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ARTICLE

Synthesis of Formic Acid Catalyzed and Cyclized Novel Modified Route for *N*,7-diphenyl-7*H*-benzo[7,8]chromeno-[2,3-*d*]pyrimidin-8-amine Derivatives and Study of their Antimicrobial Profile

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ABSTRACT

A new series of *N*,7-diphenyl-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidin-8-amine derivatives was synthesized using formic acid as catalyzed and solvent. The structures of new derivatives were confirmed by the spectral data and elemental analyses. Moreover, antimicrobial and antifungal activities has been carryout using *S. aureus*, *S. pyogenes*, *E. coli*, *P. aeruginosa*, *C. albicans*, *A. niger* and drugs nystatin, greseofulvin, ciprofloxacin, chloramphenicol for all the present compounds.

KEYWORDS

Chromene, Pyrimidine, Biological activity, Formic acid.

INTRODUCTION

Chromene derivatives possess important biological activities such as antivascular, antitumor, antioxidant, antimicrobial [1], antifungal [2], anticoagulant, estrogenic, antiviral, anticancer, antihelminthic, anti-HIV [3], antitubercular [4], analgesic, anti-inflammatory and anticonvulsant activity [5]. A key feature is that the lipophilic nature of benzopyran derivatives helps to cross the cell membrane easily. Chromene derivatives are also play an important role in the production of highly effective fluorescent dyes for synthetic fibers, daylight fluorescent pigments and electro-photographic and electroluminescent devices. Among all the heterocyclic compounds, oxygen heterocycles are special because of their wide occurrence and broad pharmaceutical significance. The pyrimidine fragment is present in number of biologically active compounds, which exhibited remarkable biological activities such as antifungal [1], antimicrobial [2], anti-inflammatory [6] and antitumor [7]. Biomolecules having fluorine containing functional groups often enhance in biological activities [8-12]. In this connection, remarkable attention has recently been paid for the synthesis of pyrimidines. Synthesis of pyrimidines involves ring formation *via* two fragments containing two electrophilic carbon atoms and two nucleophilic nitrogen atoms.

As pyrimidine and chromene ring containing very useful compounds in drug synthesis and there is lots of work done

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on this scaffolds that is why synthesis of this intermediates is quite easy. There are different methods available for synthesis and among them one was selected here. Aryl aldehyde, malononitrile and substituted phenol were converted into chromene (**2a-b**) with simple reaction with formic acid to give cyclised to quinazolinone derivatives (**3a,-b**). The compounds **3a-b** reacted with phosphorus oxychloride and different substituted anilines to give *N*,7-diphenyl-7a,11a-dihydro-7*H*-benzo[7,8]-chromeno[2,3-*d*]pyrimidin-8-amine derivatives (**5a-j**). The final product was synthesized in presence of acidic media. All final products were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

EXPERIMENTAL

Thin-layer chromatography was accomplished on 0.2 mm pre-coated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapour. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H (400 MHz),^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in $CDCl_3$ and DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected.

Synthesis of 2-amino-4-phenyl-4*H*-benzo[*h*]chromene-3-carbonitrile derivatives (2a-b): A mixture of benzaldehyde derivatives (**1a-b**) (1 mmol), malononitrile (2 mmol), α-naphthol (1 mmol) and few drop of piperidine was refluxed in ethanol for 3-4 h. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the reaction mixture was cooled and washed with cold ethanol to obtain white solid product (**2a-b**).

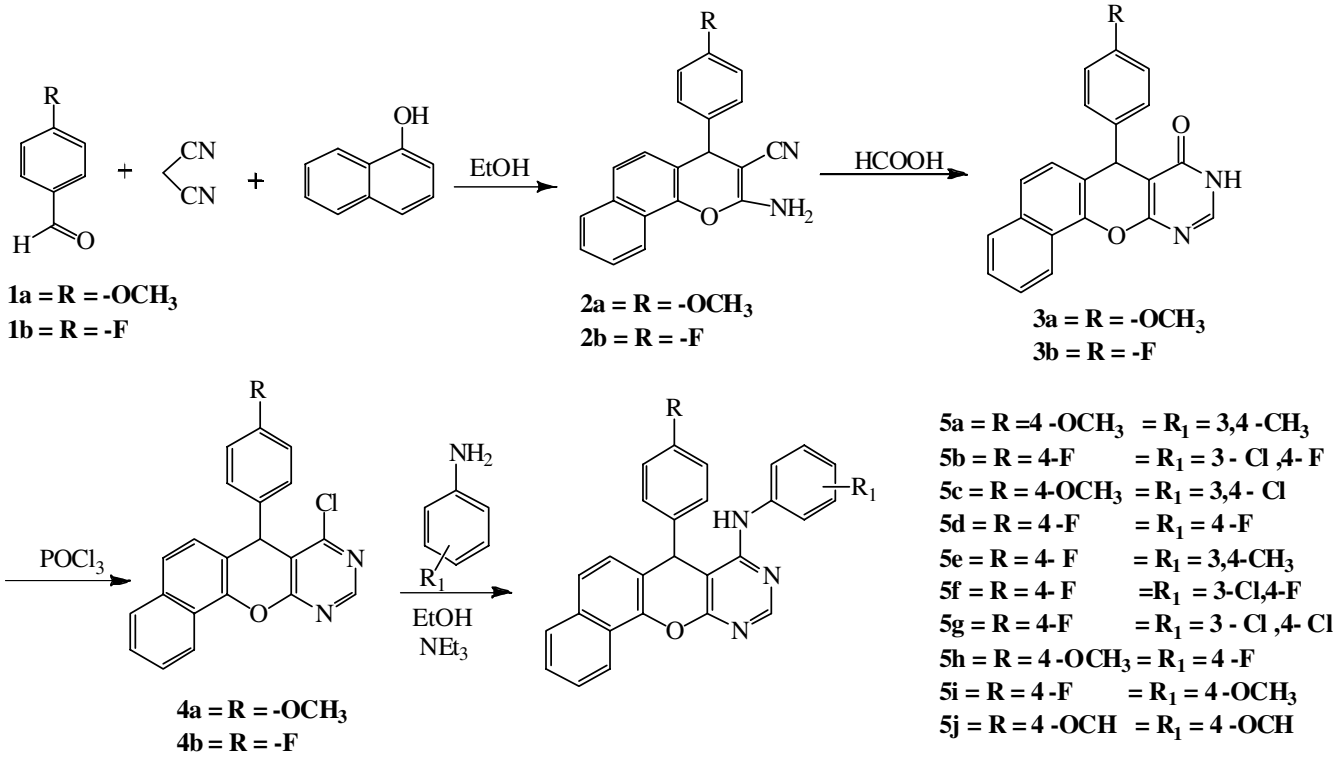
Synthesis of 7-phenyl-7,9-dihydro-8*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidin-8-one derivatives (3a-b): A solution of compound **2** (1 mmol) in formic acid (20 mL) was heated under reflux for 3 h then cooled and poured into ice-cold water. The precipitated solid was filtered, washed with water and crystallized by methanol to afford compound **3a-b**.

Synthesis of 8-chloro-7-phenyl-7*H*-benzo[7,8]chromeno-[2,3-*d*]pyrimidine derivatives (4a-b): Compound **3** (1 mmol) was reacted with phosphorous oxychloride (10 mL) under reflux for 10 h. The reaction mixture was cooled and poured into ice-cold water. The formed precipitate was filtered washed with water dried and recrystallized from ethyl acetate to afford the desired pure compound **4**.

General synthesis of *N*,7-diphenyl-7a,11a-dihydro-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidin-8-amine derivatives (5a-j): A mixture of appropriate derivative **4** (1 mmol), substituted aniline (1 mmol), triethyl amine (1 mmol) in ethanol (15 mL) was heated under reflux for 3-4 h. After cooling, the reaction mixture was diluted with water and formed precipitate was collected by filtration, washed with water and crystallized from ethanol to afford required compounds **5a-j** (**Scheme-I**).

Spectral data

***N*-(3,4-Dimethylphenyl)-7-(4-methoxyphenyl)-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidin-8-amine (5a):** White solid, yield 90 %, m.p.: 223-225 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.469-8.449 (d, 1H), 7.804 (s, 1H), 7.774-7.754 (d, 1H), 7.597-7.560 (t, 1H), 7.523-7.492 (d, 2H), 7.326-7.306 (d, 2H), 7.261-7.242 (t, 2H), 7.175-7.154 (d, 1H), 7.070-7.029 (t, 2H), 6.806-6.785 (d, 2H), 5.157 (s, 1H), 3.775-3.724 (s,3H), 2.289-2.169 (s, 6H). IR (KBr, ν_{max}, cm^{-1}): 3500, 3300, 3200,



Scheme-I

TABLE-1
ANTIMICROBIAL EVALUATION DATA

Compounds and standard drugs	Minimum inhibitory concentration (μg/mL)					
	Antibacterial activity				Antifungal acitivity	
	S. aureus	*S. pyogenes*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
5a	15.62	62.5	15.625	15.625	15.625	31.25
5b	31.25	15.625	15.625	7.82	62.5	31.25
5c	62.5	31.25	31.25	31.25	15.625	62.5
5d	15.62	62.5	31.25	62.5	15.625	62.5
5e	31.25	7.82	15.625	62.5	62.5	62.5
5f	7.81	31.25	7.82	62.5	31.25	62.5
5g	15.625	15.625	15.625	62.5	62.5	62.5
5h	7.82	7.82	31.25	31.25	31.25	62.5
5i	31.25	31.25	15.625	15.625	15.625	15.625
5j	15.62	31.25	31.25	15.625	15.625	15.625
Nystatin	–	–	–	–	31.25	31.25
Greseofulvin	–	–	–	–	15.625	15.625
Ciprofloxacin	7.8	7.8	15.625	15.625	–	–
Chloramphenicol	7.8	7.8	7.8	7.8	–	–

2800, 1600, 156, 1500, 1400, 1250. MS (*m/z*): 459. Elemental analysis of $C_{30}H_{25}N_3O_2$ %: C, 78.415; H, 5.485; N, 9.145; O, 6.960. MS (*m/z*): 459

***N*-(3-Chloro-4-fluorophenyl)-7-(4-methoxyphenyl)-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidin-8-amine (5b):** White solid, yield 82 %, m.p.: 205-207 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.456-8.435 (d, 1H), 7.796-7.760 (t, 2H), 7.611-7.445 (m, 4H), 7.304-7.255 (m, 5H), 7.147-7.125 (d, 1H), 6.827-6.806 (d, 2H), 5.053 (s, 1H), 3.737-3.470 (s, 3H). IR (KBr, ν_{max}, cm^{-1}): 3406, 3100, 3000, 1400, 1570, 1450, 750. Elemental analysis of $C_{28}H_{19}N_3O_2ClF$ %: C, 69.49; H, 3.96; N, 8.68 ; O, 6.61, Cl, 7.33; F, 3.93; MS (*m/z*): 483.

***N*-(3,4-Dichlorophenyl)-7-(4-methoxyphenyl)-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidin-8-amine (5c):** White solid, yield 86 %, m.p.: 246-248 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.450-8.430 (d, 1H), 7.796-7.760 (t, 2H), 7.611-7.445 (m, 4H), 7.304-7.255 (m, 5H), 7.147-7.125 (d, 1H), 6.827-6.806 (d, 2H), 5.053 (s, 1H), 3.737-3.470 (s, 3H). IR (KBr, ν_{max}, cm^{-1}): 3420, 3030, 1620, 1550, 1430, 1230, 730, 650. Elemental analysis of $C_{28}H_{19}N_3O_2Cl_2$ %: C, 67.21; H, 3.83; Cl, 14.17; N, 8.40; O, 6.39. MS (*m/z*): 499.

N,7-*bis*(4-Fluorophenyl)-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidin-8-amine (5d): White solid, yield 78 %, m.p.: 223-225 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.467- 8.446 (d, 1H), 7.806-7.766 (t, 2H), 7.615-7.509 (m, 4H), 7.377-7.303 (m, 4H), 7.255-7.184 (m, 2H), 7.133-7.111 (d, 1H), 6.981- 6.964 (t, 2H), 5.163 (s, 1H), 3.485-3.467 (s, 1H). IR (KBr, ν_{max}, cm^{-1}): 3450, 3120, 3080, 2890, 1600, 1530, 1430, 1370. Elemental analysis of $C_{27}H_{17}N_3OF_2$ %: C, 74.13; H, 3.92; F, 8.69; N, 9.61; O, 3.66. MS (*m/z*): 437.

***N*-(3,4-Dimethylphenyl)-7-(4-fluorophenyl)-7*H*-benzo-[7,8]chromeno[2,3-*d*]pyrimidin-8-amine (5e):** White solid,yield 78 %, m.p.: 223-225 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (s, 1H), 8.50-6.11 (m, 13H), 5.46 (s, 1H), 3.14-1.88 (m, 7H). IR (KBr, ν_{max}, cm^{-1}): 3400, 3130, 3120, 1600, 1570, 1450, 740. Elemental analysis of $C_{29}H_{22}N_3OF_2$ %: C, 77.83; H, 4.96; F, 4.25; N, 9.39; O, 3.58. MS (*m/z*): 447.17.

***N*-(3-Chloro-4-methylphenyl)-7-(4-fluorophenyl)-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidin-8-amine (5f):** White solid, yield 78 %, m.p.: 223-225 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): 9.02 (s, 1H), 8.50-6.30 (m, 13H), 5.47 (s, 1H), 3.87 (s, 1H), 2.76-1.96 (m, 3H). IR (KBr, ν_{max}, cm^{-1}): 3410, 3120, 3050, 1610, 1550, 1420, 770. Elemental analysis of $C_{28}H_{19}N_3OClF$: C, 71.87; H, 4.09; Cl, 7.58; F, 4.06; N, 8.98; O, 3.42. MS (*m/z*): 467.12.

***N*-(3,4-Dichlorophenyl)-7-(4-fluorophenyl)-7H-benzo[7,8]chromeno[2,3-*d*]pyrimidin-8-amine (5g):** White solid,yield 78 %, m.p.: 223-225 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 8.50-6.29 (m, 13H), 5.46 (s, 1H), 3.88 (s, 1H). IR (KBr, ν_{max}, cm^{-1}): 3400, 3090, 2980, 1600, 1550, 1450, 750. Elemental analysis of $C_{27}H_{16}N_3O_2Cl_2F$ %: C, 66.41; H, 3.30; Cl, 14.52; F, 3.89; N, 8.60; O, 3.28. MS (*m/z*): 487.07.

***N*-(4-Fluorophenyl)-7-(4-methoxyphenyl)-7*H*-benzo-[7,8]chromeno[2,3-*d*]pyrimidin-8-amine (5h):** White solid,yield 78 %, m.p.: 223-225 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66-6.48 (m, 15H), 5.44 (s, 1H), 4.19-3.39 (m, 3H), 2.87 (s, 1H). IR (KBr, ν_{max}, cm^{-1}): 3400, 3200, 2990, 1600, 1550, 1400, 730. Elemental analysis of $C_{28}H_{20}N_3O_2F$ %: C, 74.82; H, 4.48; F, 4.23; N, 9.35; O, 7.12. MS (*m/z*): 449.15.

7-(4-Fluorophenyl)-N-(4-methoxyphenyl)-7*H*-benzo-[7,8]chromeno[2,3-*d*]pyrimidin-8-amine (5i): White solid, yield 78 %, m.p.: 223-225 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (s, 1H), 8.50-6.38 (m, 14H), 5.45 (s, 1H), 4.19-3.39 (m, 3H), 2.64 (s, 1H). IR (KBr, ν_{max}, cm^{-1}): 3400, 3090, 3020, 1620, 1570, 1450, 740. Elemental analysis of $C_{28}H_{20}N_3O_2F$ %: C, 74.82; H, 4.48; F, 4.23; N, 9.35; O, 7.12. MS (*m/z*): 449.15.

N,7-bis(4-Methoxyphenyl)-7*H*-benzo[7,8]chromeno-[2,3-*d*]pyrimidin-8-amine (5j): White solid, yield 78 %, m.p.: 223-225 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66-6.40 (m, 15H), 5.41 (s, 1H), 4.20-3.39 (m, 6H), 2.90 (s, 1H). IR (KBr, ν_{max}, cm^{-1}): 3406, 3100, 3000, 1400, 1570, 1450, 750. Elemental analysis of $C_{29}H_{23}N_3O_3$ %: C, 75.47; H, 5.02; N, 9.10; O, 10.40. MS (*m/z*): 449.

RESULTS AND DISCUSSION

Synthesis of title compounds was initiated by the reaction of substituted aldehyde (**1a-b**), malononitrile with α-naphthol in the presence of base in ethanol to afford corresponding 2-amino-4-phenyl-4*H*-benzo[*h*]chromene-3-carbonitrile derivatives (**2a-b**). Which on reaction with formic acid undergoes cyclization to form 7-phenyl-7,9-dihydro-8*H*-benzo[7,8]chro-

meno[2,3-*d*]pyrimidin-8-one (**3a-b**). The compound 8-chloro-7-phenyl-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidine (**4a-b**) were synthesized by reacting compound 3a-b with phosphorus oxychloride as a solvent. The compound **5a-j** was synthesized by reacting substituted amine with compound **4** in ethanol in the presence of catalytic amount of triethylamine at reflux temperature for 6-7 h.

The structure of compounds **5a-j** was established on the basis of their elemental analysis, spectral data (^{1}H NMR, ^{13}C NMR, MS and IR) and selectivity of products was supported by NMR spectrum. Structure of compound **5a** was supported by its mass (*m/z* 459), which agrees with its molecular formula $C_{30}H_{25}N_3O_2$.

Antifungal activity: All the synthesized compound **5a-j** were evaluted for their antifungal activity by measuring minimum inhibitory concentration (µg/mL). The antifungal activity results (Table-1) indicated that most of the synthesized compounds **5a**, **5b**, **5c**, **5d**, **5f**, **5h**, **5i** and **5j** display very potent antifungal activity against *C. albicans* and *A. niger*, while compounds **5a**, **5i** and **5j** showed more potent activity better than nystatin, greseofulvin, ciprofloxacin and chloramphenicol.

Antibacterial activity: Based on the antimicrobial activity data of *N*,7-diphenyl-7*H*-benzo[7,8]chromeno[2,3-*d*]pyrimidin-8-amine derivatives (**5a-j**), only compounds **5a**, **5b**, **5h** and **5i** exhibited good antibacterial activity (Table-1) against Gram positive (*S. aureus* and *S. pyogenes*) and Gram negative (*E. coli* and *P. aeruginosa*) bacterial strains and MIC values were comparable to those observed against the standard drugs nystatin, greseofulvin, ciprofloxacin and chloramphenicol.

Conclusion

N,7-diphenyl-7a,11a-dihydro-7H-benzo[7,8]chromeno-[2,3-*d*]pyrimidin-8-amine derivatives (**5a-j**) were successfully synthesized, characterized and purified by column chromatography. All the compounds were screened for their antibacterial and antifungal activities. Most of the compounds have been found to have potent antibacterial and antifungal agents.

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