Antimicrobial Evaluation and Synthesis of Some Phenylpyrazolo benzothiazolo quinoxaline Derivatives

CH. SRIDEVI*, K. BALAJI, A. NAIDU and R.SUDHAKARAN

*Department of Pharmaceutical Chemistry,
Geethanjali College of Pharmacy,
Cheeryal(V), Keesara(M), Hyderabad.501301, India.
sridevi.phd@gmail.com

Received 25 November 2008; Accepted 16 January 2009

Abstract: 2,3-Diphenyl quinoxaline (SI) was fused with 2-amino benzothiazoles (SII) by a methylene bridge, which was then allowed for acetylation. The acetylated product (SIV) was made to react with different aromatic aldehydes to give chalcones (SV1-SV5). Chalcones refluxed with substituted acid hydrazides to afford different phenyl pyrazolo benzothiazolo quinoxaline derivatives (SVII-SVII15). The structure of chalcones and phenyl pyrazolo benzothiazolo quinoxaline derivatives were confirmed by M.P, TLC and spectral data. All the synthesized compounds were screened for their antimicrobial activities.

Keywords: 2,3-Diphenyl quinoxaline, 2-Amino benzothiazole, Phenyl pyrazolo benzothiazolo quinoxaline, Antimicrobial activity.

Introduction

Pharmacologically, phenyl pyrazolo benzothiazolo quinoxaline derivatives are known to exhibit important biological activities like antimicrobial¹ antitubercular², anti-inflammatory³, antioxidant⁴, antihistamic⁵, antidepressant⁶, hypoglycemic, hypotensive, anticarcinogenic activities⁷ etc. In view of these reports the synthesis of title compounds has been undertaken in the present note (Scheme 1) and their anti microbial properties are reported. In view of the above facts, it was contemplated to design and synthesize some phenyl pyrazolo benzothiazolo quinoxaline derivatives by condensing benzothiazolo quinoxaline chalcones with different aromatic acid hydrazides. All the synthesized compounds were screened for their anti microbial activities. The structure of chalcones and phenyl pyrazolo benzothiazolo quinoxaline derivatives were confirmed by M.P, TLC, and spectral data.

Scheme 1

Experimental

The melting point of the compounds was determined on a Thoshniwal electric melting point apparatus and the values were uncorrected. I.R spectra of the compounds were recorded on a Thermo Nicolet Nexus 670-FTIR, IICT, Hyderabad using KBr disc method. ^1H NMR spectra were recorded on Avance-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-((2,3-diphenylquinoxalin-6-yl) methyl)benzo[d]thiazol-2-amine(SIII)*⁸

2,3 Diphenyl quinoxaline (**SI**) and 2-aminobenzothiazole (**SII**) were prepared using following literature method. **SI** and **SII** are linked with a methylene bridge by treating equimolar quantities of **SI** and **SII** in a suitable solvent with 35 parts formaldehyde solution and 35% HCl, stirred for 4 h. at 70 °C using magnetic stirrer. Solution was made alkaline using ammonia solution. The product was filtered and recrystallized with aqueous ethanol.

*General procedure for synthesis of 1-(6-((2,3-diphenylquinoxalin-6-yl) methyl) benzo[d]thiazol – 2 –yl amino) propan-2-one (SIV)*⁹

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

*General procedure for (Z)-1-(6-((2,3-diphenylquinoxalin-6-yl) methyl) benzo[d]thiazol-2-yl amino)-4-phenylbut-3-en-2-one (SVI-SV5)*¹⁰

A solution of NaOH / KOH (8 mL, 10% in water) was added drop wise to a well stirred solution of **SIV** (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.

*General procedure for synthesis of (3-(6-((2,3diphenylquinoxalin-6yl) methyl) benzo[d]thiazol-2-yl amino) methyl)-4,5-dihydro-5-phenylpyrazol-1- yl)(phenyl) methanone (SVII– SVI15)*¹¹

Chalcone (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 °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. Physical data are shown in Table 1.

Antimicrobial evaluation

*Antifungal activity*¹²

All the compounds were evaluated *in vitro* for antifungal activity by using cup plate method by different strains of fungi like *Aspergillus fumigates*, *Candida albicans*, *Candida glabrata* and *Candida krusei*. All the compounds along with standard fluconazole were used at a concentration of 250 mg/mL. 10% DMSO in methanol was used as solvent control and sabour and dextrose agar was used as culture medium. Compounds **SVI-13**, **SVI-14**, **SVI-15** exhibited highest degree of antifungal activity and compounds **SVI-3**, **SVI-4**, **SV-5**, **SVI-8**, **SVI-9**, **SVI-10** showed moderate antifungal activity (Table 2).

*Antibacterial activity*¹³

This study was assayed by employing the cup plate method by measuring inhibition zones in mm. All the tested compounds along with standard ciprofloxacin was screened *in vitro* for antibacterial activity against gram positive *Staphylococcus aureus* and *Bacillus subtilis*, gram negative *Pseudomonas aeruginosa* and *Escherichia coli*. The sterile nutrient agar medium was melted and inoculated with 16-18 hours old broth culture at 1% level. The inoculation has to be completed under aseptic conditions and when the medium was in molten state.

The inoculated medium was transferred to sterile Petri dishes, evenly distributed and allowed to solidify. Thereafter the cups (8 mm diameter) were made by punching into the agar surface with a sterile cork borer and scooping out the punched part of the agar. Into each of these cups, 0.05 mL (50 µg) of the test compound/reference standard was added using a micropipette. The plates were incubated at 37°C for 16 h and the zone of inhibition was measured. The data indicated that compounds **SVI-5**, **SVI-10**, **SVI-15** showed excellent activity against *E.coli* and *Bacillus subtilis*. **SVI-14**, **SVI-15** showed excellent activity against *Staphylococcus aureus*. **SVI-14**, **SVI-15** showed has shown little activity against *Pseudomonas aeruginosa* Table 3.

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

Compd.	X	Ar	Molecular Formula	Melting point range °C	% Yield	R _f value
SVI1	H	C ₆ H ₅	C ₄₅ H ₃₄ N ₆ OS	120-122	70	0.89
SVI2	OH	C ₆ H ₅	C ₄₅ H ₃₄ N ₆ O ₂ S	115-116	67	0.8
SVI3	F	C ₆ H ₅	C ₄₅ H ₃₃ FN ₆ OS	114-116	66	0.87
SVI4	Cl	C ₆ H ₅	C ₄₅ H ₃₃ ClN ₆ OS	112-113	78	0.9
SVI5	OCH ₃	C ₆ H ₅	C ₄₆ H ₃₆ N ₆ O ₂ S	114-116	67	0.86
SVI6	H	OHC ₆ H ₄	C ₄₅ H ₃₄ N ₆ O ₂ S	120-124	66	0.91
SVI7	OH	OHC ₆ H ₄	C ₄₅ H ₃₄ N ₆ O ₃ S	119-120	80	0.93
SVI8	F	OHC ₆ H ₄	C ₄₅ H ₃₃ FN ₆ O ₂ S	108-110	45	0.9
SVI9	Cl	OHC ₆ H ₄	C ₄₅ H ₃₃ ClN ₆ O ₂ S	112-115	45	0.8
SVI10	OCH ₃	OHC ₆ H ₄	C ₄₅ H ₃₆ N ₆ O ₃ S	110-112	67	0.89
SVI11	H	ClC ₆ H ₄	C ₄₅ H ₃₃ ClN ₆ OS	110-112	56	0.88
SVI12	OH	ClC ₆ H ₄	C ₄₅ H ₃₃ ClN ₆ O ₂ S	120-122	78	0.82
SVI13	F	ClC ₆ H ₄	C ₄₅ H ₃₂ ClFN ₆ OS	130-131	76	0.79
SVI14	Cl	ClC ₆ H ₄	C ₄₅ H ₃₂ Cl ₂ N ₆ OS	120-124	56	0.98
SVI15	OCH ₃	ClC ₆ H ₄	C ₄₆ H ₃₅ ClN ₆ O ₂ S	123-126	54	0.8

Table 2. Antifungal activity of phenyl pyrazolo benzothiazolo quinoxaline derivatives.

Compound	Antifungal activity, diameter of the inhibition zone, mm			
	<i>Aspergillus fumigates</i>	<i>Candida albicans</i>	<i>Candida krusei</i>	<i>Candida glabrata</i>
Control	0	0	0	0
Fluconazole	10	29	19	15
SVI1	-	-	-	-
SVI2	-	-	-	-
SVI3	7	17	14	9
SVI4	7	16	12	9
SVI5	6	15	13	9
SVI6	-	-	-	-
SVI7	-	-	-	-
SVI8	6	15	10	9
SVI9	5	17	11	10
SVI10	7	15	12	9
SVI11	5	20	9	8
SVI12	7	20	12	8
SVI13	10	22	17	14
SVI14	9	22	18	15
SVI15	9	28	18	14

Table 3. Antibacterial activity of phenyl pyrazolo benzothiazolo quinoxaline derivatives.

Compound	Antibacterial activity, diameter of the inhibition zone, mm			
	<i>Staphylococcus aureus</i>	<i>Bacillus Subtilis</i>	<i>E.coli</i>	<i>Pseudomonas aeruginosa</i>
Control	0	0	0	0
ciprofloxacin	20	21	20	19
SVI1	-	-	-	-
SVI2	10	10	11	9
SVI3	15	15	15	10
SVI4	12	15	15	10
SVI5	15	19	19	-
SVI6	10	12	-	-
SVI7	11	13	14	9
SVI8	14	16	18	-
SVI9	14	19	18	-
SVI10	16	20	19	11
SVI11	10	13	12	8
SVI12	12	13	14	9
SVI13	16	11	11	13
SVI14	19	13	13	14
SVI15	20	21	20	14

Conclusions

Synthesis of some phenyl pyrazolo benzothiazolo quinoxaline derivatives by condensing benzothiazolo quinoxaline chalcones with different aromatic acid hydrazides have been done successfully. All the synthesized compounds were screened for their anti microbial activities. Compounds **SVI-13**, **SVI-14**, **SVI-15** exhibited highest degree of antifungal activity and compounds **SVI-3**, **SVI-4**, **SV-5**, **SVI-8**, **SVI-9**, **SVI-10** showed moderate antifungal activity and the compounds **SVI-5**, **SVI-10**, **SVI-15** showed excellent activity against *E.Coli* and *Bacillus subtilis*. **SVI-14**, **SVI-15** showed excellent activity against *Staphylococcus aureus*. **SVI-14**, **SVI-15** showed has shown little activity against *Pseudomonas aeruginosa*.

Acknowledgements

The authors are thankful to IICT Hyderabad, spectral analysis. Also thankful to Geethanjali College of Pharmacy for providing facilities to carry out research work.

References

1. Paget C J, Patent U S, 3, 974, 286, 10 Aug 1976, *Chem Abstract.*, 1977, **86**, 5468.
2. Pandey, Anil V & Lokhande S R, *Indian drugs*, 1982, **19**, 9.
3. Mehre S C and Zaman S J, *Indian Chem Soc.*, 1980, **57**, 829.
4. Sandeep Kotharkar and Devender B Shinda, *Bioorg Med Chem Lett.*, 2006, **16**, 6181.
5. Dubey PK, Naidu A, Vijaya S and George B, Vineel, *Indian J Chem.*, 2005, **44B**, 573.
6. Ganapathy S, Ramalingam P and Baburao Ch, *Indian J Hetero Chem.*, 2007, **16**, 283.
7. Kumar A, Sharma S, Bajaj K. *Indian J Chem.*, 2003, **42B(8)**, 1979.
8. Suthakaran R, Nagarajan G, Balasubramaniam V, Suganthi K and Velrajan G, *Indian J Heterocycl Chem.*, 2005, **14**, 201.
9. Leonard J T, Yagnapriya S, Sridhar S K and Gunasekaran V, *Indian J Heterocycl Chem.*, 2005, **14**, 377.
10. Suthakaran.R, Somasekhar G, Sridevi Ch, Mari kannan M, Suganthi K and Nagarajan G, *Asian J Chem.*, 2007, **5**, 3353.
11. Harinadha babu V, Sridevi Ch, Joseph A and Srinivasan KK, *Indian J Pharm Sci.*, 2007, **66(8)**, 470.
12. Sharma T C, Bokadia M M and Reddy N J, *Indian J Chem*, 1980, **19B**, 228.
13. Fathema.M, Bharmal, Devender and Hansa, *Indian J Heterocycl Chem.*, 2000, **12**, 189.