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Synthesis of Some Phenylpyrazolo Benzimidazolo Quinoxaline Derivatives as Potent Antihistaminic Agents

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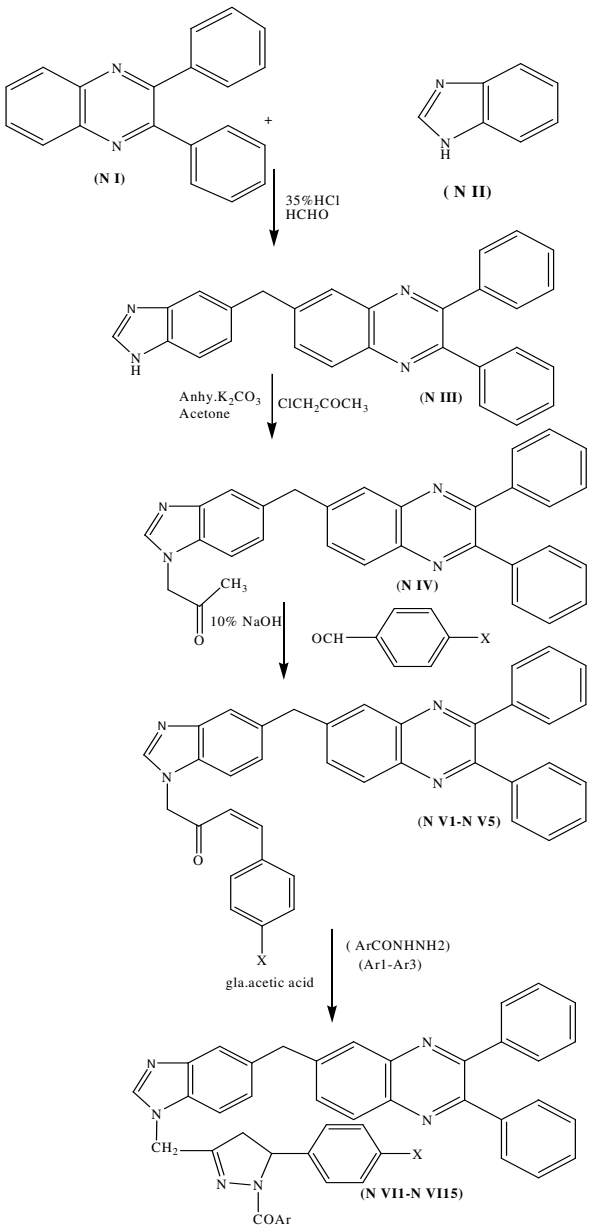
Abstract: 2,3-Diphenyl quinoxaline **(NI)** was fused with benzimidazole **(NII)** by a methylene bridge, which was then allowed for acetylation. The acetylated product **(NIV)** was made to react with different aromatic aldehydes to give chalcones **(NV1-NV5).** Chalcones refluxed with substituted acid hydrazides to afford different phenyl pyrazolo benzimidazole quinoxaline derivatives **(NVI 1-NVI 15).** The structure of chalcones and phenyl pyrazolo benzimidazole quinoxaline derivatives were confirmed by m.p, TLC and spectral data. All the synthesized compounds were screened for their antihistaminic activity. Compounds **NVI-3**, **NVI-12**, **NVI-13**, **NVI-14** and **NVI-15** were shown good % protection of antihistamic activity.

Keywords 2,3-Diphenyl quinoxaline, Benzimidazole, Phenyl pyrazolo benzimidazolo quinoxaline, Antihistaminic activity.

Introduction

Benzimidazole moiety plays an important role in heterocyclic chemistry largely due to its wide range of biological activities[1-4] such as antimicrobial, antitubercular, anti-inflammatory, anticancer *etc*. Quinoxaline derivatives have been reported to possess a wide variety of biological activities[5-7]. Notable among these are antioxidant, anti-inflammatory antimicrobial, anticancer and antihistamic activities. Drugs having pyrazoline ring system[8-10] are well known for their anti-inflammatory, antioxidant, antihistamic, antimicrobial, antidepressant, hypoglycemic, hypotensive, anticarcenogenic activities *etc*. In view of the above facts, it was contemplated to design and synthesize some phenyl pyrazolo benzimidazolo quinoxaline derivatives (Scheme 1) by condensing benzimidazole quinoxaline chalcones with different aromatic acid hydrazides. All the synthesized compounds were screened for their antihistaminic activity. The structure of chalcones and phenyl pyrazolo benzimidazolo quinoxaline derivatives were confirmed by m.p, TLC, and spectral data.



X=H, OH,Cl, F,OCH_3, Ar= -C_6H_5, -C_6H_4 OH, -C_6H_4 Cl

Scheme 1

Experimental

The melting point of the compounds were determined on a Thoshniwal electric melting point apparatus and the values were uncorrected. IR spectra of the compounds were recorded on a Thermo Nicolet Nexus670-FTIR, IICT, Hyderabad using KBr disc method. ^{1}H NMR spectra were recorded onAvance-300, IICT, Hyderabad using $CDCl_3$ as solvent. Mass spectra were recorded on HITACHI RMU GL, IICT, Hyderabad. All the solvents used were of analytical grade.

*General procedure for synthesis of 6-((1H-benzo[d]imidazol-5-yl) methyl)-2, 3-diphenylquinoxaline (**NIII**)*[8]

2,3 Diphenyl quinoxaline (**NI**) and benzimidazole (**NII**) were prepared following the literature method. **NI** and **NII** are linked with a methelyne bridge by treating equimolar quantities of **NI** and **NII** in suitable solvent with 35 parts formaldehyde solution and 35% HCl, stirring for 4 h. at 70 ^{o}C using magnetic stirrer. Solution was made alkaline using ammonia solution. Filtered the product and recrystallized with aqueous ethanol.

NIII: Yield 72%, m.p 108 ^{o}C, IR (KBr) in cm^{-1}: 1665 (C=N str.), 1340 (C-N str.), 3085 (Ar-H str.) .^{1}HNMR ($CDCl_3$) δ: 5.0 (S, 1H, N-H of benzimidazole), 3.81 (S, 2H, methylene), 7.5-7.9 (m, 3H, quinoxaline), 7.2-7.4 (m, 10H, Ar-H), 7.0-8.1 (m, 3H, benzimidazole). Mass: *m/z*: 428 (M+).

*General procedure for Synthesis of 1-(5-((2,3-diphenylquinoxalin-6-yl)methyl)-1H-benzo[d]imidazol-1-yl)propan-2-one (**NIV**)*[9]

A solution of **NIII** (0.01 M) and chloroacetone (0.01 M) were taken into 250 mL round bottom flask. Added to it 150 mL of dry acetone and 30 g of anhydride potassium carbonate and the reaction mixture were refluxed for 6 h. below 75 ^{o}C. Filterate obtained was concentrated under vacuum and recrystallized with aqueous ethanol.

N IV: Yield 68%, m.p 125 ^{o}C, IR (KBr) cm^{-1}: 1793 (C=O str.), 1668 (C=N str.), 1340 (C-N str.), 3085 (Ar-H str.), 3323 (C-H str).^{1}HNMR ($CDCl_3$) δ: 2.0 (S, 3H, methyl), 3.8,4.8 (S, 4H, methylene), 7.4-7.9 (m, 3H, quinoxaline), 7.2-7.4 (m, 10H,Ar-H), 7.0-8.0 (m, 4H, benzimidazole). Mass: *m/z*: 468.2 (M+).

*General procedure for synthesis of (Z)-4-phenyl-1-(5-((2,3-diphenylquinoxalin-6-yl)methyl)-1H-benzo[d]imidazol-1-yl)but-3-en-2-one (**NV1-NV5**)*[10]

Method of aldol condensation was followed. A solution of NaOH / KOH (8 mL, 10% in water) was added drop wise to a well-stirred solution of **NIV** (0.01 M) and (0.01 M) of appropriate aldehyde in 20 mL ethanol. The reaction mixture was stirred for 24 h. at cold conditions. Then diluted with ice water and acidified with con. HCl. Filtered the product and recrystallized with aqueous ethanol. The purity of the compound was checked by TLC and melting point.

NV 1: Yield: 73%, m.p: 113 ^{o}C, IR (KBr) cm^{-1}: 1773 (C=O str.), 1668(C=N str.), 1340 (C-N str.), 3085 (Ar-H str.), 3323 (C-H str.) cm^{-1}.^{1}HNMR ($CDCl_3$) δ: 3.8, 5.3 (S, 4H, methylene), 6.2,7.3(d, 2H,ethylene), 7.5-7.9(m, 3H, quinoxaline), 7.1-7.4 (m, 15H, Ar-H), 7.0-8.1 (m, 4H, benzimidazole). Mass: *m/z*: 556.2 (M+)

*General procedure for Synthesis 6-((1-((1-benzyl-4, 5-dihydro-5-phenyl-1H-pyrazol-3-yl) methyl)-1H Benzo [d]imidazol-5-yl) methyl)-2, 3-diphenylquinoxaline (**NVI1– NVI15**)*[11]

Chalcone **NIV** (0.01 M) and aromatic acid hydrazide (0.02 M) were taken in 20 mL glacial acetic acid and refluxed for 10 h. above 130 ^{0}C. The reaction mixture was concentrated and poured in 300 mL of ice-cold water and recrystallized with aqueous ethanol. The purity of the compound was checked by TLC and melting point.

NVI 1: Yield: 67%, m.p: 121 ^{o}C, IR (KBr) cm^{-1}: 1790 (C=O str.), 1668 (C=N str.), 1339 (C-N str.), 3035 (Ar-H str.), 3320 (C-H str.) cm^{-1}. ^{1}HNMR ($CDCl_3$): 1.79, 2.0 (m, 2H, methylene), 3.8, 3.8 (S, 4H, methylene), 4.9 (m, 1H, methine), 7.5-7.9 (m, 3H, quinoxaline), 7.12-7.95 (m, 20H, Ar-H), 7.9-8.1 (m, 4H, benzimidazole). Mass: *m/z*: 674.2 (M+).

Pharmacological evaluation

Antihistaminic activity[15]

Histamine chamber method

In this method, thirty two healthy adult guinea pigs of either sex divided into group of 2 animals each weighing around 400 g, fasted overnight, were kept in histamine chamber, and exposed to histamine aerosol (0.5% aqueous solution of histamine acid phosphate in a Nebulizer) until they collapse. Those that collapse within 2 minutes were revived with fresh air and used for this test. Twelve hours later, the animals were given an oral dose of test compound suspended in 1% acacia solution and after 1 h for absorption; the guinea pigs were again exposed to the same concentration of histamine aerosol. Those that do not collapse within 6 minutes are deemed protected. Percentage protection has been measured by using the following formula:

$$[1\text{-}T_1 / T_2] \times 100$$

Where T1 was the mean of control preconvultion time in vehicle treated group and T_2 was the mean of control preconvultion time in drug treated group. The results are shown in Table 2.

Table 2. Antihistaminic studies of phenyl pyrazolo benzimidazolo quinoxaline derivatives.

Compd.	X	Ar	Mol. formula	Onset of convulsions (s) Mean±SD	%Protection
NVI 1	H	C_6H_5	$C_{45}H_{34}N_6O$	990±90	89.3
NVI 2	OH	C_6H_5	$C_{45}H_{34}N_6O_2$	1000±98	89.5
NVI 3	F	C_6H_5	$C_{45}H_{33}FN_6O$	1150±98	90.8
NVI 4	Cl	C_6H_5	$C_{45}H_{33}ClN_6O$	993±96	89.4
NVI 5	OCH_3	C_6H_5	$C_{46}H_{36}N_6O_2$	999±91	89.4
NVI 6	H	OHC_6H_4	$C_{45}H_{34}N_6O_2$	1000±92	89.5
NVI 7	OH	OHC_6H_4	$C_{45}H_{34}N_6O_3$	1100±91	90.4
NVI 8	F	OHC_6H_4	$C_{45}H_{33}FN_6O_2$	1111±92	90.5
NVI 9	Cl	OHC_6H_4	$C_{45}H_{33}ClN_6O_2$	1020±92	89.7
NVI 10	OCH_3	OHC_6H_4	$C_{45}H_{36}N_6O_3$	1022±96	89.7
NVI 11	H	ClC_6H_4	$C_{45}H_{33}ClN_6O$	1113±92	90.5
NVI 12	OH	ClC_6H_4	$C_{45}H_{33}ClN_6O_2$	1160±95	90.9
NVI 13	F	ClC_6H_4	$C_{45}H_{32}ClFN_6O$	1170±96	91.0
NVI 14	Cl	ClC_6H_4	$C_{45}H_{32}Cl_2N_6O$	1150±92	90.8
NVI 15	OCH_3	ClC_6H_4	$C_{46}H_{35}ClN_6O_2$	1180±92	91.1
Control				105±16	
CPM				1220±65	91.3

Conclusions

Synthesis of some phenyl pyrazolo benzimidazolo quinoxaline derivatives by condensing benzothiazolo quinoxaline chalcones with different aromatic acid hydrazides have been done successfully. The structure of chalcones and phenyl pyrazolo benzimidazole quinoxaline derivatives were confirmed by M.P, TLC and Spectral data. Physical data are shown in Table 1. All the synthesized compounds were screened for their Antihistaminic activity. Compounds **NVI 3, NVI 12, NVI 13, NVI 14** and **NVI 15** were shown good % protection of antihistamic activity *i.e*., 90.8%, 90.9%, 91.0%, 90.8% and 91.1% respectively.

Table 1. Physical data of phenyl pyrazolo benzimidazolo quinoxaline derivatives.

Compd.	X	Ar	Mol. Formula	Melting point range, °C	% Yield	R_f value
NVI1	H	C_6H_5	$C_{45}H_{34}N_6O$	122-124	70	0.8
NVI2	OH	C_6H_5	$C_{45}H_{34}N_6O_2$	114-115	67	0.82
NVI3	F	C_6H_5	$C_{45}H_{33}FN_6O$	112-115	66	0.8
NVI4	Cl	C_6H_5	$C_{45}H_{33}ClN_6O$	112-114	78	0.91
NVI5	OCH_3	C_6H_5	$C_{46}H_{36}N_6O_2$	116-118	67	0.8
NVI6	H	OHC_6H_4	$C_{45}H_{34}N_6O_2$	120-124	66	0.81
NVI7	OH	OHC_6H_4	$C_{45}H_{34}N_6O_3$	120-124	80	0.9
NVI8	F	OHC_6H_4	$C_{45}H_{33}FN_6O_2$	108-110	45	0.9
NVI9	Cl	OHC_6H_4	$C_{45}H_{33}ClN_6O_2$	102-105	45	0.8
NVI10	OCH_3	OHC_6H_4	$C_{45}H_{36}N_6O_3$	110-112	67	0.83
NVI11	H	ClC_6H_4	$C_{45}H_{33}ClN_6O$	120-122	56	0.8
NVI12	OH	ClC_6H_4	$C_{45}H_{33}ClN_6O_2$	120-122	78	0.82
NVI13	F	ClC_6H_4	$C_{45}H_{32}ClFN_6O$	131-133	76	0.80
NVI14	Cl	ClC_6H_4	$C_{45}H_{32}Cl_2N_6O$	130-134	56	0.98
NVI15	OCH_3	ClC_6H_4	$C_{46}H_{35}ClN_6O_2$	123-126	54	0.81

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