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SYNTHESIS, ANTIMICROBIAL AND ANTITUBERCULAR ACTIVIES OF SOME NEW BENZOFURO [3,2-*d*] PYRIMIDINE DERIVATIVES

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The displacement reaction of 2-(4-N,N-dimethyl/nitrophenyl)-4-oxo-benzofuro [3,2-*d*] pyrimidine **1-2** with phosphorus oxychloride yielded 2-(4-N,N-dimethyl/nitrophenyl)-4-chlorobenzofuro [3,2-*d*] pyrimidines **3-4**. 2-[4-N,N-Dimethyl/nitrophenyl]-4-hydrazinobenzofuro [3,2-*d*] pyrimidines **5-6** were prepared by the reaction of **3-4** with hydrazine hydrate. Compounds **5-6** upon treatment with sodium azide and triethylorthoformate gave 5-(4-N,N-dimethyl/nitrophenyl)-triazolo [4,3-*c*] pyrimido [5,4-*b*] benzofurans **7-8** and 5-(4-N,N-dimethyl/nitrophenyl)-triazolo [1,5-*c*] pyrimido [5,4-*b*] benzofurans. **9-10**. 4-Hydrazino compounds **5-6** were also subjected to condensation with aromatic aldehydes which afforded 2-(4-N,N-dimethyl/nitrophenyl)-4-arylidene hydrazinobenzofuro [3,2-*d*] pyrimidines **11-20**. All synthesized compounds were characterized on the basis of spectral studies and further these compounds were evaluated for antimicrobial and antitubercular activities.

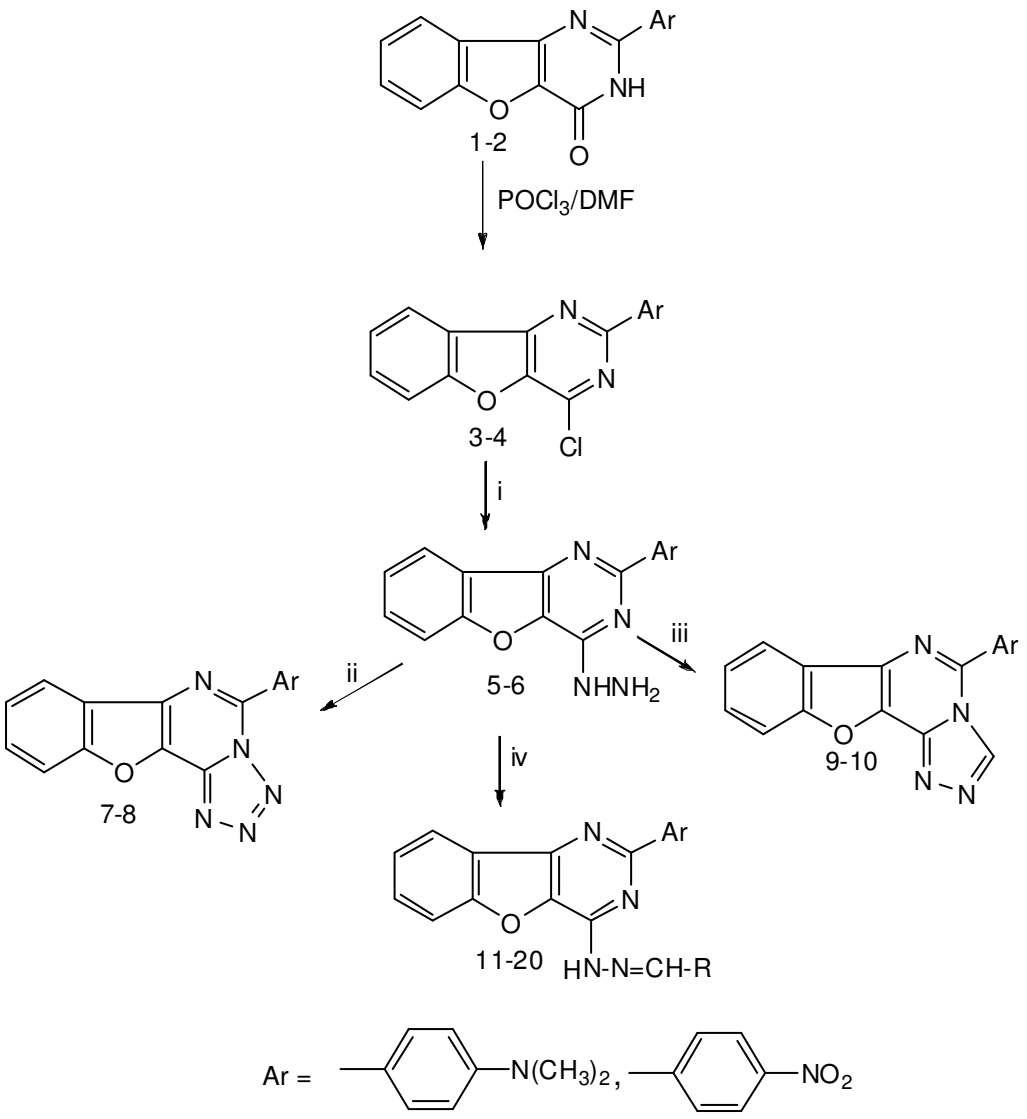
Benzofuro [3,2-*d*] pyrimidine derivatives have attracted a great interest due to their antibacterial, antifungal, antiinflammatory and analgesic activities[1-4]. We became interested in the synthesis and reactions of benzofuro [3,2-*d*] pyrimidine derivatives[5], in view of their biological potential our recent studies have disclosed that 3-amino-2-benzofuran carboxamide reacts with 4-N,N-dimethylbenzaldehyde and 4-nitrobenzaldehyde in ethanol in presence of catalytic quantity of hydrochloric acid to give good yield of 2-(4-N,N-dimethyl/nitro)-3,4-dihydro-4-oxobenzofuro [3,2-*d*] pyrimidines **1-2**. The data obtained from IR, ^{1}H NMR and mass spectra are in agreement with the proposed structures. Thus, the IR spectrum of **2** showed an strong absorption band at 1681 cm^{-1} due to characterstic of C=O of fused pyrimidone and a weak absorption band at 3169 due to ring NH streching vibration and another absorption band at 1613 due to C=N indicated the formation of pyrimidone ring system. 2-(4-N,N-Dimethyl/nitrophenyl)-4-oxobenzofuro [3,2-*d*] pyrimidines **1-2** underwent nuleophlic displacement reaction with phosphorus oxychloride to yield 2-(4-N,N-dimethyl/nitrophenyl)-4-chlorobenzofuro [3,2-*d]* pyrimidines **3-4**.

The nucleophilic displacement reaction of compounds **3-4** with hydrazine hydrate gave 2-(4-N,N-dimethyl/nitrophenyl)-4-hydrazinobenzofuro [3,2-*b*] pyrimidines **5-6**. Further the reaction of compounds **5-6** with sodium azide and triethyl orthoformate resulted in the formation of 5-(4-N,N-dimethyl/*p*-nitrophenyl)-triazolo [4,3-*c*] pyrimido [5,4-*b*] benzofurans **7-8** and 5-(4-N,N-dimethyl/*p*-nitrophenyl)-triazolo [4,3*c*] pyrimido [5,4*b*] benzofurans **9-10** respectively in good yields. The compound 2-(4-N,N-dimethyl/nitrophenyl)-4-hydrazinobenzofuro [3,2-*d*] pyrimidines **5-6** when subjected to the condensation with different aromatic aldehydes, furnished 2-(4-N,N-dimethyl/nitrophenyl)-4-arylidenehydrazinobenzofuro [3,2-*d*] pyrimidines **11-20** (Scheme-1).

Biological evaluation

Antimicrobial activity

All prepared compounds were evaluated for their antimicrobial activities such as antibacterial and antifungal activities by adopting Cup-plate diffusion method. The organisms selected were *S. epidermatitis* and *E. coli* for antibacterial and *A. niger* and *C. albicans* for antifungal activity. Ciprofloxacin and Gentamycin



Reagents : i, NH_2NH_2/MeOH, ii, NaN_3/EtOH, iii, $CH(OEt)_3$/Heat iv, R-CHO/EtOH

Where	R
11-12	C_6H_5
13-14	$C_6H_4CH_3$(*p*)
15-16	$C_6H_4OCH_3$(*p*)
17-18	C_6H_4Cl(*p*)
19-20	C_6H_4Br(*p*)

SCHEME-1

Table-1
Physical and analytical data of synthesized compounds

Compd	R	M.P. (^{0}C)	Yield (%)
3	$C_6H_4N(CH_3)_2$(*p*)	199	76
4	$C_6H_4NO_2$(*p*)	162	70
5	$C_6H_4N(CH_3)_2$(*p*)	199	76
6	$C_6H_4NO_2$(*p*)	162	70
7	$C_6H_4N(CH_3)$(*p*)	220	76
8	$C_6H_4NO_2$(*p*)	260	62
9	$C_6H_4N(CH_3)_2$(*p*)	238	70
10	$C_6H_4NO_2$(*p*)	202	68
11	C_6H_5	130	65
12	$C_6H_4(CH_3)$(*p*)	142	70
13	$C_6H_4OCH_3$(*p*)	122	65
14	C_6H_4Cl(*p*)	158	60
15	C_6H_4Br(*p*)	208	58
16	C_6H_5	165	62
17	$C_6H_4(CH_3)$(*p*)	178	57
18	$C_6H_4OCH_3$(*p*)	174	63
19	C_6H_4Cl(*p*)	188	70
20	C_6H_4Br(*p*)	162	78

All compounds gave satisfactory C,H and N analysis.

Solvent for crystallization: Ethanol.

were used as standard drugs for antibacterial and antifungal activity respectively.

The standard drug and test compounds were used at the conc of 100μg/0.1 ml. The zone of inhibition of compounds were recorded after incubation for 24 hr at 37^0.

Compounds **14,18** and **19** exhibited significant antibacterial activity against *S. epidermatitis* and *E. coli* and compounds **6,7,13** and **17** displayed moderate activity against both bacteria and remaining representative compounds of the series showed weak activity against these organisms.

Compounds **14,15,18** and **19** exhibited good antifungal activity against *A. niger* and *C. albicans* and compounds **7,10** and **17** showed moderate activity against both fungi. Other compounds of series displayed weak activity against *A. niger* and *C. albicans*.

Antitubercular activity

Benzofuro [3,2-*d*] pyrimidine derivatives (**7-10**, **11-12** and **17-18**) were evaluated for antitubercular activity against *M. Tuberculi* H_{37}Rv at a conc of 12.5, 25, 50 and 100 μg/ml using streptomycin as a standard drug at a conc of 7.5 μg/ml by using Microplate Almar Blue Dye (MABA) method. Compounds **8,10**, **18** and **19** displayed significant antitubercular activity against *Mycobacterium tuberculi* H_{37}Rv and compounds **7,9** and **10** exhibited moderate activity. Remaining compounds of series were shown to prossess moderate to weak activity.

Experimental

Melting points of all synthesized compounds were determined by open capillaries and are uncorrected. The purity of all compounds was checked by TLC using silica gel and suitable solvent system. IR spectra were recorded on a Perkin-Elmer 1000 spectrophotometer in KBr. The ^{1}H NMR spectra were recorded on a Bruker DRX-400 NMR spectrophotometer using TMS as internal standard and chemical shifts are expressed in δ ppm. Mass spectra were recorded on a GC-LC/MS 5970 mass spectrophotometer.

2-(N,N-Dimethyl/nitrophenyl)-4-chlorobenzofuro [3,2-*d*] pyrimidines 3-4 : General procedure

2-(4-N,N-Dimethyl/nitrophenyl)-3,4-dihydro-4-oxobenzofuro [3,2-*d*] pyrimidines **1-2** (0.00032 mol) in freshly distilled phosphorus oxychloride (2 ml) were heated under reflux for about 2 hr. The reaction contents were poured in to ice cold water with constant stirring. The product thus separated was filtered, washed with water and crystallized from a suitable solvent.

4: IR (KBr) cm^{-1} 1610 (C=N), 863 (C-Cl). ^{1}H NMR (δ ppm) 7.26-8.69 (m, 8H, ArH), MS: m/z 326 (M^+, 30%), 317 (100%), 279 (10%) and 108 (20%).

Table-2
Antimicroial activity of compounds 3-18

Compd	Zone of inhibition in mm*			
	Antibacterial		Antifungal	
	S. epidermatitis	*E. coli*	*A. niger*	*C. albicans*
3	13	14	10	11
4	16	17	14	15
5	14	13	14	17
6	15	18	15	18
7	17	15	12	13
8	10	11	11	09
9	12	12	11	10
10	10	11	13	12
11	20	12	14	10
12	12	17	17	15
13	14	15	10	09
14	18	21	14	13
15	18	13	15	14
16	14	08	08	08
17	16	15	11	12
18	18	21	13	11
19	18	17	15	14
20	10	08	08	08
Ciprofloxacin	20	21	-	-
Gentamycin	-	-	15	14
Control (DMF)	08	08	08	08

*Diameter of the well 8mm

Table-3
Antitubercular activity of benzofuro [3,2-*d*] pyrimidine derivatives 4a-e : Minimum inhibitory concentration

S.No.	Sample	$H_{37}Rv$ Concentration (µg/ml)			
		12.5	25	50	100
1	Streptomycin Standard drug (7.5 µg/ml)	S	S	S	S
2	7	R	S	S	S
3	8	S	S	S	S
4	9	R	S	S	S
5	10	S	S	S	S
6	11	R	R	R	R
7	12	R	R	S	S
8	17	R	S	S	S
9	18	S	S	S	S
10	19	S	S	S	S
11	20	R	R	S	S

S=SENSITIVE, R=RESISTANCE.

2-(4-N,N-Dimethyl/nitrophenyl)-4-hydrazinobenzofuro [3,2-*d*] pyrimidines 5-6 : General procedure

A mixture of chloro compound **3-4** (0.001 mol) and hydrazine hydrate (80%, 0.5 ml) in methanol (5 ml) was heated under reflux for 3 hr. Colored solid started separating after 1 hr and the heating was continued for 4 hr. The solid separated was collected and crystallized.

5: IR (KBr) 1590 (C=N), 3300-3400 ($NHNH_2$), ^1H NMR : 2.30-2.90 (s, 6H, 2-CH_3), 8.70 (s, 3H, $NHNH_2$), 7.20-7.50 (m, 8H, Ar-H).

5-(4-N,N-Dimethyl/nitrophenyl)-tetrazolo [1,5-*c*] pyrimido [5,4-*b*] benzofurans 7-8 : General procedure

To a solution of **5-6** (0.001 mol) in 1N acetic acid (8 ml) at 45^0, sodium nitrite (0.1g) was added in portions. After 2 hr, the reaction mixture was cooled and solid thus separated was collected and crystallized using a suitable solvent.

7. IR (KBr): 1605 (C=N), ^1H NMR : 2.30-3.00 (s, 6H, 2-CH_3), 7.30-8.10 (m, 8H, Ar-H).

5-(4-N,N-Dimethyl/nitrophenyl)-triazolo [4,3-*c*] pyrimido [5,4-*b*] benzofurans 9-10 :General procedure

A suspension of 2-aryl-4-hydrazinobenzofuro [3,2-d] pyrimidine **5-6** (0.001 mol) in ethylorthoformate (2 ml) was heated at 80^0 for a minute. Initially the reaction mixture formed a clear solution which then immediately turned in to a solid. The solid which separated was crystallized from a suitable solvents.

7: IR (KBr): 2923 (CH str), 3071 (CH str, Ar), ^{1}H NMR : 2.60 (s, 6H, 2-CH_3), 7.20-8.20 (m, 8H, Ar-H).

2-(4-N,N-Dimethyl/nitrophenyl)-4-arylidene hydrazino benzofuro [3,2-*d]* pyrimidines 11-20 : General procedure

2-(4-N,N-Dimethyl/nitrophenyl)-4-hydrazinobenzofuro [3,2-*d*] pyrimidine **5-6** (0.005 mol) in methanol (10 ml) was heated with aromatic aldehyde (0.005 mol) and the reaction mixture was stirred at room temp for about 2 hr. The resulting product was allowed to stand overnight and solid separated was collected and crystallized using a suitable solvent.

14. IR (KBr) 1595 (C=N), 3100 (NH), ^{1}H NMR : 2.90-3.00 (s, 6H, 2-CH_3), 4.10 (s, 1H, NH), 7.20-7.60 (m, 8H, ArH), 9.70 (s, 1H, -N=CH). MS: m/z 439 (M^+, 100%), 441 (M+2, 60%), 393 (20%), 413 (30%), 279 (80%).

15: IR (KBr): 1626 (C=N), 3314 (NH), ^{1}H NMR : 4.00 (s, 1H, NH), 7.20-7.70 (m, H, ArH), 10.74 (s, 1H, -N-CH). MS: m/z 443 (M^+, 100%), 445 (M^{+2}, 60%), 393 (20%), 413 (30%), 279 (80%).

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