WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 4, Issue 2, 1292-1298. Research Article ISSN 2277– 7105

SYNTHESIS, CHARACTERISATION AND BIOLOGICAL EVALUATION OF SOME ETHOXYPHTHALIMIDE DERIVATIVES OF THIADIAZOLE AND QUINAZOLINE

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Article Received on
07 Dec 2014,

Revised on 01 Jan 2015,
Accepted on 26 Jan 2015

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ABSTRACT

Thiosemicarbazide of isoniazide (2) was used as a starting material for the synthesis of N-ethoxyphthalimido- 3-[5-(pyridin-4-yl)-1, 3, 4-thiadiazol-2-yl] quinazoline-2, 4(1*H*,3*H*)-dione (5). Isonicotinoylthiosemicarbazide (2) was treated with conc. H_2SO_4/NH_3 to get 5-pyridin-4-yl-1,3,4-thiadiazol-2-amine (3) which gave 3-[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]quinazoline-2,4(1*H*,3*H*)-dione (4) corresponding isatoic anhydride moiety. Compounds 4 were converted to targeted molecules (5) by the base induced condensation with bromoethoxyphthalimide. Structures of all the synthesized compounds have been confirmed on the basis of physical parameters, chemical tests and spectral studies. Final compounds were screened for Antimicrobial activity.

KEYWORDS: Isoniazide, Thiadiazole, ω-bromoalkoxyphthalimide, Antimicrobial activity.

INTRODUCTION

Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have caused universal concerns due to their widely and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer,[1- 4] anti-inflammation,[5,6] anti-bacterial,[7-10] anal-gesia,[5,9] anti-virus,[11] anti-cytotoxin,[12] anti-spasm,[9,13] anti-tuberculosis,[14] anti-oxidation,[15] anti-malarial[16] anti-hypertension,[17] anti-obesity,[18] anti-psychotic,[19] anti-diabetes,[20] etc. Medicinal

chemists synthesized a variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using develop-ing synthetic methods. Pyridine derivatives are well known for their wide range of biological and pharmacological activities. Many of these are associated with antihypertensive, anti-inflammatory, antitumor, antiviral, antimalarial, and antipyretic activities.[21-28]

Numerous patents have been issued on the synthesis and use of 1,3,4-thiadiazoles as fungicides, herbicides, insecticides, bactericides, dyes, lubricant additives and vulcanization accelerators.[29] Its derivatives exhibit antiproliferative,[30] anti-infective,[31] diuretic,[32] CNS depressant,[33] anti-inflammatory,[34] anticonvulsant,[35] hypoglycemic, analgesic and antimicrobial[36] activities.

MATERIALS AND METHODS

Melting points of all synthesized compounds were taken in open capillaries and are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 1300 FT IR spectrometer and 1H NMR were determined on a Bruker WM-400 (400 MHz FT NMR) spectrometer using TMS as internal standard. Purity of compounds was checked by TLC using silica gel-G as adsorbent and visualization was accomplished with iodine. Compound **1** was synthesized by reported methods.[38]

Synthesis of isonicotinoylthiosemicarbazide (2)

Isoniazid (0.01 mole) was dissolved in a minimum amount of 1N HCl and ammonium thiocyanate (0.02 mole) was then added. The reaction mixture was heated under reflux for 8-10 hrs. After cooling the product separated out as crystals was filtered, washed with water, dried and recrystallized from absolute alcohol. Yield 67%, m.p. 240-242^{o}C, Anal. calcd. For $C_7H_8N_4OS$ (196): N, 28.55; S, 16.34. Found: N, 28.74; S, 16.59 %. IR (KBr, cm^{-1}): 3470, 3410 (NH), 3020 (Ar-H), 1587-1446 (C=N), 1125 (C=S). ^{1}H NMR, (DMSO, δ): 8.9 (s, 1H, CONH), 7.56-8.0 (m, 4H, Ar-H), 5.7 (s, 2H, NH_2).

Synthesis of 5-pyridin-4-yl-1,3,4-thiadiazol-2-amine (3)

A portion of **2** (0.01 mole) was dissolve in 4 mL of conc. sulphuric acid. Then, the solution was kept at room temperature for 2 hr with constant stirring and then poured over crushed ice. The resulting solid was kept in ammonical water for 2 hrs. and was then filtered, washed with water and recrystallized from ethanol. Yield 70%, m.p. >300^{o}C, Anal. calcd. For $C_7H_6N_4S$ (178): N, 31.44; S, 17.99. Found: N, 31.21; S, 17.64%. IR (KBr, cm^{-1}): 3436,3416

(NH), 3021 (Ar-H), 1521-1424 (C=N), 1012 (C-S). ^{1}H NMR, (DMSO, δ): 7.8-8.1 (m, 4H, Ar-H), 5.3 (s, 2H, NH_2).

Synthesis of 3-[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]quinazoline-2,4(1*H*,3*H*)-dione (4)

A mixture of **3** (0.01 mole) and isatoic anhydride (0.01 mole) in absolute alcohol, was added. The reaction mixture was heated under reflux for 4 hrs. Excess of the solvent was distilled off under reduced pressure and after cooling crystalline product was obtained. It was filtered and recrystallized from ethanol to yield needle shaped crystals. Yield 62%, m.p. 190-195^{o}C, Anal. calcd. For $C_{15}H_9N_5O_2S$ (323): N, 21.67; S, 9.90. Found: N, 20.74; S, 9.10 %. KBr IR: 3416 (N-H str.),3086 (C-H str., Ar-H), 1718, 1693 (C=O str.), 1412 (C=N), 1034 (C-S); ^{1}HNMR ($CDCl_3$) δ:8.6 (s, 1H, NH), 6.8-7.4 (m, 8H, Ar-H).

Synthesis of N-ethoxyphthalimido- 3-[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]quinazoline-2,4(1*H*,3*H*)-dione (5)

Compound (4, 0.01 mole) and bromoethoxyphthalimide (0.01 mole), were refluxed in dry acetone for 15-17 hrs. Containing K_2CO_3 (0.01 mole) as base. It was filtered and excess of solvent was removed under reduced pressure. The separated solid was filtered, washed and recrystallized from ethanol. Yield 62%, m.p. 267-272^{o}C, Anal. calcd. For $C_{25}H_{16}N_6O_5S$ (512): N, 16.40 ; S, 6.25. Found: N, 15.74; S, 5.96 %. KBr IR: 3065 (C-H str., Ar-H), 2940 (C-H str.,CH_2),1762, 1694 (C=O str., CO-N-CO), 1412 (C=N), 1355 (N-O str.), 1080 (C-O str.), 1034 (C-S); ^{1}HNMR (CDCl3) δ: 7.5-7.8(m, 12H, Ar-H), 3.64 (t, 2H, OCH_2), 3.15 (t, 2H, NCH_2).

RESULT AND DISCUSSION

The reaction sequence leading to the formation of title compounds are outlined in Scheme I. Isonicotinic acid hydrazide was converted into 5-pyridin-4-yl-1,3,4-thiadiazol-2-amine 2 by its reaction with ammonium thiocynate in 1N HCl to synthesized isonicotinoylthiosemicarbazide 2 which on cyclization in the presence of conc. H_2SO_4/NH_3 furnished 3 which was confirmed by IR 3436,3416 Cm^{-1} (NH2) two spike. Treatment of 3 with isatoic anhydride in ethanol converted to corresponding 3-[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]quinazoline-2,4(1*H*,3*H*)-dione 4. Formation of 4 was confirmed by IR absorption spectra at 3416 and 1034 cm^{-1} due to NH and C=S str. respectively and disappeared two spike peak of NH_2. in IR spectrum.

The N-H proton of 4 was replaced from ethoxyphthalimide moiety by the reaction with bromoethoxyphthalimide to give N-ethoxyphthalimido- 3-[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]quinazoline-2,4(1*H*,3*H*)-dione 5. The IR spectra of 5 show strong absorption band for CO-N-CO group around 1762, 1694 cm^{-1}, while N-O and C-O bond give relatively weak absorption bands at 1355 and 1080 cm^{-1} respectively. Disappearance of NH stretching band around 3416 cm^{-1} also confirmed the replacement of hydrogen of isatoic anhydride NH by ethoxyphthalimide, which was present in its precursor. Additional proof for the proposed structure of 5 was provided by close observation of ^{1}H NMR spectra, which showed disappearance of NH signal at δ 8.6 and presence of two triplets for NCH_2 and OCH_2 protons resonating at δ 3.64 and 4.15 respectively.

Antimicrobial Screening

Three synthesized compounds 3, 4 and 5 were *in vitro* screened for their antibacterial and antifungal activity using cup or well method [37]. Antibacterial activity of the compounds (500 ppm im DMF media) have been evaluated against four bacterial strains *viz Escherichia coli, Bacillus subtilis, Klebsilla pneumonia* and *Pseudomonas aeruginosa*. The activity was measured as a function of zone of inhibition in mm. Results were compared with the reference drug ciprofloxacin by measuring their zone of inhibition and activity index (Table I).

All the compounds show poor activity against *B. subtilis* and *K. pneumonia* where as these show moderate to strong activity against *E. coli* and *P. aeruginosa*. Compound 5 displayed activity index more then one against *E. coli* and against *P. aeruginosa*. Activity index of 5 is comparable to the standard used against *E. coli* and *P. aeruginosa*. Overall antibacterial activity of synthesized compounds is moderate as compared to ciprofloxacin but when cefuroxime was used as a reference drug, the activity looks to be strong.

Screening of above compounds in a concentration of 500 ppm for antifungal activity by the same technology was carried out against two fungal strains *viz Candida albicans* and *Aspergillus fumigates* using Amphotericin B as a control. It was pleasure to note that All compounds shows stronger activity then the standard used against *C. albicans*. Activity index for 3, 4 and 5 is more then one. Activity against *A. fumigates* using same control is insignificant (Table I).

It may be concluded from the activity study that the synthesized compounds have high versatility in activity against various microbes *viz* stronger against *C. albicans*, moderate For antifungal activity: C_1 = Amphotericin B, NA = Nil Activity against *E. coli* and *P. aeruginosa*, weaker against *B. subtilis*, *K. pneumonia* and *A. fumigates*.

TABLE I Antimicrobial activity of the synthesized compounds 3, 4 and 5.

Compd. No.	Antibacterial Activity					Antifungal Activity
	Escherichia coli	**Bacillus *subtilis***	***Klebsilla pneumonia***	***Pseudomonas aeruginosa***	***Candida albicans***	***Aspergillus fumigatus***
3	11 (0.68)	NA	5 (0.31)	9 (0.50)	15 (1.88)	NA
4	12 (0.75)	9 (0.52)	NA	14 (0.77)	19 (1.11)	NA
5	12 (0.75)	6 (0.35)	8 (0.50)	11 (0.61)	20 (1.17)	5 (0.50)
C_1	16	17	16	18	17	10

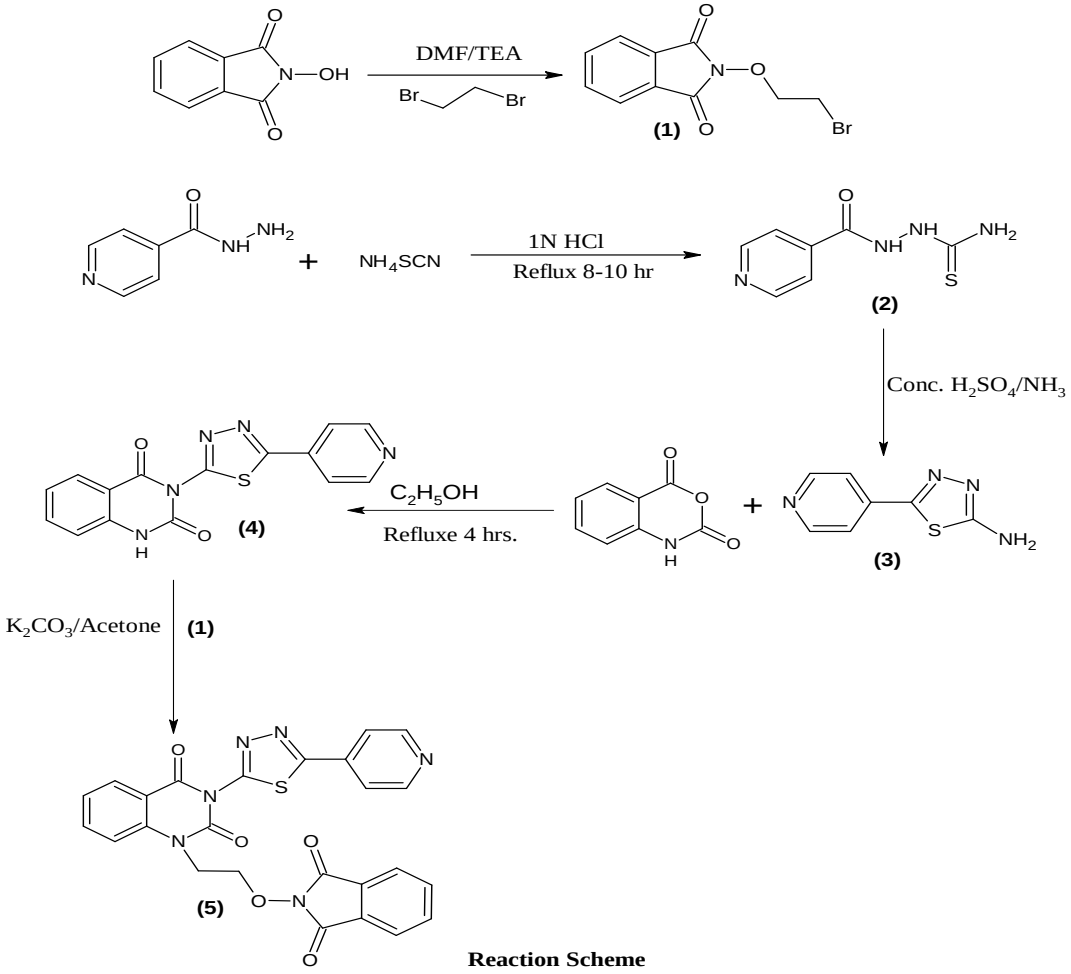
Zone of Growth Inhbition (mm) (activity index)

(Activity index) = Inhibition zone of compound/Inhibition zone of the standard drug.

For antibacterial activity: C1= Ciprofloxacin

For antifungal activity: C1 = Amphotericin B

NA = Nil Activity



Reaction Scheme

ACKNOWLEDGEMENTS

Authors are thankful to the Head, Department of Chemistry, M.L. Sukhadia University, and Udaipur for providing Laboratory facilities and Prof. J.R Luthra, Dean, Faculty of Arts, Science and Technology (FASC), Mody University of Science and Technology, for their constant encouragement during this work. The Director, RSIC, CDRI, Lucknow, India for providing spectral and analytical data

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