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Synthesis, Characterization and Evaluation of Biological Properties of Pyrazolo- and Oxazolo-pyridocarbazoles and Pyridoazacarbazoles as Potent Anti-microbial Agents

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Authors' contributions

This work was carried out in collaboration between all authors. Authors BS and DK designed the study, wrote the protocol and author BS wrote the first draft of the manuscript. Author TY managed the literature searches and analyses of the study performed the spectroscopy analysis as well as experimental process. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Fused carbazoles, azacarbazoles and quinolines are endowed with a wide array of pharmacological properties. Keeping these properties in the mind, the study was undertaken to seek structural modifications to generate novel synthetic analogues of carbazoles, azacarbazoles and quinolines and to examine their biological properties.
Methodology: Pyrazole and isoxazole condensed pyridocarbazoles and pyridoazacarbazoles were synthesized by the cyclo-condensation reactions of corresponding enol ethers, chalcones, oxoketenedithio acetals and dimethyl aminomethylene ketones with hydroxylamine hydrochloride and hydrazine hydrate respectively.
Results: Pyrazoles and isoxazoles were synthesized. 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. Formation of the compounds were also confirmed by the spectral data.

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Conclusion: Compound 8-methyl-4,5-dihydroisoxazolo[4,3-i]pyrido[2,3-a]carbazol-10-ol **(12b)** and 5-*N*-benzyl-8-methyl-3-methylthio-4*H*-pyrrazolo[4,3-i]pyrido[2,3-a]azacarbazol-10-ol **(14a)** were screened for the anti-bacterial (against *E. coli* and *B. cereus*) and anti-fungal (against *M. phaseolina* and *F. solani*) activities. Both the compounds showed moderate activities as compared to standards (Ciprofloxacin for anti-bacterial and Fluconazole for anti-fungal activity) used.

Keywords: Carbazoles; azacarbazoles; pyazoles; isoxazoles; quinolines; anti-bacterial and anti-fungal activities.

1. INTRODUCTION

Quinoline derivatives represent the major class of heterocycles and have been prepared using various methods [1-5] to synthesize many compounds with diverse pharmacological profile including anti-malarial [6-8], anti-microbial [9], anti-fungal [10], anti-bacterial, anti-oxidant [11], anti-tubercular [12-13], anti-inflammatory, anti-cancer [14], anti-HIV activity [15], *etc.* Similarly, carbazole derivatives are often found in bioactive natural products and medicinally potent compounds. They represent an important class of anti-tubercular, anti-cancer, anti-oxidant agents [16-17] which has grown considerably over the last few decades. Apart from exhibiting a wide range of biological properties of carbazoles, ranging from antibiotics to anti-tumor, their numerous derivatives are also widely used as building blocks for potential electroluminescent materials. Like carbazoles, azacarbazoles have also attracted considerable interest due to the recent discoveries of several naturally occurring compounds containing this skeleton. These compounds have displayed a wide range of important biological activities including anti-neoplastic and anti-tumor activity [18-20].

It is observed that sometimes incorporation of certain bioactive pharmacophores in the existing drug molecules exerts a significant additive effect on the overall biological profiles of the drug. Based on this trend of pharmacophores, it could be anticipated that incorporation of pyrazoles and isoxazoles on to the carbazolo (or azacarbazolo) fused quinolines could produce novel analogues with enhanced biological profiles. Keeping of this view in mind, it was thought worthwhile in present work to incorporate pyrazole and isoxazole moieties in the above established bioactive heterocyclic scaffolds.

2. EXPERIMENTAL DETAILS

2.1 Chemistry

All chemicals and reagents were purchased from commercial sources. Melting points were determined in open glass capillaries and are uncorrected. Structures of all the compounds were established on the basis of elemental analysis and spectral (IR and ^{1}H NMR, MS) data. IR spectra were recorded on FTIR-8400S (Schimadzu) using KBr pellets. ^{1}H NMR spectra were recorded on AVANCE II 400 (Bruker**)** using $CDCl_3$ or DMSO-d_6 as solvents and TMS as an internal reference. Chemical shifts are expressed in δ ppm. Physical data of all the compounds were found consistent to assign the structures of these molecules. The compounds which are given in the Scheme 1 and Scheme 2 have already been synthesized [21].

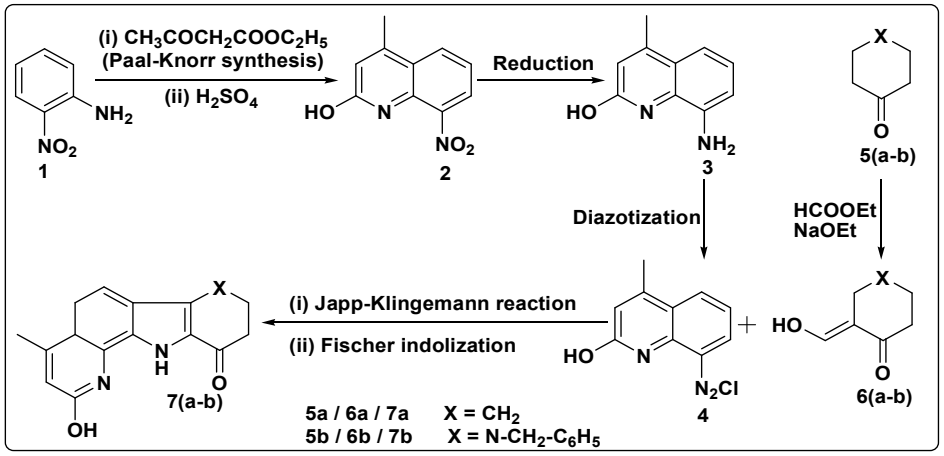
2.1.1 Preparation of 8-methyl-4,5-dihydropyrazolo[4,3-i]pyrido[2,3-a] carbazol-10-ol (12a)

A solution of 9-(ethoxymethylene)-8,9-dihydro-2-hydroxy-4-methyl-7*H*-pyrido[2,3-a]carbazol-10(11*H*)-one **(8a)** or 9-((dimethylamino) methylene)-8,9-dihydro-2-hydroxy-4-methyl-7*H*-pyrido[2,3-a]carbazol-10(11*H*)-one **(11a)** (10mmol) in glacial acetic acid (25mL) was stirred with hydrazine hydrate (15mmol) for 6-8 hrs at 70-80ºC. The solvent was removed under reduced pressure and the residue was diluted with water. It was extracted with ethyl acetate, washed with saturated $NaHCO_3$ solution, water, brine solution and dried over Na_2SO_4. Crude product was purified by re-crystallization from ethanol to furnish compound **12a**. Same procedure was followed in the preparation of compound **12b, 12c** and **12d** by using of hydroxylamine hydrochloride and hydrazine hydrate. **12a:** IR (KBr) cm^{-1}: 3430 (O-H str.), 2925 & 2895 (C-H str.), 1685 (C=N str.), 1310 (C-N str.), 785 (C-H bend.); ^{1}H NMR (δ ppm): 12.51 (s, 1H, NH), 12.07 (s, 1H, OH), 11.34 (s, 1H, NH), 8.12 (d, 1H, CH), 8.1 (s, 1H, CH), 7.69 (d, 1H, CH), 7.56 (d, 1H, CH), 6.31 (s, 1H, CH), 2.93 (t, 2H, CH_2), 2.87 (t, 2H, CH_2), 2.83 (t, 2H, CH_2), 2.61 (s, 3H, CH_3). **12b:** IR (KBr) cm^{-1}: 3450 (O-H str.), 2930 & 2875 (C-H str.), 1695 (C=N str.), 1530-1400 (C=C str.), 1315 (C-N str.), 772 (C-H bend); ^{1}H NMR (δ ppm): 12.06 (s, 1H, OH), 11.30 (s, 1H, NH), 8.13 (d, 1H, CH), 8.1 (s, 1H,

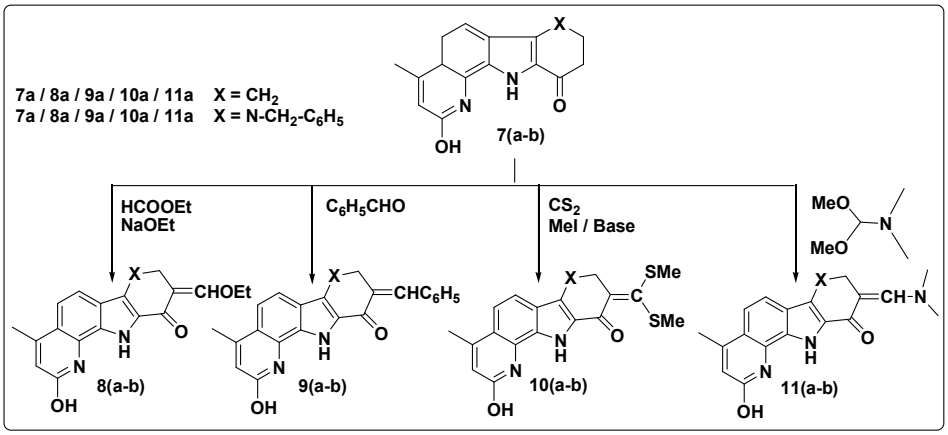
CH), 7.66 (d, 1H, CH), 6.32 (s, 1H, CH), 2.94 (t, 2H, CH_2), 2.86 (t, 2H, CH_2), 2.62 (s, 3H, CH_3); MS [m/z]: 291.30 (19%), 265.5 (26%), 264.5 (99%). **12c:** IR (KBr) cm^{-1}: 3440 (O-H str.), 2945 & 2890 (C-H str.), 1672 (C=N str.), 1530-1470 (C=C str.), 1395 (C-N str.), 785 (C-H bend); ^{1}H NMR (δ ppm): 12.53 (s, 1H, NH), 12.07 (s, 1H, OH), 11.36 (s, 1H, NH), 8.11 (d, 1H, CH), 7.68 (d, 1H, CH), 7.56 (d, 1H, CH), 7.33-7.23 (m, 5H, ArH), 6.32 (s, 1H, CH), 4.71 (s, 2H, CH_2), 4.33 (s, 2H, CH_2), 2.60 (s, 3H, CH_3); MS [m/z]: 381.43 (12%), 361.6 (83%), 360.6 (99.2%). **12d:** IR (KBr) cm^{-1}: 3435 (O-H str.), 2920 & 2880 (C-H str.), 1682 (C=N str.), 1545-1465 (C=C str.), 1295 (C-N str.), 780 (C-H bend); ^{1}H NMR (δ ppm): 12.07 (s, 1H, OH), 11.34 (s, 1H, NH), 8.12 (d, 1H, CH), 8.1 (s, 1H, CH), 7.69 (d, 1H, CH), 7.33-7.23 (m, 5H, ArH), 6.31 (s, 1H, CH), 4.71 (s, 2H, CH_2), 4.32 (s, 2H, CH_2), 2.61 (s, 3H, CH_3).

2.1.2 Preparation of 8-methyl-3-phenyl-4,5-dihydro-*3H*-isoxazolo[4,3-i]pyrido[2,3-a]carbazol-10-ol (13b)

Anhydrous sodium acetate (0.001 mol) dissolved in a minimum amount of hot acetic acid was added to a solution of hydroxylamine hydrochloride (0.01mol) in ethanol. This was added to a solution of 9-benzylidene-8,9-dihydro-2-hydroxy-4-methyl-7*H*-pyrido[2,3-a]carbazol-10 (11*H*)-one **(9a)** (0.01mol) in 15mL ethanol. The mixture was refluxed on a sand-bath for 2-3 hrs. The contents were poured into crushed ice, filtered and re-crystallized from ethanol to give **13b**. Same procedure was followed for the preparation of compound **13a, 13c** and **13d** by using of hydroxylamine hydrochloride and hydrazine hydrate. 13a: IR (KBr) cm-1: 3455 (O-H str.), 2982 & 2897 (C-H str.), 1622 (C=N str.),



Scheme 1. Synthesis of oxocarbazoles and oxoazacarbazoles



Scheme 2. Synthesis of enol ethers, chalcones, oxoketenedithio acetales and dimethyl aminomethylene ketones

1515-1430 (C=C str.), 1320 (C-N bend.);^{1}H NMR (δ ppm): 12.07 (s, 1H, OH), 11.63 (s, 1H, NH), 8.12 (d, 1H, CH), 7.69 (d, 1H, CH), 7.40-7.27 (m, 5H, ArH), 7.0 (s, 1H, NH), 6.31 (s, 1H, CH), 3.90 (t, 1H, CH), 2.68 (t, 2H, CH_2), 2.61 (s, 3H, CH_3), 2.10 (q, 1H, CH),1.50 (q, 2H, CH_2); MS [m/z]: 368.43 (12%), 361.5 (86%), 260.6 (99.1%). **13b:** IR (KBr) cm^{-1}: 3545 (O-H str.), 3130 (N-H str.), 3020 (C-H str.), 2982 & 2858 (C-H str.), 1725 (C=N str.), 1605-1455 (C=C str.), 1345 (C-H bend.), 1330 (C-N str.). ^{1}H NMR (δ ppm): 12.07 (s, 1H, OH), 11.63 (s, 1H, NH), 8.12 (d, 1H, CH), 7.69 (d, 1H, CH), 7.38-736 (m, 5H, ArH), 6.31 (s, 1H, CH), 4.50 (d, 1H, CH), 2.68 (t, 2H, CH_2), 2.61 (s, 3H, CH_3), 2.0 (q, 1H, CH), 1.75 (q, 2H, CH_2). **13c:** IR (KBr) cm^{-1}: 3515 (O-H str.), 2985 & 2892 (C-H str.), 1630 (C=N str.), 1520-1460 (C=C str.), 1330 (C-N bend.), 790 (C-H str.); ^{1}H NMR (δ ppm): 12.07 (s, 1H, OH), 11.63 (s, 1H, NH), 8.12 (d, 1H, CH), 7.69 (d, 1H, CH), 7.40-7.23 (m, 10H, ArH), 7.0 (s, 1H, NH), 6.31 (s, 1H, CH), 4.32 (s, 2H, CH_2), 3.90 (t, 1H, CH), 3.0 (d, 2H, CH_2), 2.61 (s, 3H, CH_3), 2.30 (q, 1H, CH). **13d:** IR (KBr) cm^{-1}: 3415 (O-H str.), 2950 & 2880 (C-H str.), 1605 (C=N str.), 1535-1480 (C=C str.), 1310 (C-N bend.), 775 (C-H str.); ^{1}H NMR (δ ppm): 12.08 (s, 1H, OH), 11.63 (s, 1H, NH), 8.13 (d, 1H, CH), 7.68 (d, 1H, CH), 7.38-7.23 (m, 10H, ArH), 6.30 (s, 1H, CH), 4.50 (d, 1H, CH), 4.31 (s, 2H, CH_2), 3.25 (d, 2H, CH_2), 2.61 (s, 3H, CH_3), 2.20 (q, 1H, CH).

2.1.3 Preparation of 5-*N*-benzyl-8-methyl-3-methylthio-4*H*-pyrazolo[4,3-i]pyrido[2,3-a]azacarbazol-10-ol (14c)

Hydrazine hydrate (0.1mol) and 9-(bis(methylthio)methylene)-8,9-dihydro-2-hydroxy-4-methyl-7H-pyrido[2,3-a]carbazol-10(11H)-one **(10a)** (0.001mol) were taken in 50mL of ethanol and refluxed for 3 hours. The solvent was removed and the residue was extracted with 20mL of chloroform. On removal of the solvent, **14c** was obtained as crystalline solid. Same procedure was followed in the preparation of compound **14a, 14b** and **14d** by using of hydroxylamine hydrochloride and hydrazine hydrate. **14a:** IR (KBr) cm^{-1}: 3405 (O-H str.), 2970 & 2885 (C-H str.), 1670 (C=N str.), 1510-1450 (C=C str.), 1330 (C-N bend.), 785 (C-H str.); ^{1}H NMR (δ ppm): 13.70 (s, 1H, NH), 12.05 (s, 1H, OH), 11.34 (s, 1H, NH), 8.12 (d, 1H, CH), 7.67 (d, 1H, CH), 6.31 (s, 1H, CH), 2.92 (t, 2H, CH_2), 2.88 (t, 2H, CH_2), 2.63 (s, 3H, CH_3), 2.54 (s, 3H, CH_3). **14b:** IR (KBr) cm^{-1}: 3425 (O-H str.), 2980 & 2895 (C-H str.), 1645 (C=N str.), 1515-1450 (C=C str.), 1335 (C-N bend.), 780 (C-H str.); ^{1}H NMR (δ ppm): 12.07 (s, 1H, OH), 11.34 (s, 1H, NH), 8.12 (d, 1H, CH), 7.69 (d, 1H, CH), 6.31 (s, 1H, CH), 2.93 (t, 2H, CH_2), 2.87 (t, 2H, CH_2), 2.61 (s, 3H, CH_3), 2.53 (s, 3H, CH_3). 14c: IR (KBr) cm-1: 3475 (O-H str.), 2985 & 2892 (C-H str.), 1645 (C=N str.), 1515-1430 (C=C str), 1310 (C-N bend.), 765 (C-H str.). 1H NMR (δ ppm): 13.7 (s, 1H, NH), 12.07 (s, 1H, OH), 11.34 (s, 1H, NH), 8.12 (d, 1H, CH), 7.69 (d, 1H, CH), 7.33-7.23 (m, 5H, ArH), 6.31 (s, 1H, CH), 4.71 (s, 2H, CH2), 4.32 (s, 2H, CH2), 2.61 (s, 3H, CH3), 2.53 (s, 3H, CH3). 14d: IR (KBr) cm-1: 3515 (O-H str.), 2970 & 2892 (C-H str.), 1685 (C=N str.), 1520-1450 (C=C str.), 1360 (C-N bend.), 772 (C-H str.); 1H NMR (δ ppm): 12.07 (s, 1H, OH), 11.34 (s, 1H, NH), 8.12 (d, 1H, CH), 7.69 (d, 1H, CH), 7.33-7.23 (m, 5H, ArH), 6.31 (s, 1H, CH), 4.71 (s, 2H, CH2), 4.32 (s, 2H, CH2), 2.61 (s, 3H, CH3), 2.53 (s, 3H, CH3); MS [m/z]: 428.51 (27%), 360.6 (66%), 264.5 (99%).

2.2 Biology

2.2.1 Anti-bacterial activity

Anti-bacterial activity was carried out in the Department of Bioscience and Biotechnology, Banasthali Vidyapith by using standard methods [22-23]. *E. coli* (MTCC119) and *B. cereus* (MTCC430) strains were used for anti-bacterial activity. Stock solution of the sample was prepared and 400, 200, 100µg/ml dilutions were made from the stock solution. Disc diffusion method was used for evaluation of the activity. After 24 hours of incubation, the plates were analyzed and the diameter of the zones of inhibition was measured to the nearest whole in millimeter with a sliding calipers. Ciprofloxacin was used as standard drug for anti-bacterial activity.

2.2.2 Anti-fungal activity

Anti-fungal activity was also done in the same Department by using standard methods [22-23]. *Macrophomina phaseolina* (MTCC166) and *Fusarium solani* (MTCC350) strains were used. Similar method, as used for anti-bacterial activity, was adopted for anti-fungal activity. Fluconazole was used as standard drug for anti-fungal activity.

3. RESULTS AND DISCUSSION

3.1 Chemistry

In the present work, the pyrazole and isoxazole derivatives of pyridocarbazoles and pyridoa-

zacarbazoles were synthesized by the cyclo-condensation reactions of enol ethers [24], chalcones [25], oxoketene dithioacetals [26-28] and dimethyl aminomethylene ketones [29] with hydrazine hydrate and hydroxylamine hydrochloride respectively (Scheme 3). The reactive intermediates **8(a-b), 9(a-b), 10(a-b)** and **11(a-b),** which have been synthesized in our laboratory [21], were treated with hydrazine hydrates to furnish the corresponding pyrazole derivatives **12(a,c), 13(a,c)** and **14(a,c)**. Formation of the pyrazole ring was confirmed by the IR, ^{1}H NMR and MS data. IR stretching peaks at 1630 and 1650 cm^{-1} of C=O group for the compounds **8a** and **11a** were disappeared in the compound **12a** and a new peak between 3140 to 3250 cm^{-1} appeared due to N-H stretching. ^{1}H NMR signal at δ12.51 was also appeared for the compound **12a**. Similarly, the reactive intermediates **8(a-b), 9(a-b), 10(a-b)** and **11(a-b)** were treated with hydroxylamine hydrochloride to give the corresponding isoxazole derivatives **12(b,d), 13(b,d)** and **14(b,d)**. Formation of isoxazoles was also confirmed by comparison of the IR spectra of the intermediates and synthesized isoxazoles in which a peak between 1650 to 1740 cm^{-1} disappeared completely in isoxazoles. Physical and analytical data of the synthesized compounds are given in the Table 1.

3.2 Biology

3.2.1 Anti-bacterial activity

Results of the anti-bacterial activity against *E. coli* and *B. cereus* showed by the compound 8-methyl-4,5-dihydroisoxazolo[4,3-i]pyrido[2,3-a] carbazol-10-ol **(12b)** and 5-*N*-benzyl- 8-methyl-3-methylthio- 4*H*-pyrrazolo[4,3-i]pyrido[2,3-a] azacarbazol-10-ol **(14a)** are given in the Table 2. Both the compounds exhibited moderate anti-bacterial activity as compared to the standard drug Ciprofloxacin. The results clearly indicated that increase in the concentration of compounds, increased the anti-bacterial activity. A regular fall in anti-bacterial activity was recorded when the concentration of compounds was reduced. The results of anti-bacterial activity revealed that both the compounds showed almost similar anti-bacterial activity with *B. cereus* and *E. coli.*

3.2.2 Anti-fungal activity

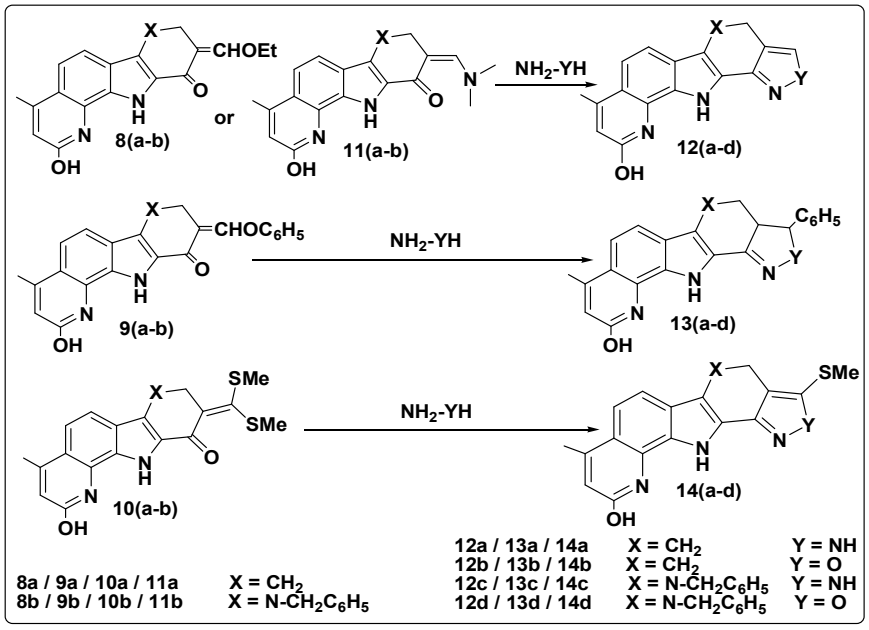
Results of the anti-fungal screening against *M. phaseolina* and *F. solani* showed by the compound 8-methyl-4,5-dihydroisoxazolo[4,3-i]pyrido[2,3-a]carbazol-10-ol **(12b)** and 5-*N*-benzyl-8-methyl-3-methylthio-4*H*-pyrrazolo[4,3-i]pyrido[2,3-a]azacarbazol-10-ol **(14a)** are given in the Table 2. Both the compounds exhibited the moderate activity as compared to the standard drug Fluconazol. The results clearly indicated that increase in the concentration of compounds, increased the anti-fungal activity. A regular fall in anti-fungal activity was recorded when the concentration of compounds was reduced. The results of anti-fungal activity revealed that both the compounds showed almost similar anti-fungal activity with *F. solani* as compared to *M. phaseolina.*

Table 1. Physical and analytical data of compounds

Comp.	Formula	Molecular weight	Yield (%)	M.P. (ºC)	Elemental analysis Calcd. / found	
					N	S
12a	$C_{17}H_{14}N_4O$	290.32	56	232-234	19.30/18.96	-
12b	$C_{17}H_{13}N_3O_2$	291.30	54	221-223	14.42/14.14	-
12c	$C_{23}H_{19}N_5O$	381.43	59	303-305	18.36/17.98	-
12d	$C_{23}H_{18}N_4O_2$	382.41	57	316-318	14.65/14.33	-
13a	$C_{23}H_{20}N_4O$	368.43	70	246-248	15.21/14.87	-
13b	$C_{23}H_{19}N_3O_2$	369.42	69	252-255	11.37/11.12	-
13c	$C_{29}H_{25}N_5O$	459.54	72	274-276	15.24/14.94	-
13d	$C_{29}H_{24}N_4O_2$	460.53	66	313-315	12.17/11.82	-
14a	$C_{18}H_{16}N_4OS$	336.41	65	295-297	16.65/16.27	9.53/9.31
14b	$C_{18}H_{15}N_3O_2S$	337.40	61	301-302	12.45/12.11	9.50/9.13
14c	$C_{24}H_{21}N_5OS$	427.52	63	244-246	16.38/15.86	7.50/6.97
14d	$C_{24}H_{20}N_4O_2S$	428.51	64	262-263	13.07/12.75	7.48/6.96

Table 2. Anti-bacterial and anti-fungal activities of the synthesized compounds

S. no.	Comp.	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	**12b**	400	16	57.14	16	53.33	19	73.07	16	55.17
		200	12	54.55	11	47.82	13	65.00	11	47.82
		100	8	50.00	7	41.17	8.5	56.67	8	44.44
2	**14a**	400	20	71.42	22	73.33	21	80.76	20	68.96
		200	14	63.64	15	62.21	14	70.00	13	56.52
		100	9	56.25	9	52.94	9.5	63.33	9.5	52.78
3.	Ciprofloxacin	400	28	100	30	100	--	--	--	--
	(Standard)	200	22	100	23	100				
		100	16	100	17	100				
4.	Fluconazole	400					26	100	29	100
	(Standard)	200	--	--	--	--	20	100	23	100
		100					15	100	18	100



Scheme 3. Synthesis of pyrazole derivatives of carbazolo and azacarbazolo fused quinoline

4. CONCLUSION

Isoxazolo & pyrazolo[4,3-i]pyrido[2,3-a]carbazol-10-ols and Isoxazolo & pyrazolo[4,3-i]pyrido[2,3-a]azacarbazol-10-ols with methyl, aryl and thiomethyl groups have been synthesized. Compound 8-methyl-4,5-dihydroisoxazolo[4,3-i]pyrido[2,3-a]carbazol-10-ol **(12b)** and 5-*N*-benzyl-8-methyl-3-methylthio-4*H*-pyrrazolo[4,3-i]pyrido[2,3-a]azacarbazol-10-ol **(14a)** have been screened for the anti-bacterial (against *E. coli* and *B. cereus*) and anti-fungal activity (against *M. phaseolina* and *F. solani*). Both the compounds showed moderate activities as compared to standards (Ciprofloxacin for anti-bacterial and Fluconazole for anti-fungal activity) used.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

All authors have declared that no competing interests exist.

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