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Synthesis and microbial studies of imidazolone based azetidinone analogues

Snehal Lokhandwala and Nikhil M. Parekh

Shroff S. R. Rotary Institute of Chemical Technology, Block No: 402, At: Vataria, Ankleshwar-Valia Road, Ta: Valia, Dist: Bharuch, Gujarat

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ABSTRACT

In the present study we have reviewed the synthesis and different biological activities of some azetidinone derivatives. A series of new azetidinone class of bioactive agents based on imidazol-4-one nucleus have been synthesized by a simple and efficient synthetic protocol. The 3-(4-amino-phenyl)-5-benzylidene-2-methyl-3,5-dihydro-imidazol-4-one nucleus formed from 4-benzylidene-2-methyl-4H-oxazol-5one using p-phynelenediamine in pyridine followed by reaction with various substituted aromatic aldehyde to form the corresponding Schiff base intermediates. Effort has been made to derive final azetidinone analogues from Schiff bases by using chloroacetyl chloride. Newer analogues were characterized by IR, ^{1}H NMR, and elemental analyses. The newly synthesized analogues were then examined for their antimicrobial activity against some bacterial and fungal strains to develop a novel class of antimicrobial agents.

Keywords: 1,3 oxazolone, imidazol-5-one, azetidinone, antimicrobial activity

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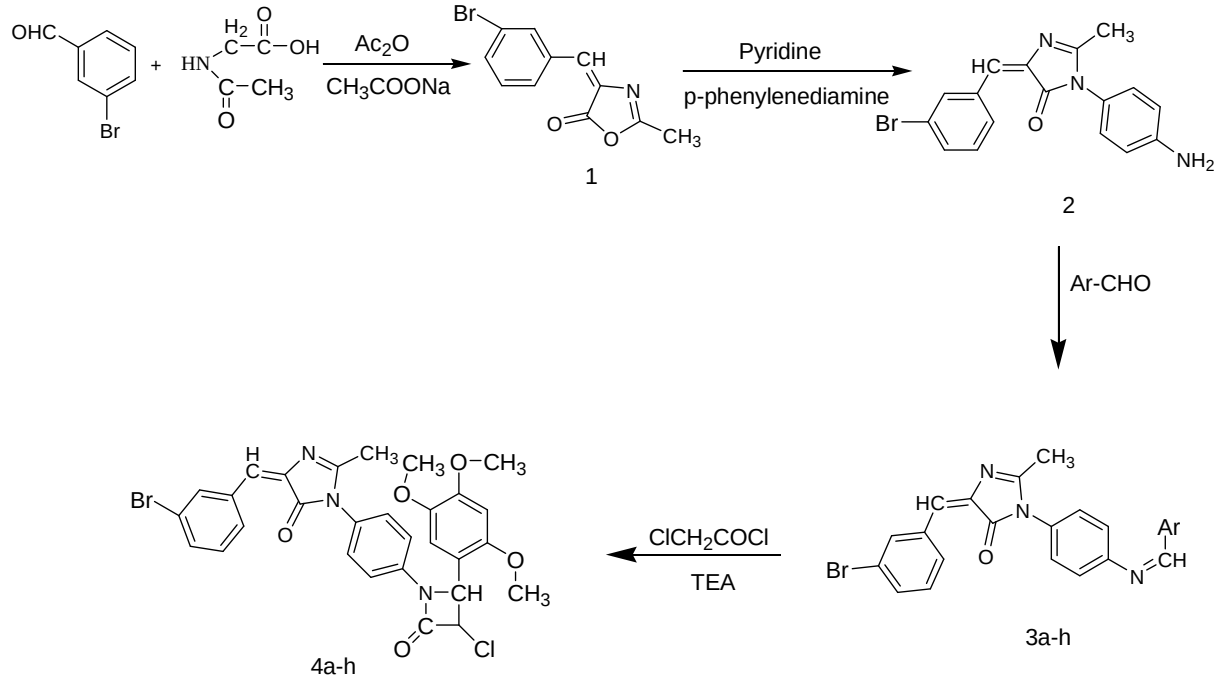
INTRODUCTION

Azetidinone which are the part of antibiotics structure are recognized to exhibit motivating biological activities. 2-Azetidines have been broadly examined by the organic chemists due to their close involvement with miscellaneous types of biological activities [1-4]. Azetidine-2-ones also have enormous implication because of the use of b-lactam derivatives as an antibacterial agent [5]. The antibiotic activity is closely related to the substituted b-lactam ring structure [6]. More particularly and recently these types of compounds have been found in the treatment of T.B. and other chemotherapeutic diseases [7]. Moreover, during the past few decades a large number of imidazolone containing compounds have been in the market with diverse pharmacological properties e.g. clonidine, phentolamine for the treatment of hypertension, cimetidine as antiulcer, dacarbazine as anticancer, metronidazole as antiprotozoal drug , ketoconazole, econazole as antifungal agents [8] and two imidazolines priscol and privine are vasodilating and vasoconstricting drugs [9]. This observation prompted us to synthesize new imidazolones based azetidinone analogues and evaluate their antimicrobial activity. Moreover, azetidinone derivatives were reported to possess antibacterial, antifungal [10,11], antituberculor activity[12], anti-HIV [13], analgesic, anti inflammatory [14] and ulcerogenic activity. Therefore it was envisioned that compounds containing both the chemical moieties would result in compounds of interesting biological activities. In this present study 3-(4-amino-phenyl)-5-benzylidene-2-methyl-3,5-dihydro-imidazol-4-one nucleus formed from 4-benzylidene-2-methyl-4H-oxazol-5one using *p*-phynelenediamine in pyridine followed by reaction with various substituted aromatic aldehyde to form the corresponding Schiff base intermediates. Effort has been made to derive final azetidinone analogues from Schiff bases by using chloroacetyl chloride.

MATERIALS AND METHODS

All chemicals were of analytical grade and used directly. All melting points were determined in PMP-DM scientific melting point apparatus and are uncorrected. The purity of all Compounds was determined by thin-layer chromatography (TLC) using silica gel-G coated Al-plates (0.5 mm thickness, Merck). Infrared spectra were recorded on a Shimadzu FT-IR 8400S model using KBr pellets. ^{1}H NMR spectra were acquired on a Varian 400 MHz model spectrophotometer using DMSO as a solvent and TMS as internal reference (chemical shifts in δ, ppm). Elemental analysis carried on Carlo Erba 1108 instrument.



Synthesis of 4-(3-Bromo-benzylidene)-2-methyl-4H-oxazol-5-one (1)

A mixture of 3-bromo benzaldehyde (0.01 mole), N-acetyl glycine (0.007mol) acetic anhydride (0.017 mole) and sodium acetate (0.003 mole) was heated on electric hot plate with constant shaking in a conical flask. As soon as the mixture was liquefied completely, the flask heated on water bath for two hours. Ethanol (5 mL) was added slowly to the contents of flask, the mixture was allowed to stand overnight. The separated crystalline solid was filtered, washed with ice-cold alcohol and hot water successively to obtain **(1)**.

Synthesis of 3-(4-Amino-phenyl)-5-(3-bromo-benzylidene)-2-methyl-3,5-dihydro-imidazol-4-one (2)

A mixture of 4-(3'-bromo benzylidene)-2-methyl-1,3-oxazol-5-one (0.01 mol) and different substituted aromatic amines (0.01 mol) , Acetone (15ml), pyridine (2 ml) and 1-2 pellets of KOH were taken in a round bottom flask and refluxed for 4 h on sand bath. After that the reaction mixture was a poured into crushed ice and neutralized with conc. HCl. The solid separated out was filtered, washed with water, dried and recrystalized from ethyl alcohol to give (**2**).

Synthesis of Azetidin-2-one derivatives (4a-h)

Compound (2) was allowed to react with different aromatic aldehyde in presence of ethanol and acid catalyst to get the corresponding Schiff bases (3a-h). The above synthesized Schiff bases and triethyl amine (1:3) was dissolved in DMF in a RBF and chloroacetyl chloride was added slowly with constant stirring. The reaction mixture was stirred at RT for an hour and then refluxed for 8-10 hours. Excess of solvent was then removed by distillation. The solid thus separated was filtered, washed and dried. The crude product was then recrystalized with glacial acetic acid.

Compound 4a: Yield 69%; m.p. 136°C; IR (KBr) cm^{-1}: 3076 (C-H), 1710 (C=O), 1558 (C-N), 1607 (C=N), 1525 (N=O), 754 (C-Cl), 589 (C-Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.17 (1H, s, -C-H of azetidinone), 5.46 (1H, s, -CH-Cl of azetidinone ring), 7.18-8.00 (13H, m. Ar-H); Anal. Calcd. for $C_{26}H_{18}N_4O_4BrCl$: C, 55.19; H, 3.21; N, 9.9. Found: C, 55.26; H, 3.19; N, 9.64.

Compound 4b: Yield: 71%; m.p. 152°C; IR (KBr) cm^{-1}: 3080 (C-H), 1695 (C=O), 1560 (C-N), 1610 (C=N), 760 (C-Cl), 592 (C-Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.20 (1H, s, -C-H of azetidinone), 5.48 (1H, s, -CH-Cl of

azetidinone ring), 7.12-8.02 (18H, m. Ar-H); Anal. Calcd. For $C_{32}H_{23}N_3O_3BrCl$: C, 62.71; H, 3.78; N, 6.86. Found: C, 62.75; H, 3.75; N, 6.82.

Compound 4c: Yield: 80%; m.p. >300°C; IR (KBr) cm^{-1}: 3074 (C-H), 1708 (C=O), 1572 (C-N), 1618 (C=N), 1535 (N=O), 750 (C-Cl), 589 (C-Br); ^1H NMR (400 MHz, DMSO-d_6): δ = 5.18 (1H, s, -C-H of azetidinone), 5.40 (1H, s, -CH-Cl of azetidinone ring), 7.01-7.48 (13H, m. Ar-H); Anal. Calcd. for $C_{26}H_{18}N_4O_4BrCl$: C, 55.19; H, 3.21; N, 11.31. Found: C, 55.16; H, 3.25; N, 11.27.

Compound 4d: Yield: 73%; m.p. 200°C; IR (KBr) cm^{-1}: 3079 (C-H), 1710 (C=O), 1558 (C-N), 1607 (C=N), 770 (C-Cl), 580 (C-Br); ^1H NMR (400 MHz, DMSO-d_6): δ = 5.16 (1H, s, -C-H of azetidinone), 5.44 (1H, s, -CH-Cl of azetidinone ring), 7.18-8.00 (14H, m. Ar-H); Anal. Calcd. for $C_{26}H_{18}N_3O_2BrCl$: C, 60.08; H, 3.49; N, 8.08. Found: C, 60.04; H, 3.52; N, 8.14.

Compound 4e: Yield: 80%; m.p. 206°C; IR (KBr) cm^{-1}: 3084 (C-H), 1700 (C=O), 1565 (C-N), 1607 (C=N), 754 (C-Cl), 590 (C-Br); ^1H NMR (400 MHz, DMSO-d_6): δ = 3.73 (1H, s, $-CH_3$), 5.20 (1H, s, -C-H of azetidinone), 5.32 (1H, s, -CH-Cl of azetidinone ring), 7.08-7.92 (13H, m. Ar-H); Anal. Calcd. for $C_{27}H_{21}N_3O_3BrCl$: C, 55.87; H, 3.84; N, 7.63. Found: C, 55.93; H, 3.87; N, 7.68.

Compound 4f: Yield: 82%; m.p. 110°C; IR (KBr) cm^{-1}: 3076 (C-H), 1710 (C=O), 1558 (C-N), 1612 (C=N), 752 (C-Cl), 595 (C-Br); ^1H NMR (400 MHz, DMSO-d_6): δ = 3.75 (1H, s, $-CH_3$), 5.21 (1H, s, -C-H of azetidinone), 5.49 (1H, s, -CH-Cl of azetidinone ring), 6.98-8.00 (13H, m. Ar-H); Anal. Calcd. for $C_{29}H_{27}N_3O_5BrCl$: C, 56.83; H, 4.44; N, 6.86. Found: C, 56.88; H, 4.39; N, 6.89.

Compound 4g: Yield: 74%; m.p. 220°C; IR (KBr) cm^{-1}: 3078 (C-H), 1710 (C=O), 1558 (C-N), 1607 (C=N), 754 (C-Cl), 582 (C-Br); ^1H NMR (400 MHz, DMSO-d_6): δ = 5.17 (1H, s, -C-H of azetidinone), 5.46 (1H, s, -CH-Cl of azetidinone ring), 7.18-8.00 (13H, m. Ar-H); Anal. Calcd. for $C_{26}H_{18}N_3O_2BrCl_2$: C, 56.24; H, 3.27; N, 7.57. Found: C, 56.26; H, 3.31; N, 7.61.

Compound 4h: Yield: 78%; m.p. 180°C; IR (KBr) cm^{-1}: 3076 (C-H), 1710 (C=O), 1558 (C-N), 1607 (C=N), 754 (C-Cl), 589 (C-Br); ^1H NMR (400 MHz, DMSO-d_6): δ = 5.22 (1H, s, -C-H of azetidinone), 5.52 (1H, s, -CH-Cl of azetidinone ring), 7.12-7.94 (13H, m. Ar-H);Anal. Calcd. for $C_{26}H_{18}N_3O_2Br_2Cl$: C, 52.07; H, 3.03; N, 5.34. Found: C, 52.11; H, 3.07; N, 5.29.

RESULTS AND DISCUSSION

Chemistry

In this paper we have synthesized imidazolol-4-one based azetidinone derivatives. 3-bromobenzaldehyde on reaction with acetyl amino acetic acid in presence of acetic anhydride and sodium acetate which act as base gave 4-(3-Bromo-benzylidene)-2-methyl-4H-oxazol-5-one (1). Compound 1 on further reaction with *p*-phenylenediamine in pyridine gave 3-(4-Amino-phenyl)-5-(3-bromo-benzylidene)-2-methyl-3,5-dihydro-imidazol-4-one (2). The IR spectrum of compounds **2** showed sharp peak near 1710 cm^{-1} indicates the presence of ketone (–C=O) functional group of imidazolone ring. A corresponding peak of C–N–CO was observed at 1535 cm^{-1}. Chlorine functional group exhibited a peak at 770 cm^{-1}. Compound 2 on further reaction with various aromatic aldehydes gave serious of Schiff base (3). Schiff base compounds (3a-h) showed most prominent peak of imine function group (–C=N–) at 1645 $cm^{-1.}$ The substituted Schiff base derivatives **3a-h** on reaction with chloroacetylchloride in presence of triethylamine which act as a catalyst in 1, 4 dioxane to undergo cyclization to obtain azetidin-2-one derivatives **4a-h.** The IR spectrum of compounds **4a-h** showed sharp peak near 1736 cm^{-1} indicates the presence of ketone (–C=O) functional group of azetidinone ring. A corresponding peak of C–N–CO was observed at 1535 cm^{-1}. Chlorine functional group exhibited a peak at 770 cm^{-1}. The ^1H NMR spectra of compounds **4a-h** was showed the signal at 5.67 ppm due to –CH–Cl on azetidinone ring. Doublets were observed at 6.75 ppm due to CH–N proton on azetidinone ring, while remaining all aromatic protons resonated in the range of 6.8-8.5 ppm.

Antimicrobial activity

The antimicrobial bioassay results summarized in table 1 revealed that some of the newly synthesized azetidinone indicated excellent growth inhibitory profiles. It was observed that newly synthesized analogues with electro withdrawing nitro and electro withdrawing halo (-Cl, -Br) substituent demonstrated potential antimicrobial properties.

Table 1: Microbial Activity of synthesized compounds (4a-h)

Comp. (100 µg/disc)	Ar-CHO	Zone of inhibition [mm (MIC in µg/mL)		
		Gram negative	Gram positive	Fungal species
		S. aureus	***E. coli***	***C. albicans***
4a	2-NO_2	17(100)	<10 (100)	<10 (100)
4b	3-OC_6H_5	<10 (100)	<10 (100)	<10 (100)
4c	3-NO_2	18(50)	<10 (100)	13(100)
4d	H	19(100)	17(100)	17(100)
4e	4-OCH_3	25(25)	**24(12.5)**	20(100)
4f	3,4,5-OCH_3	21(50)	21(62.5)	21(62.5)
4g	3-Cl	26(25)	22(62.5)	20(100)
4h	3-Br	23(50)	23(50)	22(50)
Tetracyline (100 µg/disc)		30 (≤4)	32 (≤1)	-
Ceftriaxene (100 µg/disc)		30 (≤4)		33 (≤1)
DMSO		-		-

Compound 4e and 4g shows very good antibacterial activity at 25 MIC while compound 4c, 4f and 4h shows good activity and compound 4a, 4b and 4d indicate moderate to good activity against gram negative bacteria S. Aureus. Compound 4e shows excellent activity at 12.5 while compound 4f and 4h shows good activity at 62.5 MIC. Compound 4a, 4b, 4c, 4d show moderate to good activity against gram positive bacteria E. coli. All the synthesized compounds show moderate to good antifungal activity against Candida Albicans. Overall, Compound 4e and 4h found to be most effective antimicrobial agents due to the presence of additional halo atom in the ring.

CONCLUSION

In summary, we have developed a novel, efficient and potent imidazolone based azetidinone analogues. Imidazolone nucleus is one of the active constituents present in many standard drugs, and is known to increase the pharmacological activities of the molecule. The presence of substituted aldehyde is also an instrumental in contributing the net biological activity. Briefly, high potency has been observed with the final scaffolds in the form of azetidinone bearing various aldehydes containing halogen(s) such as chloro, bromo and nitro functional groups. The final results indicated that imidazolone based azetidinone nucleolus having additional halo functional groups are more efficious antimicrobial agents compared to imidazolone based azetidinone nucleolus analogues having nitro group. Hence, there is enough scope for further study in developing such compounds as a good lead activity. Overall conclusion placed for synthesized compounds is that most of the compounds shown moderate to promising activity as compared to standard drug against all representative panel of bacterial and fungal strains.

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