REPORT

SYNTHESIS AND EVALUATION OF MANNICH BASES OF BENZIMIDAZO [1,2-C] QUINAZOLIN- 6(5*H*)-THIONE FOR ANTIMICROBIAL ACTIVITY

SARASWATHI M, ROHINI RM*, RANAPRATHAPSINGH AND NAIRA NAYEEM

Department of Pharmaceutical Chemistry, Krupanidhi College of Pharmacy, Bangalore, India

ABSTRACT

The intermediate Benzimidazo[1,2-c] quinazolin-6(5*H*)-thione **(1)** was obtained by cyclization of 2-(2'-aminophenyl) benzimidazole with carbon disulfide. Mannich base **(2a-d)** of compound **(1)** was obtained on treatment with Para formaldehyde and secondary aliphatic amines, similarly treatment of **(1)** with different ketones afforded respective mannich bases **(3 e-h)**. All derivatives synthesized were characterized from IR and ^{1}HNMR spectral data's. Moderate anti bacterial activity was exhibited from **2a-d** and from **3f, 3h** against *S. aureus, E. coli,* and *E. fecalis* but very negligent activity were seen from these compounds when screened against *P aeruginosa*

Keywords: Mannich base, Benzimidazo [1,2-c] quinazoline–6(5*H*)-thione, antimicrobial activity.

INTRODUCTION

Quinazoline derivatives are pharmaceutically interesting compounds and many of them have been registered as drugs. Quinazolin-4-ones derivatives have been reported for hypnotic (Santhosh *et al.,* 2006), anti-inflammatory and analgesic (Tyagi *et al.,* 1998), antiallergic (Farghaly *et al,* 1990), antifungal (Rajendran *et al.,* 2002), antimicrobial activity (Farghaly *et al.,* 1990) and cytotoxic activity (Murugesan *et al.,* 2003). Benzimidazo nucleus is widely accepted for its antiallergic (Nakano *et al.,* 1999), anti-inflammatory (Sham *et al.,* 2002, Richards *et al.,* 2006), antimalarial (Smith *et al.,* 2004), anthelmentic (Mckellar *et al.,* 1990). Benzimidazo-1,2 quinazolin-6 (5*H*)-2-thione is reported for bronchodilatory activity and anti histamine activity (Rao *et al.,* 1999). Based on the above findings, the present study was designed to screen the mannich base derivatives of the fused benzimidazo [1,2-c] quinazoline for antibacterial activity. Mannich bases of wide variety of heterocyclic/non-heterocyclic nucleus have been revealed to possess cytotoxic, anti-bacterial, antifungal, anticonvulsant, anti-inflammatory and antimalarial activity. Mannich bases of quinazolinone nucleus have been screened for antitubercular as well as antimicrobial activity. The Mannich bases of benzimidazo[1,2-c] quinazolin- 6(5*H*)-thione were obtained on treatment with paraformaldehyde and various secondary amines/ ketones in presence of glacial acetic acid in absolute ethanol.

EXPERIMENTAL

MATERIALS AND METHODS

All chemicals were procured from SD Fine chemicals; IR spectra were recorded on Perkin Elmer 600 and ^{1}H NMR on AMX 400 MHz FT-NMR spectrophotometer. Chemical shift are reported in ppm (δ) using tetramethylsilane as internal reference and solvent used was DMSO.

Synthesis of Benzimidazo[1,2-c] quinazolin-6(5H)-thione (1)

2-(2'-aminophenyl) benzimidazole (0.01moles) was refluxed with alcoholic KOH (0.01moles) solution and carbon disulphide (8ml) for 12 hours. Carbon disulphide was distilled off and the residue neutralized with 5N hydrochloric acid, filtered, washed with water.

Mannich reaction of benzimidazo [1,2-c] quinazolin-6(5H)-thione with various secondary amines 2(a-d)

Paraformaldehyde (0.03 moles), appropriate secondary amines (0.03 moles) and 1ml of glacial acetic acid in 10ml of absolute ethanol were refluxed till paraformaldehyde completely solubilized. Benzimidazo [1,2-c] quinazolin-6(5*H*)-thione (0.004 mol) in 10 ml of absolute ethanol was heated for 10min. The mixtures were combined and refluxed for 6 - 8 h. The solid product separated was recrystallized.

Mannich reaction of of benzimidazo [1,2-c] quinazolin-6(5H)-thione with various ketones 3 (e-h)

Paraformaldehyde(0.03 moles), benzimidazo [1,2-c] quinazolin-6(5*H*)-thione(0.004 moles), appropriate ketones(0.03 moles) and 1ml of glacial acetic acid in 20 ml of absolute ethanol were refluxed for 6 - 8 h. The resultant mixture was left overnight and solid product separated was recrystallized from ethanol.

Antimicrobial activity

The anti microbial screening of the synthesized mannich bases of benzimidazo [1,2-c] quinazolin-6(5*H*)-thione were carried following agar diffusion method at

**Corresponding author*: e-mail: rm_rohini@rediffmail.com

concentration 30 µg/ml of the synthesized compounds were evaluated against *Staphylococcus aureus, Enterococcus fecalis, Pseudomonas aeruginosa* and *Escherichia coli.* The zone of inhibition was compared with standard amipicillin 10 µg/ml and control DMSO.

RESULTS

The structures of the synthesized title compounds were characterized from IR and ^{1}HNMR spectral data's.

5-(N,N-dimethylaminomethyl)benzimidazo[1,2-c]quinazolin-6-thione (2a)
IR (KBr cm^{-1}) - 3022 (C-H), 1490 (C=C), 1327 (C-N), 1643(C=N), 1259 (C=S). ^{1}H NMR (δ ppm) 7.5-8.7 (m, 8H Ar-H), 4.7 (s, 2H, CH_2), 3.3 (s, 6H, CH_3).

5-(N,N-diethylaminomethy)benzimidazo[1,2-c]quinazolin-6-thione (2b)
IR (KBr cm^{-1}) - 3021 (C-H), 1476 (C=C), 1324 (C-N), 1633 (C=N), 1278 (C=S). ^{1}H NMR (δ ppm) 7.5- 8.5(m, 8H, Ar-H), 4.8 (s, 2H, CH_2), 3.6 (q, 4H, CH_2), 2.4 (t, 6H, CH_3).

5-(N'-methylmorpholinyl)benzimidazo[1,2-c]quinazolin-6-thione (2c)
IR (KBr cm^{-1}) - 3056 (C-H), 1504 (C=C), 1324 (C-N), 1644 (C=N), 1224 (C=S), 1164 (C-O). ^{1}H NMR (δ ppm) 7.5 - 8.5(m, 8H, Ar-H), 4.9 (s, 2H, CH_2), 4.3 (t, 4H, CH_2), 3.4 (t, 4H, CH_2).

5-(N'-methylpiperidinyl)benzimidazo[1,2-c]quinazolin-6-thione (2d)
IR (KBr cm^{-1}) - 3031 (C-H), 1492 (C=C), 1318 (C-N), 1652 (C=N), 1224 (C=S). ^{1}H NMR (δ ppm) 7.5-8.7 (m, 8H, Ar-H), 4.9 (s, 2H, CH_2), 3.4 (t, 4H, CH_2), 2.6 (m, 6H, CH_2).

5-(1'-(propyl-1-oxo)phenyl)benzimidazo[1,2-c]quinazolin-6-thione (3e)
IR (KBr cm^{-1})-3029 (C-H Ar), 1494 (C=C), 1323 (C-N), 1648 (C=N), 1221 (C=S), 1703 (C=O). ^{1}H NMR (δ ppm) 7.4 - 8.7 (m, 13H, Ar-H), 4.7 (t, 2H, CH_2), 3.3 (t, 2H, CH_2).

5-(1'-(propyl-1-oxo)-3'-nitrophenyl)benzimidazo[1,2-c]quinazolin-6-thione (3f)
IR (KBr cm^{-1})-3030 (C-H Ar), 1480 (C=C), 1327 (C-N), 1643 (C=N), 1223 (C=S), 1702 (C=O), 1342 (C-NO_2). ^{1}H NMR (δ ppm)7.4 - 8.9 (m, 12H, Ar-H), 4.8 (t, 2H, CH_2), 3.3 (t, 2H, CH_2).

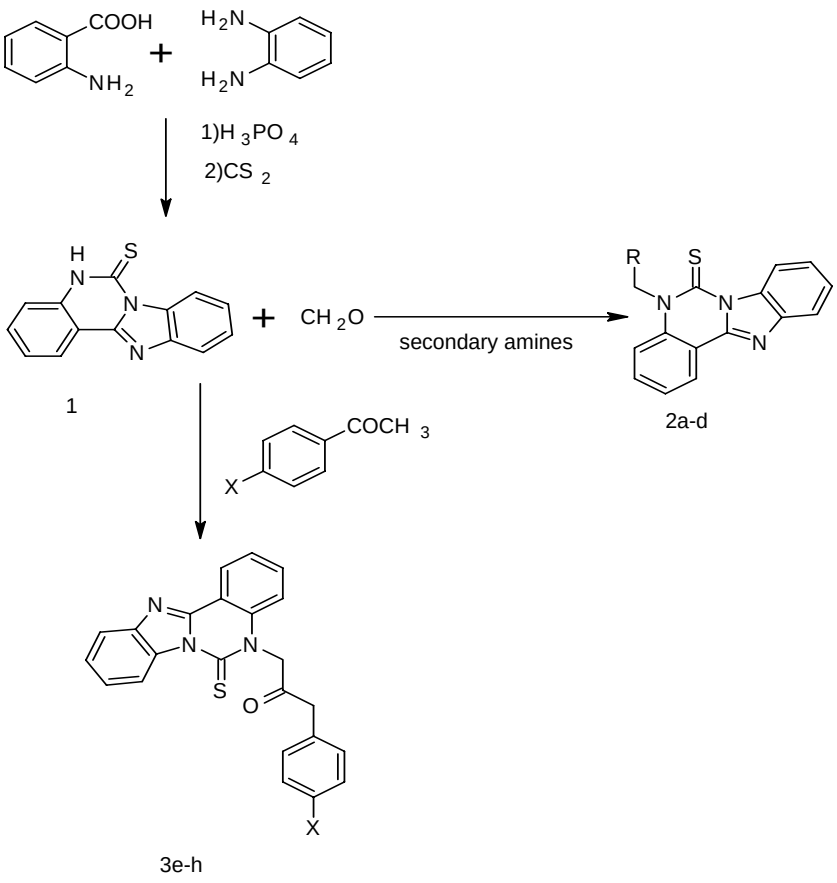
5-(1'-(propyl-1-oxo)-3'-methoxyphenyl)benzimidazo[1,2-c]quinazolin-6-thione (3g)
IR (KBr cm^{-1})-3041 (C-H Ar), 1492 (C=C), 1324 (C-N), 1644 (C=N), 1224 (C=S), 1703 (C=O), 1164 (C-O). ^{1}H NMR (δ ppm) 7.4 - 8.4 (m, 12H, Ar-H), 4.8 (t, 2H, CH_2), 3.8(s, 3H, CH_3), 3.3 (t, 2H, CH_2).

5-(1-(propyl-1-oxo)-4-hydroxyphenyl)benzimidazo[1,2-c]quinazolin-6-thione (3h)
IR (KBr cm^{-1})-3032 (C-H Ar), 1501 (C=C), 1320 (C-N), 1652 (C=N), 1224 (C=S), 1699 (C=O). ^{1}H NMR (δ ppm) 7.5 - 8.7 (m, 12H, Ar-H), 4.8 (t, 2H, CH_2), 3.6 (s, 1H, OH), 3.3 (t, 2H, CH_2).

Anti bacterial activity
Table 1 depicts the antibacterial activity of the synthesized derivatives against *S. aureus E. fecalis, P. aeruginosa and E. coli*. The zone of inhibition was measured and ampicillin 10µg/ml showed potent antibacterial activity, while the synthesized derivatives exhibited moderate activity but failed to show activity against *P.aeruginosa.*

Table 1: Anti microbial activity of Mannich base of benzimidazo [1,2-c] quinazolin- 6(5*H*)-thione derivatives

Compound	Antibacterial activity zone of inhibition (mm)			
	Staphylococcus aureus	*Enterococcus faecalis*	*Pseudomonas aeruginosa*	*Escherichia coli*
2a	07	08	02	07
2 b	09	09	03	09
2 c	08	07	05	08
2 d	07	07	03	09
3e	04	03	02	03
3 f	08	09	02	08
3 g	03	04	02	03
3 h	09	08	03	09
Ampicillin (10µg/ml)	12	12	12	11



R		X	
(2a) -	—N(CH3)(CH3)	(3e) -	—H
(2b) -	—N(C2H5)(C2H5)	(3f) -	—NO2
(2c) -	N-morpholino	(3g) -	—OCH3
(2d) -	N-piperidino	(3h)-	—OH

Scheme of synthesis of Mannich base derivatives

DISCUSSION

The benzimidazo[1,2-c]quinazoline-6(5H)-thione **(2)** was synthesized by refluxing from 2-(2'-aminophenyl) benzimidazole with CS_2 and alcoholic KOH at room temperature , Mannich base from this intermediate were obtained on treatment with various secondary amines and ketones in presence of paraformaldhye and glacial acetic acid . The loss of water formed during the reaction was collected from dean stalk apparatus indicated the progress of the reaction. The synthesized derivatives showed characteristic IR absorption- (KBr $cm^{-1)}$ 3056 (C-H), 1504 (C=C), 1324 (C-N), 1644 (C=N), 1224 (C=S), 1164 (C-O). ^{1}H NMR (δ ppm) 7.5 - 8.5(m, 8H, Ar-H), 4.9 (s, 2H,

CH_2), 4.3 (t, 4H, CH_2), 3.4 (t, 4H, CH_2) for the secondary amine derivatives. IR (KBr cm^{-1}) - 3041 (C-H Ar), 1492 (C=C), 1324 (C-N), 1644 (C=N), 1224 (C=S), 1703 (C=O), 1164 (C-O). ^{1}H NMR (δ ppm) 7.4 - 8.4 (m, 12H, Ar-H), 4.8 (t, 2H, CH_2), 3.8(s, 3H, CH_3), 3.3 (t, 2H, CH_2) for the ketone derivatives. A triplet at δ 4.8 for the methylene protons (N–CH_2) and triplet at δ 3.3 for methylene protons (CH_2-CO) and a singlet at 4.9 (s, 2H, CH_2), reveals the formation of mannich base with respective ketones and secondary amines used in the reaction. The characteristic IR absorption is seen at (cms^{-1}) 1703 for C=O, 1224 for C=S, 1324 (C-N), 1644 for C=N stretching vibrations of the mannich base formed. No significant activity was seen for the synthesized derivatives against *P aeruginosa* but moderate antibacterial activity was noted against S *aureus, E coli,* and *E faecalis* . Significant activity was not seen from mannich base formed from unsubstituted acetophenone **(3h).** Derivatives containing dimethyl amino and diethyl amino **(2a &2 b)** exhibited moderate activity against S *aureus, E coli* and *E faecalis;* while mannich base substituted with para hydroxyl and para nitro acetophenones **(3h & 3g)** showed similar activity against the organism used indicating the influence of these groups for activity.

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