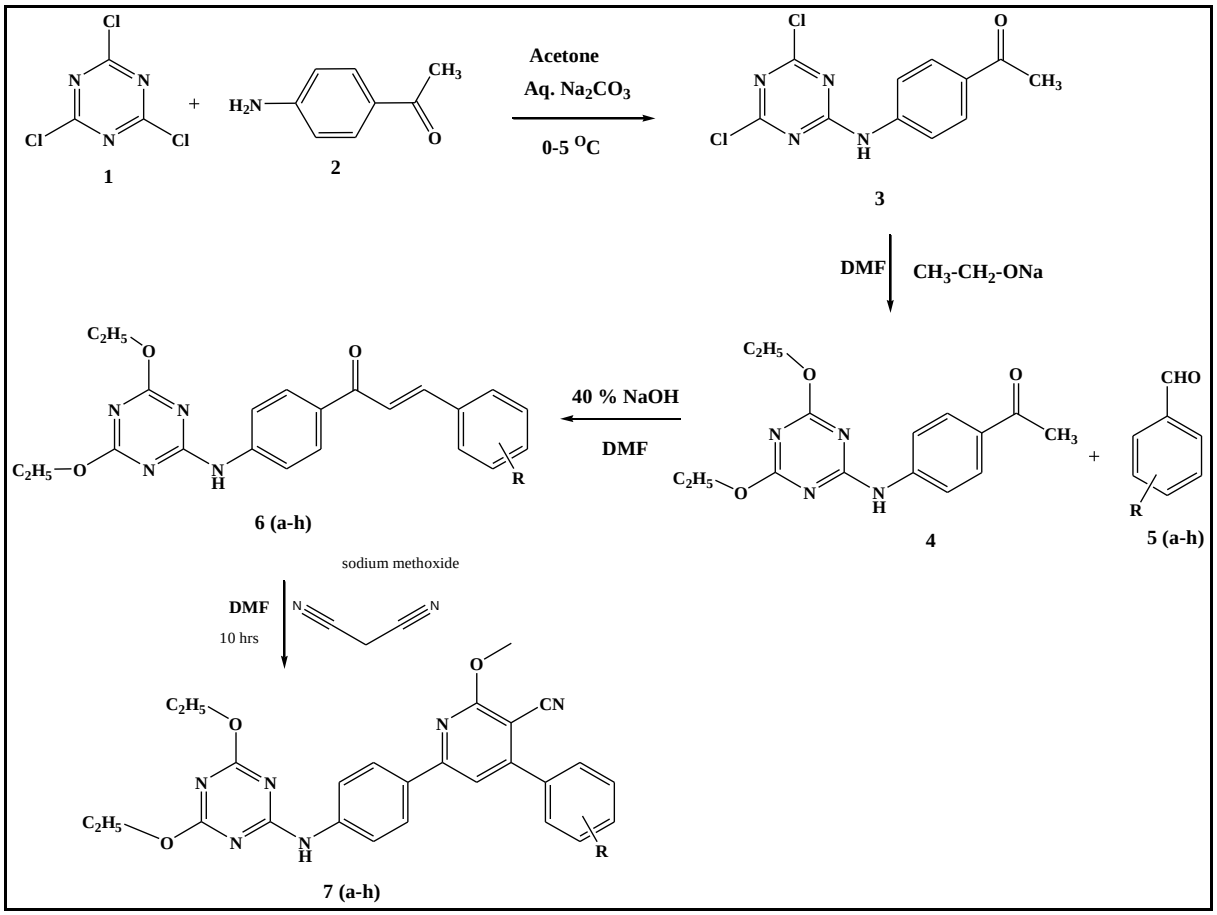
General procedure for the synthesis of substituted 1-(4-(4,6-diethoxy-1,3,5-triazin-2-yl amino)phenyl)-3-phenylprop-2-en-1-one (Chalcone) (6a-h)

Compound **4** (0.01 mole) was dissolved in DMF (25 ml) and substituted benzaldehyde**(5a-h)** (0.01mole) was added with constant stirring at room temperature for 30 minute, then sodium hydroxide (40% w/v) was added to reaction mixture which was again stirred at R.T. for 24 hrs. The progress of reaction was monitored by TLC. After completion of the reaction,crushed ice was added in the reaction mixture and neutralized with HCl. The product separated was filtered, washed with water, dried and recrystallized from DMF to get pure product (Chalcone) **(6a-6h).**

General procedure for the synthesis of substituted 6-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-4-(phenyl)-2-methoxypyridine-3-carbonitrile .(7a-7h)

A mixture of substituted 1-(4-(4,6-diethoxy-1,3,5-triazin-2-yl-amino)phenyl)-3-phenylprop-2-en-1-one (Chalcone) **(6a-h)** (0.01 mole),Malono Nitrile (0.01mole) and Sodium Methoxide(0.01 mole)in 25 ml of DMF was refluxed for 10 Hrs.After completion of reaction (checked by TLC), the reaction mixture was cooled and poured into ice cold water. The separated solid product was filtered, washed with cold water, dried and then recrystallized from DMF.

Scheme-I



Results and Discussion

The chalcones, (E)-1-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-3-(substituted phenyl)prop-2-en-1-one**.(6a-6h**) are synthesized by treating 1-(4-(4,6-dichloro-1,3,5-triazin-2-yl amino) phenyl)ethanone**(3)** with substituted Benzaldehyde **(5a-5h**) in DMF.Thechalcones undergoes Ring formation reaction via condensation with Malono Nitrile and sodium Methoxide to give substituted6-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-4-(phenyl)-2-methoxypyridine-3-carbonitrile **.(7a-7h)** The synthesis of Title compound is described in **scheme- I.**

The structure of all synthesized compounds was confirmed by elemental analysis and spectral data (IR,H^1NMR,and Mass spectroscopy) The IR spectrum of compounds chalcones**(6a-6h)** in KBr shows the characteristic band in the region of 1650cm^{-1} which indicate the presence of -C=O group. The IR spectral of **(7a-7h)**shows characteristic band in region the of 2155-2191 cm^{-1} due to –C≡N group.3198-3079(Ar-H), 2978Ali(C-H), 1505(C=N), 1330(C-N) But In (7a-7h) there is no Band at 1650 cm^{-1} to 1700 cm^{-1} which confirmed formation of **(7a-7h).**[15-17]

Further their ^{1}H NMR ($DMSO_{d6}$) spectrum appearance signals atδ 3.73-3.29 (singlet 3H),and signals at δ 6.55-8.34(m,8H,Ar-H) confirmed the presence of cyanopyridine ring The synthetic pathway followed for the synthesis of the title compounds is described in Scheme-I.

Spectral data of synthesized compounds(7a-7h):

(7a):6-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-2-methoxy-4-p-tolylpyridine-3-carbonitrile

Yield 62%; m.p. 81^{0}C: Elemental analysis Calcd for ($C_{27}H_{26}N_6O_3$) ;C, 67.21; H, 5.43; N, 17.42; found C, 67.16; H, 5.40; N, 17.38%;IR (KBr pellets Cm^{-1}):3331 (N-H), 3198(Ar-H), 2932 Ali(C-H),2155 (–C≡N), 1506(C=N), 1385(C-N):^{1}H NMR ($DMSO_{d6}$, 400 MHz), δ8.04 (s, 1H, N-H), 8.20-6.50 (m, 9H, Ar-H),

3.74(s,3H,-OCH_3), 2.90-2.80 (q, 4H,CH_2-CH_3),2.71 (s, 3H, Ar-CH_3).2.60-2.50) (t, 6H, CH_3-CH_2-)MS: m/z 483 (M+1)..

(7b):6-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-2-methoxy-4-(4-methoxyphenyl)pyridine-3-carbonitrile

Yield 58%; m.p. 77^{0}C: Elemental analysis Calcd for ($C_{27}H_{26}N_6O_4$)C, 65.05; H, 5.26; N, 16.86; found C, 64.00; H, 5.19; N, 16.79; %; IR (KBr pellets Cm^{-1}): 3329 (N-H), 3100(Ar-H), 2934 Ali(C-H),2157 (–C≡N), 1508(C=N), 1383(C-N):^{1}H NMR (DMSOd6, 400 MHz), δ 8.02 (s, 1H, N-H), 8.18-6.48 (m, 9H, Ar-H), 3.69(s, 6H, -OCH3), 2.92-2.78 (q, 4H, CH2-CH3), 2.57-2.47) (t, 6H, CH3-CH2-)MS: m/z 499 (M+1)...

(7c): 6-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-2-methoxy-4-(2,3,4-trimethoxyphenyl)pyridine-3-carbonitrile

Yield 60 %; m.p. 85^{0}C: Elemental analysis Calcd for ($C_{29}H_{30}N_6O_6$) C, 62.36; H, 5.41; N, 15.05; found C, 62.33; H, 5.38; N, 15.00%; IR (KBr pellets Cm^{-1}): 3327 (N-H), 3108(Ar-H), 2931 Ali(C-H),2159 (–C≡N), 1506(C=N), 1381(C-N):^{1}H NMR (DMSOd6, 400 MHz), δ 8.06 (s, 1H, N-H), 8.21-6.52 (m, 7H, Ar-H), 3.73(s, 12H, -OCH3), 2.95-2.80 (q, 4H, CH2-CH3), 2.54-2.45) (t, 6H, CH3-CH2-).MS: m/z 559 (M+1)...

(7d) 6-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-2-methoxy-4-(3,4,5-trimethoxyphenyl)pyridine-3-carbonitrile

Yield 54 %; m.p. 82^{0}C: Elemental analysis Calcd for ($C_{29}H_{30}N_6O_6$) C, 62.36; H, 5.41; N, 15.05; found C, 62.30; H, 5.37; N, 15.01;%; IR (KBr pellets Cm-1):3331 (N-H), 3112(Ar-H), 2935 Ali(C-H),2163 (–C≡N), 1510(C=N), 1385(C-N):^{1}H NMR (DMSOd6, 400 MHz), δ 8.10 (s, 1H, N-H), 8.25-6.56 (m, 7H, Ar-H), 3.77(s, 12H, -OCH3), 2.99-2.84 (q, 4H, CH2-CH3), 2.58-2.49) (t, 6H, CH3-CH2-).MS: m/z 559 (M+1)...

(7e) 6-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-4-(4-fluorophenyl)-2-methoxypyridine-3-carbonitrile

Yield 50 %; m.p. 79^{0}C: Elemental analysis Calcd for ($C_{26}H_{23}FN_6O_3$)C, 64.19; H, 4.77; F, 3.91; N, 17.27; found C, 64.16; H, 4.74; F, 3.88; N, 17.24;%; IR (KBr pellets Cm-1): 3326 (N-H), 3107(Ar-H), 2930 Ali(C-H),2158 (–C≡N), 1505(C=N), 1380(C-N):^{1}H NMR (DMSOd6, 400 MHz), δ 8.15 (s, 1H, N-H), 8.30-6.60 (m, 9H, Ar-H), 3.82(s, 3H, -OCH3), 2.94-2.81 (q, 4H, CH2-CH3), 2.53-2.44) (t, 6H, CH3-CH2-).MS: m/z 487 (M+1)...

(7f) 6-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-4-(2-chlorophenyl)-2-methoxypyridine-3-carbonitrile

Yield 56 %; m.p. 76^{0}C: Elemental analysis Calcd for ($C_{26}H_{23}ClN_6O_3$)C, 62.09; H, 4.61; N, 16.71; found C, 62.07; H, 4.60; N, 16.70;%; IR (KBr pellets Cm-1): 3330 (N-H), 3110(Ar-H), 2926 Ali(C-H),2160 (–C≡N), 1508(C=N), 1386(C-N):^{1}H NMR (DMSOd6, 400 MHz), δ 8.20 (s, 1H, N-H), 8.35-6.66 (m, 9H, Ar-H), 3.85(s, 3H, -OCH3), 2.98-2.79 (q, 4H, CH2-CH3), 2.56-2.48) (t, 6H, CH3-CH2-).MS: m/z 503 (M+1)...

(7g) 6-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-4-(4-chlorophenyl)-2-methoxypyridine-3-carbonitrile

Yield 53 %; m.p. 80^{0}C: Elemental analysis Calcd for ($C_{26}H_{23}ClN_6O_3$) C, 62.09; H, 4.61; N, 16.71; found C, 62.05; H, 4.58;N, 16.65;%; IR (KBr pellets Cm-1): 3331 (N-H), 3111(Ar-H), 2927 Ali(C-H),2161 (–C≡N), 1511(C=N), 1388(C-N):^{1}H NMR (DMSOd6, 400 MHz), δ 8.24 (s, 1H, N-H), 8.33-6.63 (m, 9H, Ar-H), 3.82(s, 3H, -OCH3), 2.95-2.76 (q, 4H, CH2-CH3), 2.53-2.45) (t, 6H, CH3-CH2-).MS: m/z 503 (M+1)...

(7h) 6-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-4-(2,4-dichlorophenyl)-2-methoxypyridine-3-carbonitrile

Yield 53 %; m.p. 78^{0}C: Elemental analysis Calcd for ($C_{26}H_{22}C_{l2}N_6O_3$) C, 58.11; H, 4.13; N, 15.64 found C, 58.05; H, 4.08; N, 15.58 %; IR (KBr pellets Cm-1): 3325 (N-H), 3106(Ar-H), 2921 Ali(C-H),2156 (–C≡N), 1505(C=N), 1382(C-N):^{1}H NMR (DMSOd6, 400 MHz), δ 8.18 (s, 1H, N-H), 8.27-6.57 (m, 9H, Ar-H), 3.76(s, 3H, -OCH3), 2.89-2.70 (q, 4H, CH2-CH3), 2.47-2.39) (t, 6H, CH3-CH2-).MS: m/z 537 (M+1)...

Biological activity:

Antimicrobial activity

Newly prepared all compounds were tested for anti-bacterial activity using species E. coli, Salmonella typhi and Staphylococcus aureus by disc diffusion method[18-19].using Penicilline as a standard drug and anti-fungal activity using species likeAspergillusniger, Aspergillusflavus, Penicilliumchrysogenum by poison plate method .[20]using Griseofulvin as reference standard and DMSO as a control solvent. Some of compounds show significant property of anti-bacterial and some of the compounds show moderately active. Study of anti-fungal activity shows that some of compounds are promisingly active while others are no activity. . The results are shown in **Table 1 and 2** respectively.

Table 1-Antibacterial screening results of the compounds 7a-h

Sr. No.	Compounds	E. coli	Salmonella typhi	Staphylococcus aureus
1	7a	10	13	15
2	7b	15	17	16
3	7c	17	19	28
4	7d	20	22	25
5	7e	12	14	18
6	7f	16	19	17
7	7g	17	18	21
8	7h	17	20	19
9	Penicillin	22	25	35
10	DMSO	-ve	-ve	-ve

Table 2: Antifungal screening results of the compounds 7a-7h.

S. No.	Compounds	Aspergillus niger	Aspergillus flavus	Penicillium chrysogenum
1	7a	+ve	RG	+ve
2	7b	-ve	+ve	+ve
3	7c	-ve	-ve	-ve
4	7d	-ve	-ve	-ve
5	7e	+ve	+ve	+ve
6	7f	RG	-ve	-ve
7	7g	-ve	+ve	+ve
8	7h	-ve	-ve	RG
9	Greseofulvin	-ve	-ve	-ve
10	DMSO	+ve	+ve	+ve
-ve: No growth, Antifungal activity present; +ve: Growth, Antifungal activity absent; RG: Reduced growth				

Conclusion

From the results of Anti-Bacterial and Anti-Fungal Activity; it can be concluded that compounds having chloro and Methoxy groups shows significant activity than other compounds They showed good anti-bacterial and anti-fungal activity. Therefore it may considered as a further design and development of new chemical entities.

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