



SYNTHESIS OF 2-PHENYL BENZIMIDAZOLE DERIVATIVES AND THEIR SCHIFF BASES AS POSSIBLE ANTIMICROBIAL AGENTS

Prem Shankar Misra¹, P.Shanmugasundaram², Rakhi Chaudhary³ and M.Vijey Aanandhi*¹

¹Department of Pharmaceutical Chemistry, Vel's college of pharmacy.Chennai.Tamilnadu

²Department of Chemistry,Thiruvalluvar Government arts college.Rasipuram.Tamilnadu

³SRMSCET Bareilly.Uttarpradesh

E-mail: samsimahe@gmail.com

ABSTRACT

The novel reaction of 3-(2-methylbenzimidazol-1-yl) propanoic acid hydrazide with CS₂/KOH gave Oxadiazole derivative which under went Mannich reaction to give 3-[(dialkylamino) methyl]-2phenyl-4(3H)-quinazolinone. All compounds were characterized by physical, chemical, analytical and spectral data. All compounds have been screened for their antimicrobial activity and anti-inflammatory activity.

Keywords: 4(3H)-Quinazolinones, Niementowski Reaction, N-Mannich reaction, Antimicrobial agent.

INTRODUCTION

It is established that quinazolinone is a versatile lead molecule for designing potential bioactive agents. 4(3H)-quinazolinone and its derivatives have been reported to exhibit analgesic, anaesthetic, anticancer, anticonvulsant, antimicrobial, antihypertensive, anti-inflammatory, muscle-relaxant, sedative, diuretic, CNS-depressant activity and tranquilizer properties¹⁻⁵. This work was undertaken with a view to explore the possibility of antimicrobial activity in the present nucleus, which has both 4(3H)-quinazolinone and N-Mannich reaction in it⁶⁻⁷.

The synthesis of title compounds were affected as outlined in the Scheme I. All title compounds were characterized by TLC method, melting point determination and spectral studies. The antimicrobial activities of the compounds were carried out according to the standard procedures.

EXPERIMENTAL

The melting points were carried out in an open capillary tube and were uncorrected. Thin layer chromatography was performed using silica gel coated on a glass plate and spots were visualized by exposure to iodine vapor. IR spectra in Nujol were recorded on a Shimadzu IR spectrophotometer. ¹H NMR spectra were recorded in MeOD on an av500 spectrometer using TMS as an internal standard (chemical shifts in δ , ppm). The spectral data of synthesized compounds are shown later.

Synthesis of 2-alkyl-4(3H)-quinazolinone (a to c):

Anthranilic acid (0.1mole) was dissolved in 100ml of methanolic potassium hydroxide. Then gradually added alkyl amide (0.1mole). The contents were refluxed for 3 hours and were cooled to room temperature. The reaction mixture was filtered and washed with methanol and dried. The dried crude product was recrystallized from methanol to get the compound and thin layer chromatography was eluted in methanol: methyl acetate (70:30).

2-methyl-4(3H)-quinazolinone (Compound a): Yield-79%, m.p.-289-291⁰C, IR (Nujol): 3425-3396, 2988, 1533, 1380 cm⁻¹, ¹H-NMR (CH₃OD): δ 8.0 (1H), 7.2-6.6 (4H), 1.1-0.9 (3H).

4(3H)-quinazolinone (Compound b): Yield-80%, m.p.-260-262^oC, IR (Nujol): 3429-3326, 1608-1583, 1027, 661 cm⁻¹, ¹H-NMR (CH₃OD): δ 8.0 (1H), 7.2-7.0 (4H).

2-phenyl-4(3H)-quinazolinone (Compound c): Yield-80.8%, m.p.-301-302^oC, IR (Nujol): 3429-3326, 1658-1577, 1122-1026 cm⁻¹, ¹H-NMR (CH₃OD): δ 8.0 (1H), 7.4-7.29 (9H).

1. Synthesis of 3-[(dialkylamino) methyl]-2-methyl-4(3H)-quinazolinone (a₁ & a₂):

2-alkyl-4(3H)-quinazolinone (0.01mole) was taken in 5ml ethanol and slurry was formed. To this gradually added 37% formaldehyde (0.02mole) and dialkylamine (0.01mole). A clear solution was obtained. To this solution 30ml ethanol was added and it was concentrated by evaporation on a hot plate until a semisolid was formed. This was purified by recrystallization with 30ml of ethanol and thin layer chromatography was eluted in methanol: methyl acetate (50:50).

3-[(dimethyl amino) methyl]-2-methyl-4(3H)-quinazolinone (Compound a₁): Yield-78%, m.p-290-292^oC, IR (Nujol): 3359-3340, 2918-2850, 1668-1573, 1016 cm⁻¹, ¹H-NMR (CH₃OD): δ 8.0 (1H), 7.2-6.6 (4H), 1.1-0.9 (3H), 5.22 (2H).

3-[(diphenyl amino) methyl]-2-methyl-4(3H)-quinazolinone (Compound a₂): Yield-81%, m.p-305-306^oC, IR (Nujol): 3425-3396, 2988, 1533, 1380 cm⁻¹.

2. Synthesis of 3-[(dialkylamino) methyl]-4(3H)-quinazolinone (b₁ & b₂):

4(3H)-quinazolinone (0.01mole) was taken in 5ml ethanol and slurry was formed. To this gradually added 37% formaldehyde (0.02mole) and dialkylamine (0.01mole). A clear solution was obtained. To this solution 30ml ethanol was added and it was concentrated by evaporation on a hot plate until a semisolid was formed. This was purified by recrystallization with 30ml of ethanol and thin layer chromatography was eluted in methanol: methyl acetate (50:50).

3-[(diethyl amino) methyl]-4(3H)-quinazolinone (Compound b₁): Yield-75%, m.p-263-264^oC, IR (Nujol): 3384-3361, 1608-1558, 1018 cm⁻¹, ¹H-NMR (CH₃OD): δ 8.0 (1H), 7.2-7.0 (4H).

3-[(diphenyl amino) methyl]-2-4(3H)-quinazolinone (Compound b₂): Yield-68.4%, m.p-270-272^oC, IR (Nujol): 3406-3382, 3041, 1296-1024 cm⁻¹.

3.Synthesis of 3-[(dialkylamino) methyl]-2-phenyl-4(3H)-quinazolinone (c₁ & c₂):

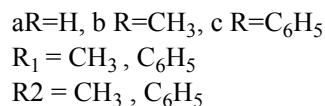
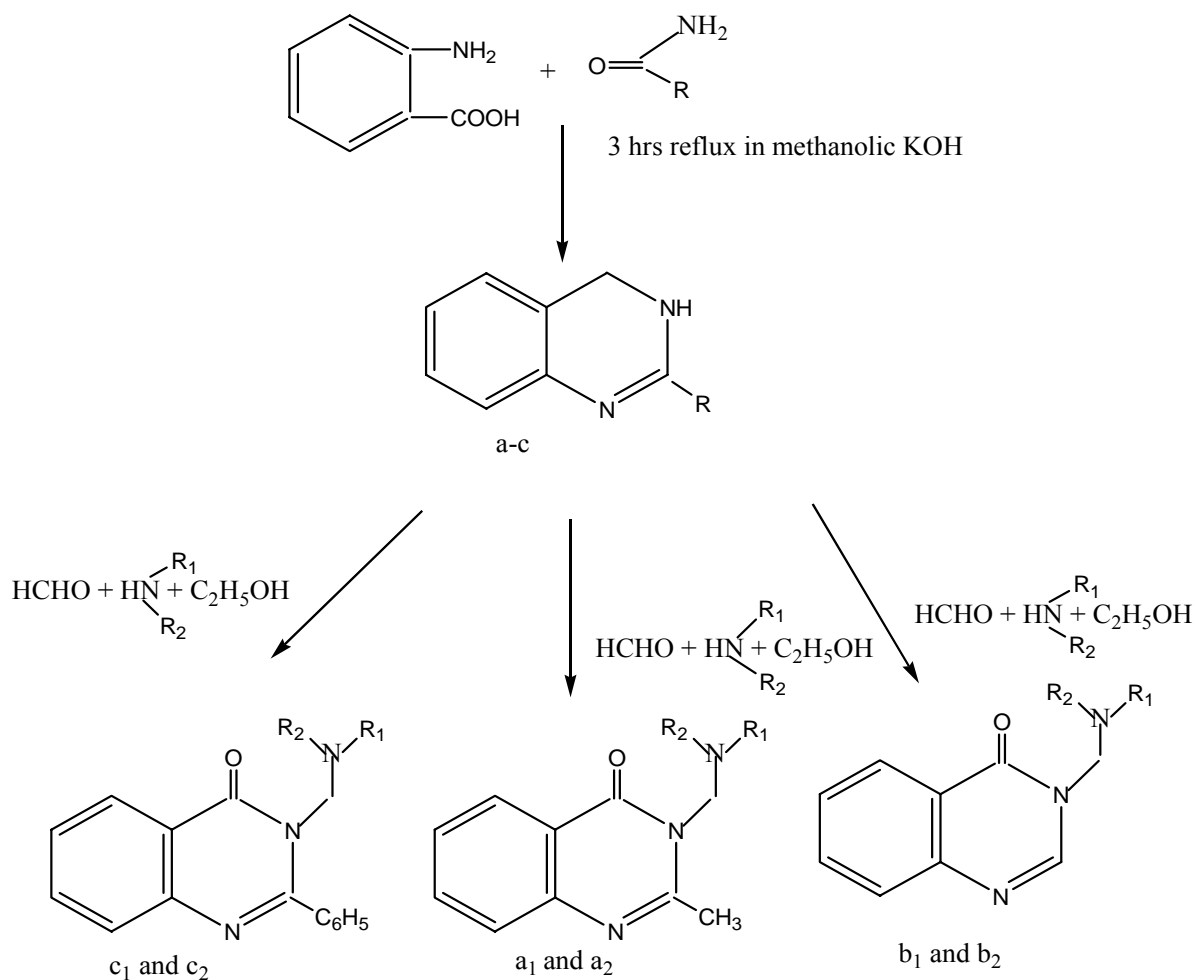
2-phenyl-4(3H)-quinazolinone (0.01mole) was taken in 5ml ethanol and slurry was formed. To this gradually added 37% formaldehyde (0.02mole) and dialkylamine (0.01mole). A clear solution was obtained. To this solution 30ml ethanol was added and it was concentrated by evaporation on a hot plate until a semisolid was formed. This was purified by recrystallization with 30ml of ethanol and thin layer chromatography was eluted in solvent methanol and ethyl acetate (70:30).

3-[(dimethyl amino) methyl]-2-phenyl-4(3H)-quinazolinone (Compound c₁): Yield-69.8%, m.p-302-303^oC, IR (Nujol): 3429-3326, 1658-1577, 1122-1026 cm⁻¹, ¹H-NMR (CH₃OD): δ 8.0 (1H), 7.4-7.29 (9H), 3.63 (3H).

3-[(diphenyl amino) methyl]-2-phenyl-4(3H)-quinazolinone (Compound c₂): Yield-69%, m.p-307-308^oC, IR (Nujol): 3382-3359, 1645-1600, 1114-1027, 690 cm⁻¹, ¹H-NMR (CH₃OD): δ 10.42 (4H), 7.4-7.29 (9H), 5.28 (2H).

Antimicrobial activity

The synthesized compounds in the present investigation have been tested for antimicrobial activity by cup-plate diffusion method. The organisms selected for antibacterial activity were *Bacillus subtilis* (MTCC-441), *Staphylococcus aureus* (ATCC-3750) and *Escherichia coli* (MTCC-443). The antifungal activity was carried out by using *Aspergillus niger* (MTCC-282) and *Candida albicans* (MTCC-227). The concentration of testing compounds was 100µg/ml and 150µg/ml. Norfloxacin and Fluconazole were used as standard drugs for antibacterial and antifungal activity respectively. The plates are prepared as per the standard methods^{8,9,10}. The outcome is presented in Table-1.



Scheme-1

RESULTS AND DISCUSSION

All the synthesized compounds were confirmed by spectral data and then screened for antibacterial activity against *B. subtilis*, *S. aureus* and *E. coli* and for antifungal activity against *C. albicans* and *A. niger*. Synthesized compounds a₁, b₁, c₁ shown the highest antibacterial activity when compared with standard drug Norfloxacin. Compounds a₁, b₁, and c₁ have shown high activity against both fungi and remaining compounds exhibited either moderate or weak activity against *C. albicans* and *A. niger*. Antibacterial and antifungal activities are presented in Table-1. In conclusion, the present study reveals

that the some N-Mannich derivatives of 4(3H)-quinazolinones could be used as a template for the future development through modification or derivatization to design a more potent antimicrobial agent.

Table-1: Antimicrobial Activity of Compounds a₁ to c₂

Compound	Zone of inhibition in mm									
	Antibacterial				Antifungal					
	<i>B. subtilis</i>		<i>E. coli</i>		<i>S. aureus</i>		<i>A. niger</i>		<i>E. coli</i>	
100 μg	150μ g	100 μg	150 μg	100 μg	150 μg	100 μg	150 μg	100 μg	150μg	
a ₁	18	20	17	19	20	21	15	19	10	12
a ₂	-	15	-	14	-	-	10	11	10	12
b ₁	20	21	17	19	18	20	16	18	11	13
b ₂	14	16	15	17	13	15	11	15	09	12
c ₁	21	22	18	20	17	19	18	20	14	16
c ₂	15	18	16	18	15	17	-	15	-	12
Norfloxacin	22	25	22	25	22	25	-	-	-	-
Fluconazole	-	-	-	-	-	-	22	24	16	18

REFERENCES

1. S.M. Mosaad, K.I.Mohammed, M.A.Ahmed, S.G.Abdel-Hamide, *J. of Biol. Sci.*, **4(4)**, 504-509 (2004).
2. W.Fathalla, P. Pazdera, *Molecules.*, **5**, 1210-1223 (2004).
3. A.R.Desai, K.R.Desai, *ARIKOV*, **13**, 98-108 (2005).
4. E. Comanita, G. Roman, I. Popovici, B. Comonita, *J. Serb. Chem. Soc.*, **66(1)**, 9-16 (2001).
5. V.B.Kurteva, V.N. Zlatanova, and V.D Dimitrov, *ARIKOV*, **1**, 46-56 (2006).
6. S.N.Pandeya, S.Smitha, M. Jyoti, S.K. Sridhar, *Acta Pharm.*, **27**, 27-46 (2005).
7. A. Kumar, M. Tyagi, V.K. Srivastava, *Indian J. Chem.*, **42B**, 2142-2145 (2003).
8. J. Versha, S.K. Jain, P. Mishra, *Indian. J. Pharm. Sci.*, **68**, 360-363(2006).
9. V. Alagarsamy, R. Giridhar, M.R. Yadav, K. Ruckmani, *Indian J. Pharm. Sci.*, **68**, 532-535 (2006).
10. V. Alagarsamy, A. Thangathirupathy, S.C. Mandal, S.Rajsekaran, S. Rajesh, *Indian. J. Pharm. Sci.*, **68**, 108-110 (2006).

(Received: 26 October 2009

Accepted: 13 November 2009

RJC-337)

If you think that you may be a potential reviewer in field of your interest, write us at rasayanjournal@gmail.com with your detailed resume and recent color photograph.