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Synthesis of Pyrimidine Derivatives of Carbazolo and Azacarbazolo Fused Quinoxalines

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Abstract: ***Pyrimidine derivatives of carbazolo and azacarbazolo fused quinoxalines 11(a-d) and 12(a-d) have been synthesized by the cyclocondensation reactions of corresponding enol-ethers 9(a-b) and chalcones 10(a-b) of carbazolo and azacarbazolo fused quinoxalines with urea and guanidine nitrate respectively. The structures of all the compounds have been established on the basis of their elemental analysis and spectral (IR, ^{1}H NMR and MS) data.***

Keywords: Enol ethers, chalcones, oxoketene dithioacetals, dimethyl aminomethylene ketones, pyrimidines, carbazoles azacarbazoles.

1. Introduction

The enol ethers, chalcones, oxoketene dithioacetals and dimethyl aminomethylene ketones offer unprecedented opportunities to a chemist for the synthesis of a wide variety of heterocycles[1-4]. The ubiquitous presence of carbazoles, azacarbazoles, quinoxaline, pyrazoles and isoxazoles in a wide array of molecules exhibiting impressive biological properties has stimulated interest on the synthesis of their structural analogues where different constitution and biological activity could allow them to be used as novel chemotherapeutic agents. This aroused our interest in the synthesis of hetero ring fused pyrimidines from enol ethers, chalcones, oxoketenedithioacetals and dimethyl aminomethylene ketones derived from the quinoxalino condensed carbazole and azacarbazole derivatives.

Pyrimidines form the building block of DNA and RNA. In view of this, the study of pyrimidines is of immense significance. Fused pyrimidines *e.g.* pyrrolopyrimidine, pyrimidopyrimidines, purines, pteridines, *etc.* are found in a variety of natural products, agrochemicals, pharmaceuticals and veterinary products. Annelated pyrimidine derivatives continue to attract interest of researchers due to wide variety of biological activities and pharmacological profile[5]. Pyrimidine systems are present in several vitamins, coenzymes, nucleic acids, *etc*. to impart in various biological processes in living oragnisms. The pyrimidine nucleus also occurs in a considerable number of natural products of vital importance. As a structural component of key bio-molecules, the pyrimidine moiety is widely incorporated in the design of privileged structures. In view of the impressive pharmacodynamic applications of pyrimidine and condensed pyrimidine derivatives, it was considered worthwhile in present work to synthesize pyrimidine ring fused derivatives from enolic ethers, chalcones, dimethyl aminomethylene ketones, oxoketene dithioacetals [6-10].

2. Experimental Section

Chemicals were purchased from Aldrich Chemical Company (USA) and solvents were used after purification by distillation. Melting points were determined in open glass capillaries and are uncorrected. The reaction completion of the compounds was checked by TLC on silica gel G plates. IR spectra were recorded on FTIR-8400S (Shimadzu). ^{1}H NMR spectra were recorded on model AC 300F (Bruker) using $CDCl_3$ and DMSO-d_6 solvents. Chemical shift is expressed in δ ppm. Before analysis, all the samples were dried for one hour under reduced pressure. Mass spectra were recorded on a waters mass spectrometer. Column chromatography was performed on silica gel (Merck). Anhydrous sodium sulfate was used as a drying agent for the organic phase. Elemental and spectral data are given in the **Table-1** and **Table-2**.

2.1 Preparation of 2-amino-6,13-dihydro-5H-pyrazino[2,3-h]pyrimido[4,5-a]carbazole-9,10-diol (11c)

A mixture of **9a** (0.02mol) and guanidine nitrate (0.02mol) was heated in an oil bath at 120°C for 4h with constant stirring. The temperature was raised to 180°C and finally the mixture was heated at 220°C for 4h. On cooling, the product solidified which was re-crystallized from DMF-EtOH mixture to give **11c**. Yield 3.54g (60%). Similarly, other compounds were prepared from the reaction of **9(a-b)** with urea and guanidine respectively.

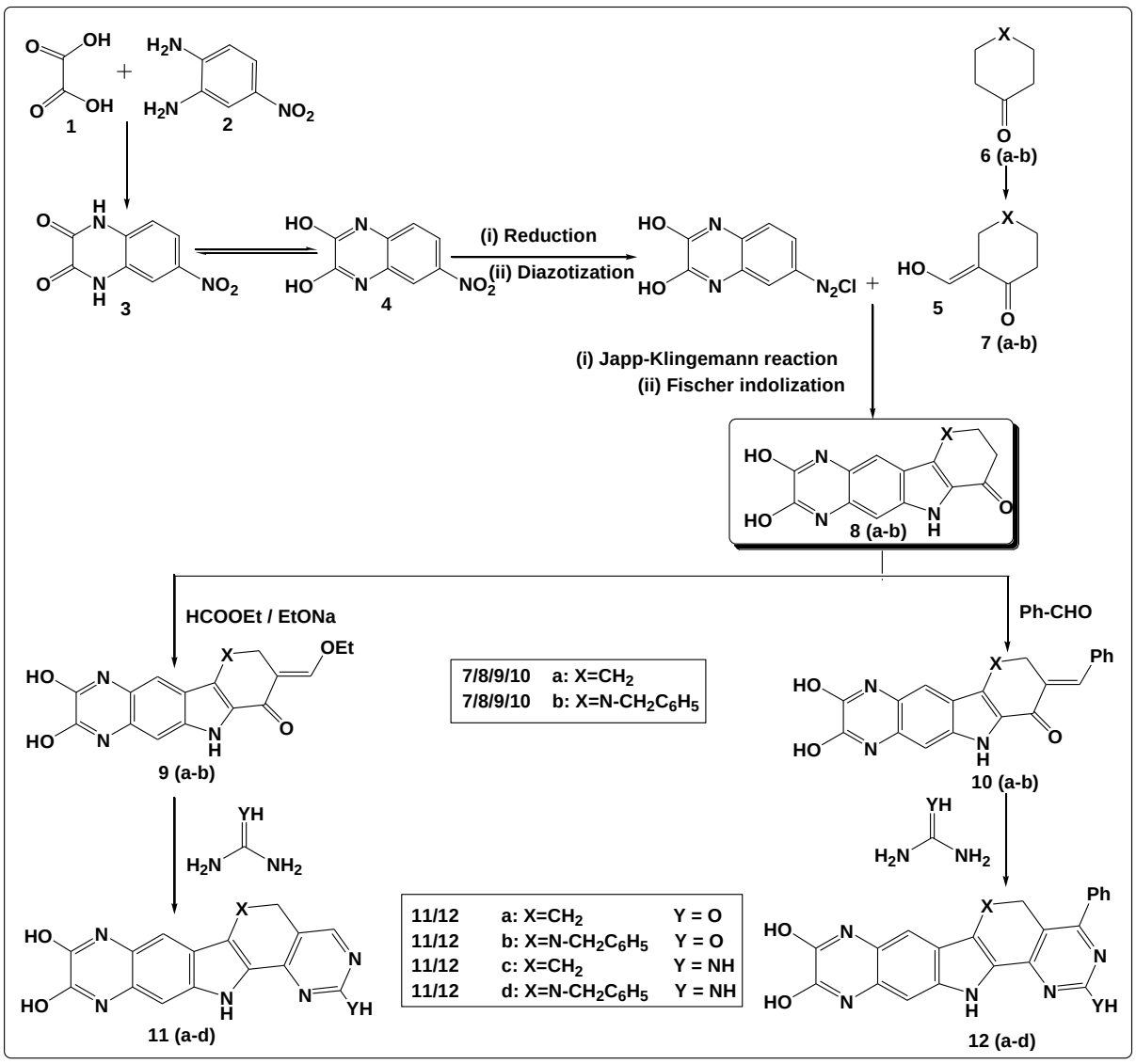
2.2 Preparation of 4-phenyl-6,13-dihydro-5H-pyrazino[2,3-h]pyrimido[4,5-a]carbazole-2,9,10-triol (12a)

To a solution of **10a** (0.0015mol) and urea (0.3g) in 20 mL ethanol and 5 ml of conc. HCl, the appropriate chalcone was added and the mixture was refluxed for 15h and then concentrated to half its volume and cooled. It was neutralized with ammonium hydroxide solution and the solid obtained was re-crystallized from ethanol to give **12a.** Yield: 0.49g (72%). Similarly, other compounds were prepared from reaction of **10a-b** with urea and guanidine respectively.

3. Results and Discussion

In the present work, the synthesis of pyrimidine derivatives of quinoxalino fused carbazoles and azacarbazoles were carried out by the cyclo-condensation reactions of corresponding enol ethers and chalcones with urea and guanidine respectively. Synthesis of enol ethers **9(a-b)** and

chalcones **10(a-b** has already been described [11]. On treatment of compounds **9(a-b)** and **10(a-b)** with urea and guanidine nitrate corresponding pyrimidine derivatives **11(a-d)** and **12(a-d)** were obtained **(Scheme-1)**. Formation of pyrimidines from enol ethers and chalcones was confirmed by the spectral data. For example, IR peak of the C=O group at 1670-1680 cm^{-1} of enol ethers disappeared and peak of OH group at 3510-3540 cm^{-1} appeared in the pyrimidines.



Scheme 1

Table 1: Physical and Analytical data of Compounds

Comp. No.	Molecular formula	Mol. Wt.	Yield (%)	M.P. (^oC)	Elemental Analysis Calculated / Found	
					N	S
11a	$C_{19}H_{13}N_7O_3$	387	60	262-264	25.80/25.31	-
11b	$C_{25}H_{18}N_8O_3$	478	64	248-252	24.21/23.42	-
11c	$C_{19}H_{13}N_7O_2S$	403	61	324-325	24.70/24.30	8.40/7.95
11d	$C_{25}H_{18}N_8O_2S$	494	63	282-284	23.29/22.66	6.84/6.48
12a	$C_{22}H_{17}N_5O_3$	399	72	270-272	18.28/17.53	-
12b	$C_{22}H_{17}N_5O_2S$	415	74	288-290	17.38/16.86	8.17/7.72
12c	$C_{28}H_{22}N_6O_3$	490	68	310-312	17.77/17.13	-
12d	$C_{28}H_{22}N_6O_2S$	506	64	272-274	16.94/16.59	6.80/6.33

Anti-fungal and Anti-bacterial Activities

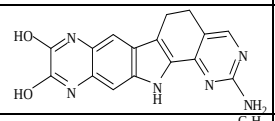
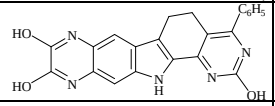
Synthesized compounds were screened for anti-fungal and anti-bacterial activities against randomly chosen two different fungal as well as bacterial strains. *Macrophomina phaseolina* (MTCC 166) & *Fusarium solani* (MTCC 350) and *E. coli* (MTCC 119) & *Bacillus cereus* (MTCC 430) were chosen for anti-fungal and anti-bacterial activities respectively. Fluconazole and ciproflaxacin were taken as the standards for both the activities. Results are given in the **Table-3**.

Table 2: Spectral data of Compounds

Comp. No.	*IR(KBr) cm^{-1}*	*^1H NMR ($CDCl_3$) δ ppm*

11a	3510 (O-H str.), 3200 (N-H str.), 1570 (C=N str.), 1560 (C=C str.), 1530 (C=C str.).	11.87 (2H,s,OH), 11.34 (1H,s,NH), 8.16 (1H,s,CH), 8.07 (2H,s,CH), 8.0 (1H,s,NH), 6.90 (2H,s,NH_2), 2.93 (2H,t,CH_2), 2.87 (2H,t,CH_2).
11b	3230 (N-H str.), 1550 (C=C str.), 1490 (C=N str.), 1680 (C=O str.).	11.87 (2H,s,OH), 11.34(1H,s,NH), 8.35 (1H,s,CH), 8.07 (2H,s,CH), 8.0 (1H,s,NH), 7.33-7.23 (5H,m,ArH), 6.90 (2H,s,NH_2), 4.71 (2H,s,CH_2), 4.32 (2H,s,CH_2).
11c	3505 (O-H str.), 3230 (N-H str.), 1530 (C=C str.), 1560 (C=N str.), 780 (C=S str.).	11.87 (2H,s,OH),11.34 (1H,s,NH), 8.16 (1H,s,CH), 8.07 (2H,s,CH), 6.90 (2H,s,NH_2), 4.0 (1H,s,NH), 2.93 (2H,t,CH_2), 2.87 (2H,t,CH_2).
11d	3530 (O-H str.), 3300 (N-H str.), 1556 (C=C str.), 1570 (C=N str.), 760 (C=S str.)	11.87 (2H,s,OH),11.34 (1H,s,NH), 8.35 (1H,s,CH), 8.07 (2H,s,CH), 7.33-7.23 (5H,m,ArH), 6.90 (2H,s,NH_2), 4.71 (2H,s,CH_2), 4.32 (2H,s,CH_2), 4.00 (1H,s,NH).
12a	3550 (O-H str.), 1580 (C=C str.), 1560 (C=N str.), 770 (C=S str.).	11.87 (2H,s,OH), 11.63 (1H,s,NH), 8.07 (2H,s,CH), 8.00 (1H,s,NH), 7.40-7.27 (5H,m,ArH), 4.9(1H, d, CH), 2.5(1H,q,CH), 2.68 (2H,t,CH_2), 1.55 (2H,q,CH_2).
12b	2940 and 2860 (CH str.), 1590, 1460 (C=C str.), 1570 (C=N str.), 1350 (C-H bend.), 780 (C=S str.).	11.87 (2H,s,OH),11.63 (1H,s,NH), 8.07(2H,s,CH), 7.40-7.27 (5H,m,ArH), 3.9 (1H,d,CH), 2.68 (2H,t,CH_2), 2.1 (1H,q,CH), 2.0 (1H,s, NH), 1.55 (2H,q,CH_2).
12c	3510 (O-H str.), 3230 (N-H str.), 1480 (C=C str.), 1590 (C-N str.), 1670 (C=O str.).	11.87 (2H,s,OH), 11.63 (1H,s,NH), 8.07 (2H,s,CH), 8.00 (1H,s,NH), 7.40-7.23 (10H,m,ArH), 4.9 (1H,d,CH), 4.32 (2H,s,CH_2), 3.05(2H,d,CH_2), 2.7 (1H,q,CH).
12d	3530 (O-H str.), 3230 (N-H str.), 1497 (C=C str.), 1595 (C=N str.), 780 (C=S str.).	11.87 (2H,s,OH), 11.63 (1H,s,NH), 8.07 (2H,s,CH), 7.40-7.23 (10H,m,ArH), 4.32 (2H,s,CH_2), 3.9 (1H,d,CH), 3.05 (2H,d,CH_2), 2.3 (1H,q,CH), 2.0 (1H,s,NH).

Table-3: Antimicrobial activities of the synthesized compounds

S. No.	Structure of compounds	Conc. (µg/ml)	*Anti-bacterial Activity*				*Anti-fungal Activity*			
			E. Coli		*B. cereus*		*M. phaseolina*		*F. solani*	
			Zone of inhibition (mm)	% activity compared to the standard	Zone of inhibition (mm)	% activity compared to the standard	Zone of Inhibition (mm)	% activity compared to the standard	Zone of Inhibition (mm)	% activity compared to the standard
1.		400 200 100	20.0 14.0 8.0	83.33 77.78 66.67	17.0 10.0 6.0	94.44 83.33 75.0	18.0 12.0 7.2	69.23 60.0 51.43	21.0 15.0 9.0	70.0 62.5 50.0
2.		400 200 100	19.0 12.0 7.0	79.16 66.67 58.33	15.0 9.0 5.5	83.33 75.0 68.75	19.0 13.8 9.0	73.07 69.0 64.29	23.0 17.0 12.0	76.66 70.83 66.67
3,	**Ciproflaxin (Standard)**	400 200 100	24 18 12	100 100 100	18 12 8	100 100 100	--	--	--	--
4.	**Fluconazole (Standard)**	400 200 100	--	--	--	--	26 20 14	100 100 100	30 24 18	100 100 100

4. Conclusion

The research work was designed to synthesize pyrimidine fused quinoxalinocarbazoles and azacarbazoles from the enol ether and chalcone intermediates with the reactions of urea and guanidine via cyclo-condensation reaction. The structural elucidation of synthesized compounds were carried out via spectral data and the antimicrobial (antibacterial and antifungal) activities of compounds were also studied.

5. Future Scope

Enol ethers and chalcones are versatile reactive intermediates to prepare variety of heterocycles as well as aromatic compounds. These reactive intermediates will be utilized to synthesize another bioactive heterocycles.

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