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Synthesis of New 2-Azetidinone Derivatives and Related Schiff Bases from 3-Phenyl-2,3,6,7-tetrahydroimidazo [2,1-b] Thiazolo [5,4-d] Isoxazole

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2-Azetidinones, commonly known as β-lactams, are well-known heterocyclic compounds. Herein, we describe the synthesis of a series of novel β-lactams. The efficient and rapid synthesis of novel β-lactams has been established in good yields starting from (R)-3-phenyl-2,3, 6,7-tetrahydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazole 1. First, condensation of (R)-3-phenyl-2,3,6,7-tetrahydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazole 1 with ethylchloro acetate yielded ethyl (R) 2-(3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazole-2(3H)-yl) acetate 2, that subsequently yielded (R) 2-(3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetohydrazide 3 through amination with hydrazine hydrate. Then, condensation between compound 3 and various aromatic aldehydes led to the Schiff base derivatives 4a-j, which upon dehydrative annulation in the presence of chloroacetyl chloride and triethylamine yielded N-((3S,4S)-3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-((R)-3-(Aryl)-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetamide 5a-j. All synthesized compounds were characterized by elemental analyses, IR, ^{1}H NMR and ^{13}C NMR data.

Keyword: Condensation, Synthesis, Schiff bases, 2-Azetidinones, β-Lactam

INTRODUCTION

Monocyclic β-lactams are an important class of hetero cyclic compounds. 2-Azetidinone skeleton is well established as the key pharmacophores of β-lactam antibiotics. Recently, some other types of biological activity and even antioxidant activity have been reported in compounds containing 2-azetidinone ring [1-3]. A large number of 3-chloro monocyclic β-lactams having substitution at positions 1 and 4 possess powerful anti-bacterial, anti-microbial, sedative, anti-fungal and anti-tubercular activity [4-12].

The β-lactams also serve as synthons for many biologically important classes of organic compounds [13], and that is why, the chemistry and biology of these compounds continue to appeal the synthetic and medicinal organic chemists [14-16]. They also function as enzyme inhibitors and are effective on the central nervous system [17]. Schiff base derivatives have also been found to be potent drug in pharmaceutical industries and possess a wide spectrum of biological activities. Schiff's bases derivatives are well known intermediate for the preparation of azetidinone, thiazolidinone, formazan, arylacetamide and many other derivatives [18-24]. In this paper we turned our attention to synthesis of new 2-azetidinone derivatives and their related Schiff bases obtained from the reaction of (R) 2-(3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl)acetohydrazide 3 with various aldehydes. Then, condensation between compound 3 with chloroacetyl chloride and triethylamine yielded 5a-j (Scheme 1).

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded for potassium bromide discs on Mattson Galaxy series FT-IR 5000

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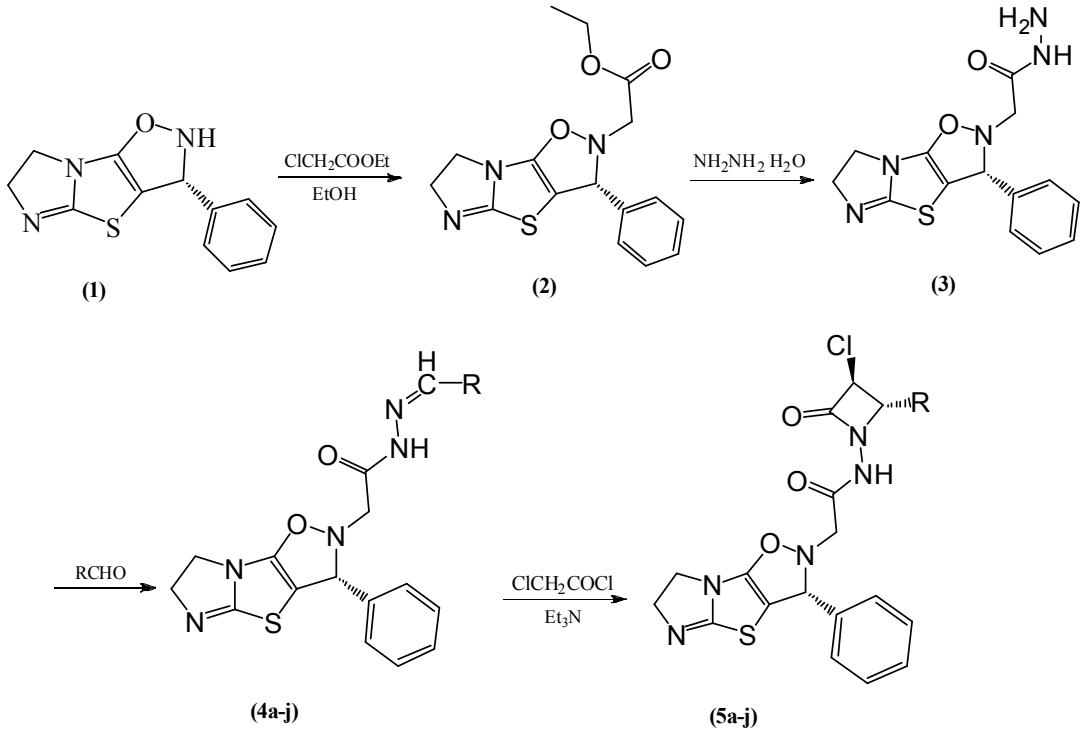

Scheme 1. Synthetic pathway for preparation of 5a-j

spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Brucker DRX-300 spectrometer in $CDCl_3$ and DMSO-d_6 as solvent at 300 and 75 MHz, respectively using TMS as an internal standard, respectively. All chemical shifts were reported as (ppm) values. Elemental analysis was performed on an Elemental Analyzer (Vario EL III). The reactions were monitored and the purity of products was checked out on pre-coated TLC plates (silica gel, aluminum sheets 60 F254, Merck). Spectral data (IR, NMR) confirmed the structures of the synthesized compounds. Elemental (C, H, N) analysis indicated that the calculated and observed values were within the acceptable limits (±0.4%). Synthetic route is depicted in Scheme 1.

Synthesis of Ethyl (R) 2-(3-Phenyl-6,7-dihydroimidazo [2',1':2,3] Thiazolo [5,4-d] isoxazole-2(3H)-yl) Acetate (2)

To a solution of 3-phenyl-2,3,6,7-tetrahydroimidazo [2,1-b] thiazolo [5,4-d] isoxazole 1 (0.003 mol, 0.7359 g) in absolute ethanol (20 ml), ethyl chloroacetate (0.006 mol, 0.7355 g) was added. The mixture was refluxed under stirring for 2 h in the presence of KOH (0.003 mol, 0.1683 g). Then, the reaction mixture was evaporated under reduced pressure and the residue was purified by H_2O: EtOH (1:1) to give pure products.

Synthesis of (R) 2-(3-Phenyl-6,7-dihydroimidazo [2',1':2,3] Thiazolo [5,4-d] Isoxazol-2(3H)-yl) acetohydrazide (3)

A mixture of compound 2 (0.002 mol, 0.66278 g) and 80% hydrazine hydrate (0.003 mol, 0.15 g) in ethanol (10 ml) was refluxed for about 3 h. The solvent was then removed under reduced pressure and a solid was obtained. Then, the solid was filtered off and crystallized from CH_3Cl to afford compounds 3.

General Procedure for the Synthesis of Schiff Bases (4a-j)

To a solution of 3 (0.0006 mol, 0.1904 g) in ethanol (7 ml), an appropriate amount of aldehyde (0.0006 mol), and 4-5 drops of glacial acetic acid (as a catalyst) were added. The reaction mixture was refluxed for 2-6 h. The reaction

mixture was allowed to cool, and then was poured into water (15-20 ml). The solid substance was filtered off and crystallized from ethanol at room temperature to furnish compound 4a-j.

General Procedure for the Synthesis of Compounds (5a-j)

To a magnetically stirred solution of Schiff base 4a-j (0.05 mol) and Et_3N (0.01 mol) in dioxane (50 ml), $ClCH_2COCl$ (0.01 mol) was added dropwise at 0-5 °C .The reaction mixture was stirred for about 4 h and the precipitated amine hydrochloride was filtered off. The filtrate was refluxed for about 3-6 h and excess of solvent was evaporated under reduced pressure. The obtained solid was washed with water (30 ml), filtered and dried. The crude product was purified by an appropriate solvent to give compounds 5a-j.

Ethyl (R) 2-(3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazole-2(3H)-yl) acetate (2). IR (KBr, cm^{-1}): υ = 1720 (C=O), 1636 (C=N), 1592 (C=C), 1247, 1108 (C-N). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.25 (t, 3H, *J* = 7.0 Hz, -$COCH_2\underline{CH_3}$), 3.34 (t, 2H, *J* = 5.1 Hz, CH_2), 3.43 (t, 2H, *J* = 5.8 Hz, CH_2), 3.57 (s, 2H, N-CH_2-CO), 4.20 (q, 2H, *J* = 7.1 Hz, -$COO\underline{CH_2}CH_3$), 4.55 (s, 1H, C_3-H), 7.42 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 15.3, 41.1, 47.2, 57.4, 61.4, 68.3, 98.6, 126.4, 126.5, 126.8, 134.8, 149.1, 169.3, 171.0. Anal. Calcd. for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68; S, 9.68%. Found: C, 57.93; H, 5.13; N, 12.61; S, 9.63%.

(R) 2-(3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetohydrazide (3). IR (KBr, cm^{-1}): υ = 3345, 3371 ($NHNH_2$), 1672 (C=O), 1629 (C=N), 1596 (C=C), 1129 (C-N). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.40 (t, 2H, *J* = 5.2 Hz, CH_2), 3.49 (t, 2H, *J* = 5.8 Hz, CH_2), 3.63 (s, 2H, N-CH_2-CO), 4.47 (s, 2H, NH_2), 4.63 (s, 1H, C_3-H), 7.68 (m, 5H, Ar-H), 7.80 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 40.7, 46.0, 59.7, 67.8, 98.6, 126.9, 127.0, 127.1, 133.8, 149.2, 170.1, 170.5. Anal. Calcd. for $C_{14}H_{15}N_5O_2S$: C, 52.98; H, 4.76; N, 22.07; S, 10.10%. Found: C, 52.92; H, 4.72; N, 22.12; S, 10.04 %.

(R,Z)-N'-benzylidene-2-(3-phenyl-6,7-dihydro-imidazo [2',1':2,3] thiazolo [5,4-d] isoxazol 2(3H)-yl) acetohydrazide (4a). IR (KBr, cm^{-1}): υ = 3468 (NH), 1658 (C=O), 1622 (C=N), 1593 (C=C), 1540 (N=CH). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.51 (t, 2H, *J* = 4.70 Hz, CH_2), 3.51 (s, 2H, N-CH_2-CO), 3.71 (t, 2H, *J* = 5.85 Hz, CH_2), 4.66 (s, 1H, C_3-H), 7.22-7.75 (m, 10H, ArH), 7.93 (s, 1H, N=CH), 10.88 (s, 1H, NH).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 41.4, 46.6, 61.4, 69.06, 98.1, 126.2, 126.3, 126.4, 127.1, 127.3, 129.56, 131.1, 135.5, 141.5, 149.3, 169.8, 171.1. Anal. Calcd. for $C_{21}H_{19}N_5O_2S$: C, 62.21; H, 4.72; N, 17.27; S, 7.91%. Found: C, 62.16; H, 4.68; N, 17.23; S, 7.87%.

(R,Z)-N'-(4-methylbenzylidene)-2-(3-phenyl-6,7-di-hydroimidazo [2',1':2, 3] thiazolo [5,4-d] isoxazol 2(3H)-yl) acetohydrazide (4b). IR (KBr, cm^{-1}): υ = 3455 (NH), 1666 (C=O), 1619 (C=N), 1598 (C=C), 1544 (N=CH). ^{1}H NMR (300 MHz, CDCl3) δ (ppm): 2.41 (t, 3H, *J* = 4.62 Hz, CH_3), 3.52 (t, 2H, *J* = 5.80 Hz, CH_2), 3.64-3.71 (m, 4H, CH_2 + N-CH_2-CO), 4.52 (s, 1H, C_3-H), 7.14-7.52 (m, 9H, ArH), 8.10 (s, 1H, N=CH), 10.83 (s, 1H, NH). ^{13}C NMR (75 MHz, CDCl3) δ (ppm): 22.1, 40.9, 46.0, 60.8, 69.0, 98.93, 126.2, 126.3, 126.5, 128.2, 128.4, 129.0, 134.6, 138.4, 142.3, 149.8, 170.0, 170.3. Anal. Calcd. for $C_{22}H_{21}N_5O_2S$: C, 62.99; H, 5.05; N, 16.69; S, 7.64%. Found: C, 63.05; H, 4.98; N, 16.62; S, 7.59%.

(R,Z)-N'-(3-methoxybenzylidene)-2-(3-phenyl-6,7-diihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol 2(3H)-yl) acetohydrazide (4c). IR (KBr, cm^{-1}): υ = 3460 (NH), 1662 (C=O), 1629 (C=N), 1614 (C=C), 1550 (N=CH). ^{1}H NMR (300 MHz, CDCl3) δ (ppm): 2.82 (t, 2H, *J* = 4.63 Hz, CH_2), 3.32 (t, 2H, *J* = 5.72 Hz, CH_2), 3.54 (s, 2H, N-CH_2-CO), 3.65 (s, 3H, OCH_3), 4.54 (s, 1H, C_3-H), 6.94-7.58 (m, 9H, ArH), 8.07 (s, 1H, N=CH), 10.80 (s, 1H, NH). ^{13}C NMR (75 MHz, CDCl3) δ (ppm): 41.3, 46.4, 57.2, 61.3, 68.8, 99.4, 117.6, 118.1, 120.4, 126.3, 126.5, 126.6, 128.0, 132.84, 135.4, 142.3, 150.0, 158.7, 169.8, 170.9. Anal. Calcd. for $C_{22}H_{21}N_5O_3S$: C, 60.67; H, 4.86; N, 16.08; S, 7.36%. Found: C, 60.61; H, 4.80; N, 16.13; S, 7.32%.

(R,Z)-N'-(3-chlorobenzylidene)-2-(3-phenyl-6,7-di-hydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol 2(3H)-yl) acetohydrazide (4d). IR (KBr, cm^{-1}): υ = 3462 (NH), 1660 (C=O), 1633 (C=N), 1592 (C=C), 1551 (N=CH). ^{1}H NMR (300 MHz, CDCl3) δ (ppm): 3.42 (t, 2H, *J* = 4.73 Hz, CH_2), 3.60 (s, 2H, N-CH_2-CO), 3.79 (t, 2H, *J* = 5.65 Hz, CH_2), 4.67 (s, 1H, C_3-H), 7.04-7.51 (m, 9H, ArH), 8.01 (s, 1H, N=CH), 10.78 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$)

δ (ppm): 41.1, 46.3, 59.6, 68.7, 99.0, 126.3, 126.4, 126.6, 127.69, 128.3, 128.5, 128.7, 131.0, 132.4, 135.1, 141.05, 149.9, 169.8, 170.2. Anal. Calcd. for $C_{21}H_{18}N_5O_2SCl$: C, 57.33; H, 4.12; N, 15.92; S, 7.29%. Found: C, 57.28; H, 4.08; N, 15.89; S, 7.33%.

(R,Z)-N'-(3-bromobenzylidene)-2-(3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol 2(3H)-yl) acetohydrazide (4e). IR (KBr, cm^{-1}): υ = 3471 (NH), 1659 (C=O), 1637 (C=N), 1607 (C=C), 1540 (N=CH). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.31 (t, 2H, *J* = 4.85 Hz, CH_2), 3.50 (s, 2H, N-CH_2-CO), 3.76 (t, 2H, *J* = 5.78 Hz, CH_2), 4.49 (s, 1H, C_3-H), 7.10-7.62 (m, 9H, ArH), 8.08 (s, 1H, N=CH), 10.82 (s, 1H, NH). ^{13}C NMR (75 MHz, CDCl3) δ (ppm): 41.1, 46.2, 59.7, 68.5, 98.1, 125.6, 126.2, 126.3, 126.58, 126.7, 128.2, 128.4, 129.0, 132.5, 135.0, 142.25, 149.9, 169.7, 170.2. Anal. Calcd. for $C_{21}H_{18}N_5O_2SBr$: C, 52.07; H, 3.75; N, 14.46; S, 6.62%. Found: C, 52.02; H, 3.73; N, 14.43; S, 6.60%.

(R,Z)-N'-(2-hydroxybenzylidene)-2-(3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol 2(3H)-yl) acetohydrazide (4f). IR (KBr, cm^{-1}): υ = 3585 (ArOH), 3462 (NH), 1652 (C=O), 1622 (C=N), 1603 (C=C), 1538 (N=CH). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.36 (t, 2H, *J* = 4.86 Hz, CH_2), 3.51 (s, 2H, N-CH_2-CO), 3.80 (t, 2H, *J* = 5.66 Hz, CH_2), 4.56 (s, 1H, C_3-H), 6.91-7.49 (m, 9H, ArH), 7.98 (s, 1H, N=CH), 9.63 (s, 1H, ArOH), 10.75 (s, 1H, NH). ^{13}C NMR (75 MHz, CDCl3) δ (ppm): 40.7, 46.1, 60.2, 69.1, 97.8, 118.5, 119.1, 120.2, 126.3, 126.4, 126.5, 128.3, 129.1, 135.1, 141.6, 149.8, 158.6, 169.5, 170.0. Anal. Calcd. for $C_{21}H_{19}N_5O_3S$: C, 59.84; H, 4.54; N, 16.62; S, 7.61%. Found: C, 59.80; H, 4.51; N, 16.67; S, 7.57%.

(R,Z)-N'-(2-nitrobenzylidene)-2-(3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol 2(3H)-yl) acetohydrazide (4g). IR (KBr, cm^{-1}): υ = 3470 (NH), 1658 (C=O), 1639 (C=N), 1615 (C=C), 1558 (N=CH), 1521, 1344 (NO_2). ^{1}H NMR (300 MHz, CDCl3) δ (ppm): 3.45 (t, 2H, *J* = 5.10 Hz, CH_2), 3.62 (s, 2H, N-CH_2-CO), 3.76 (t, 2H, *J* = 5.88 Hz, CH_2), 4.60 (s, 1H, C_3-H), 7.36-7.91 (m, 9H, ArH), 8.14 (s, 1H, N=CH), 10.89 (s, 1H, NH). ^{13}C NMR (75 MHz, CDCl3) δ (ppm): 41.3, 45.8, 59.8, 69.2, 98.1, 125.3, 126.3, 126.4, 126.5, 127.13, 129.4, 130.1, 132.6, 134.9, 140.9, 147.2, 149.7, 169.3, 170.2. Anal. Calcd. for $C_{21}H_{18}N_6O_4S$: C, 55.99; H, 4.03; N, 18.66; S, 7.12%. Found: C, 55.96; H, 3.97; N, 18.61; S, 7.07%.

(R,Z)-N'-(3-nitrobenzylidene)-2-(3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol 2(3H)-yl) acetohydrazide (4h). IR (KBr, cm^{-1}): υ = 3345 (NH), 1667 (C=O), 1629 (C=N), 1596 (C=C), 1550 (N=CH), 1515, 1338 (NO_2). ^{1}H NMR (300 MHz, CDCl3) δ (ppm): 3.36 (t, 2H, *J* = 5.12 Hz, CH_2), 3.54 (s, 2H, N-CH_2-CO), 3.82 (t, 2H, *J* = 5.75 Hz, CH_2), 4.52 (s, 1H, C_3-H), 7.43-8.12 (m, 10H, ArH + N=CH), 10.74 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 41.2, 46.0, 60.2, 69.3, 98.7, 121.4, 125.6, 126.1, 126.2, 126.3, 128.1, 130.5, 131.8, 135.7, 141.2, 146.11, 149.6, 169.5, 170.1. Anal. Calcd. for $C_{21}H_{18}N_6O_4S$: C, 55.99; H, 4.03; N, 18.66; S, 7.12%. Found: C, 55.95; H, 4.07; N, 18.62; S, 7.09%.

(R,Z)-N'-(4-nitrobenzylidene)-2-(3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol 2(3H)-yl) acetohydrazide (4i). IR (KBr, cm^{-1}): υ = 3467 (NH), 1671 (C=O), 1636 (C=N), 1597 (C=C), 1555 (N=CH), 1516, 1337 (NO_2). ^{1}H NMR (300 MHz, CDCl3) δ (ppm): 3.46 (t, 2H, *J* = 4.98 Hz, CH_2), 3.60 (s, 2H, N-CH_2-CO), 3.71 (t, 2H, *J* = 5.73 Hz, CH_2), 4.50 (s, 1H, C_3-H), 7.31-8.01 (m, 9H, ArH), 8.15 (s, 1H, N=CH), 10.79 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 41.3, 46.1, 59.21, 70.0, 98.5, 125.6, 125.9, 126.17, 126.2, 128.1, 133.4, 135.6, 140.6, 148.1, 150.7, 170.1, 170.2. Anal. Calcd. for $C_{21}H_{18}N_6O_4S$: C, 55.99; H, 4.03; N, 18.66; S, 7.12%. Found: C, 55.93; H, 3.98; N, 18.61; S, 7.10%.

(R,Z)-N'-(furan-2-ylmethylene)-2-(3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol 2(3H)-yl) acetohydrazide (4j). IR (KBr, cm^{-1}): υ = 3455 (NH), 1664 (C=O), 1639 (C=N), 1607 (C=C), 1548 (N=CH). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.52-3.61 (m, 4H, CH_2 + N-CH_2-CO), 3.85 (t, 2H, *J* = 5.15 Hz, CH_2), 4.55 (s, 1H, C_3-H), 6.45-7.97 (m, 8H, ArH), 8.07 (s, 1H, N=CH), 10.77 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 41.6, 46.7, 61.1, 69.8, 97.9, 112.9, 113.1, 126.3, 126.4, 126.6, 130.7, 131.5, 138.9, 140.0, 149.4, 169.2, 170.2. Anal. Calcd. for $C_{19}H_{17}N_5O_3S$: C, 57.71; H, 4.33; N, 17.71; S, 8.11%. Found: C, 57.76; H, 4.29; N, 17.68; S, 8.09%.

N-((3S,4S)-3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-((R)-3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetamide (5a). IR (KBr, cm^{-1}): υ= 3466 (NH), 1749 (CO, β-lactam), 1661 (CONH), 1635 (C=N), 1613 (C=C), 1250, 1049 (C-S-C), 1109 (C-N), 714

(C-Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.36 (t, 2H, *J* = 5.02 Hz, CH_2), 3.49 (s, 2H, N-CH_2-CO), 3.66 (t, 2H, *J* = 5.70 Hz, CH_2), 4.47 (s, 1H, C_3-H), 5.21 (d, 1H, *J* = 4.95 Hz, CH-Ar), 5.47 (d, 1H, *J* = 4.95 Hz, CH-Cl of azetidinone ring), 7.19-7.71 (m, 10H, ArH), 8.34 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 42.1, 47.0, 59.6, 63.7, 65.4, 68.8, 99.1, 125.7, 125.8, 126.0, 126.2, 126.3, 126.4, 135.2, 141.2, 150.0, 162.4, 169.2, 170.3. Anal. Calcd. for $C_{23}H_{20}N_5O_3SCl$: C, 57.32; H, 4.18; N, 14.53; S, 6.65%. Found: C, 57.28; H, 4.15; N, 14.49; S, 6.61%.

N-((3S,4S)-3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-((R)-3-(p-tolyl)-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetamide (5b). IR (KBr, cm^{-1}): υ = 3454 (NH), 1753 (CO, β-lactam), 1668 (CONH), 1639 (C=N), 1603 (C=C), 1246, 1042 (C-S-C), 1132 (C-N), 719 (C-Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.25 (s, 3H, CH_3), 3.34 (t, 2H, *J* = 5.15 Hz, CH_2), 3.50 (s, 2H, N-CH_2-CO), 3.61 (t, 2H, *J* = 5.68 Hz, CH_2), 4.58 (s, 1H, C_3-H), 5.17 (d, 1H, *J* = 5.05 Hz, CH-Ar), 5.36 (d, 1H, *J* = 5.05 Hz, CH-Cl of azetidinone ring), 7.12-7.49 (m, 9H, ArH), 8.29 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 23.6, 41.7, 47.3, 59.6, 62.7, 63.8, 68.4, 101.0, 126.3, 126.4, 126.6, 126.8, 127.1, 134.1, 135.0, 139.1, 150.0, 161.2, 169.3, 169.8. Anal. Calcd. for $C_{24}H_{22}N_5O_3SCl$: C, 58.12; H, 4.47; N, 14.12; S, 6.46%. Found: C, 58.10; H, 4.43; N, 14.16; S, 6.42%.

N-((3S,4S)-3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-((R)-3-(3-methoxyphenyl)-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetamide (5c). IR (KBr, cm^{-1}): υ = 3461 (NH), 1746 (CO, β-lactam), 1650 (CONH), 1643 (C=N), 1597 (C=C), 1254, 1053 (C-S-C), 1112 (C-N), 722 (C-Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.49 (t, 2H, *J* = 5.13 Hz, CH_2), 3.63-3.92 (m, 7H, CH_2 + N-CH_2-CO + OCH_3), 4.53 (s, 1H, C_3-H), 5.10 (d, 1H, *J* = 5.10 Hz, CH-Ar), 5.31 (d, 1H, *J* = 5.10 Hz, CH-Cl of azetidinone ring), 7.02-7.45 (m, 9H, ArH), 8.31 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 41.8, 46.7, 56.1, 60.2, 63.4, 65.6, 69.1, 99.8, 111.5, 114.1, 118.3, 125.7, 125.9, 126.1, 128.4, 135.0, 142.9, 150.2, 161.1, 162.4, 169.2, 170.2. Anal. Calcd. for $C_{24}H_{22}N_5O_4SCl$: C, 56.30; H, 4.33; N, 13.68; S, 6.26%. Found: C, 56.24; H, 4.37; N, 13.62; S, 6.22%.

N-((3S,4S)-3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-((R)-3-(3-chlorophenyl)-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetamide (5d). IR (KBr, cm^{-1}): υ = 3442 (NH), 1748 (CO, β-lactam), 1659 (CONH), 1648 (C=N), 1610 (C=C), 1268, 1041 (C-S-C), 1127 (C-N), 718 (C-Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.18 (t, 2H, *J* = 5.05 Hz, CH_2), 3.41 (s, 2H, N-CH_2-CO), 3.71 (t, 2H, *J* = 5.60 Hz, CH_2), 4.54 (s, 1H, C_3-H), 5.27 (d, 1H, *J* = 4.85 Hz, CH-Ar), 5.41 (d, 1H, *J* = 4.85 Hz, CH-Cl of azetidinone ring), 6.98-7.51 (m, 9H, ArH), 8.15 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 41.6, 47.3, 60.2, 62.1, 63.8, 69.1, 100.3, 125.7, 126.1, 126.2, 126.3, 126.4, 126.6, 129.2, 129.4, 134.8, 142.2, 149.6, 161.6, 169.8, 170.1. Anal. Calcd. for $C_{23}H_{19}N_5O_3SCl_2$: C, 53.49; H, 3.71; N, 13.56; S, 6.21%. Found: C, 53.42; H, 3.68; N, 13.52; S, 6.17%.

N-((3S,4S)-3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-((R)-3-(3-bromophenyl)-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetamide (5e). IR (KBr, cm^{-1}): υ = 3449 (NH), 1756 (CO, β-lactam), 1644 (CONH), 1643 (C=N), 1605 (C=C), 1256, 1062 (C-S-C), 1119 (C-N), 723 (C-Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.22 (t, 2H, *J* = 4.98 Hz, CH_2), 3.43 (s, 2H, N-CH_2-CO), 3.58 (t, 2H, *J* = 5.65 Hz, CH_2), 4.49 (s, 1H, C_3-H), 5.14 (d, 1H, *J* = 5.05 Hz, CH-Ar), 5.52 (d, 1H, *J* = 5.05 Hz, CH-Cl of azetidinone ring), 7.13-7.67 (m, 9H, ArH), 8.12 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 42.0, 47.3, 59.6, 62.5, 63.61, 69.1, 99.11, 123.2, 125.6, 126.1, 126.3, 126.4, 128.8, 129.1, 129.6, 134.1, 143.4, 150.2, 162.0, 169.6, 169.9. Anal. Calcd for $C_{23}H_{19}N_5O_3SBrCl$: C, 49.25; H, 3.41; N, 12.49; S, 5.72%. Found: C, 49.21; H, 3.37; N, 12.43; S, 5.77%.

N-((3S,4S)-3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-((R)-3-(2-hydroxyphenyl)-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetamide (5f). IR (KBr, cm^{-1}): υ = 3582 (Ar-OH), 3463 (NH), 1752 (CO, β-lactam), 1646 (CONH), 1630 (C=N), 1607 (C=C), 1232, 1029 (C-S-C), 1124 (C-N), 716 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.13 (t, 2H, *J* = 5.10 Hz, CH_2), 3.40 (s, 2H, N-CH_2-CO), 3.55 (t, 2H, *J* = 5.70 Hz, CH_2), 4.51 (s, 1H, C_3-H), 5.31 (d, 1H, *J* = 5.10 Hz, CH-Ar), 5.57 (d, 1H, *J* = 5.10 Hz, CH-Cl of azetidinone ring), 6.67-6.94 (m, 9H, ArH), 7.91 (s, 1H, NH), 9.73 (s, 1H, Ar-OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 41.8, 47.2, 57.4, 61.12, 65.7, 68.6, 98.4, 116.6, 120.09, 126.5, 126.6, 126.7, 126.96, 127.0, 128.2, 135.0, 150.2, 152.2, 163.3, 169.4, 169.8. Anal.

Calcd. for $C_{23}H_{20}N_5O_4SCl$: C, 55.48; H, 4.05; N, 14.06; S, 6.44%. Found: C, 55.43; H, 3.98; N, 14.11; S, 6.42%.

N-((3S,4S)-3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-((R)-3-(2-nitrophenyl)-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetamide (5g). IR (KBr, cm^{-1}): υ = 3450 (NH), 1749 (CO, β-lactam), 1648 (CONH), 1523, 1334 (NO_2), 1644 (C=N), 1613 (C=C), 1238, 1038 (C-S-C), 1121 (C-N), 721 (C-Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.31 (t, 2H, *J* = 5.03 Hz, CH_2), 3.51 (s, 2H, N-CH_2-CO), 3.72 (t, 2H, *J* = 5.65 Hz, CH_2), 4.46 (s, 1H, C_3-H), 5.25 (d, 1H, *J* = 5.12 Hz, CH-Ar), 5.40 (d, 1H, *J* = 5.12 Hz, CH-Cl of azetidinone ring), 7.41-8.11 (m, 9H, ArH), 8.23 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 42.0, 47.1, 58.1, 61.7, 62.7, 69.2, 100.3, 124.1, 126.4, 126.5, 126.6, 126.7, 126.8, 133.2, 135.1, 138.04, 145.3, 150.1, 160.4, 169.3, 170.0.
Anal. Calcd. for $C_{23}H_{19}N_6O_5SCl$: C, 52.42; H, 3.63; N, 15.95; S, 6.08%. Found: C, 52.38; H, 3.67; N, 15.92; S, 6.04%.

N-((3S,4S)-3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-((R)-3-(3-nitrophenyl)-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol -2(3H)-yl) acetamide (5h). IR (KBr, cm^{-1}): υ = 3446 (NH), 1752 (CO, β-lactam), 1654 (CONH), 1520, 1338 (NO_2), 1649 (C=N), 1611 (C=C), 1249, 1034 (C-S-C), 1123 (C-N), 718 (C-Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.47 (t, 2H, *J* = 5.11 Hz, CH_2), 3.63 (s, 2H, N-CH_2-CO), 3.81 (t, 2H, *J* = 5.65 Hz, CH_2), 4.58 (s, 1H, C_3-H), 5.12 (d, 1H, *J* = 4.95 Hz, CH-Ar), 5.43 (d, 1H, *J* = 4.95 Hz, CH-Cl of azetidinone ring), 7.18-7.98 (m, 9H, ArH), 8.25 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 41.7, 47.0, 59.7, 60.0, 64.6, 68.76, 99.1, 123.3, 124.2, 126.3, 126.4, 126.6, 127.0, 131.1, 135.0, 143.4, 146.4, 149.6, 163.1, 169.3, 170.1. Anal. Calcd. for $C_{23}H_{19}N_6O_5SCl$: C, 52.42; H, 3.63; N, 15.95; S, 6.08%. Found: C, 52.47; H, 3.60; N, 15.91; S, 6.02%.

N-((3S,4S)-3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-((R)-3-(4-nitrophenyl)-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetamide (5i). IR (KBr, cm^{-1}): υ = 3457 (NH), 1757 (CO, β-lactam), 1650 (CONH), 1524, 1331 (NO_2), 1636 (C=N), 1615 (C=C), 1248, 1041 (C-S-C), 1130 (C-N), 720 (C-Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.38 (t, 2H, *J* = 5.05 Hz, CH_2), 3.58 (s, 2H, N-CH_2-CO), 3.65 (t, 2H, *J* = 5.70 Hz, CH_2), 4.51 (s, 1H, C_3-H), 5.19 (d, 1H, *J* = 5.10 Hz, CH-Ar), 5.38 (d, 1H, *J* = 4.80 Hz, CH-Cl of azetidinone ring), 7.36-8.10 (m, 9H, ArH), 8.31 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 42.15, 46.8, 61.0, 62.7, 65.1, 69.1, 99.8, 124.5, 126.0, 126.1, 126.2, 126.4, 134.7, 144.5, 148.4, 150.0, 162.4, 169.2, 170.2. Anal. Calcd. for $C_{23}H_{19}N_6O_5SCl$: C, 52.42; H, 3.63; N, 15.95; S, 6.08%. Found: C, 52.39; H, 3.58; N, 15.91; S, 6.11%.

N-((3S,4S)-3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-((R)-3-(furan-2-yl)-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetamide (5j). IR (KBr, cm^{-1}) υ = 3452 (NH), 1751 (CO, β-lactam), 1652 (CONH), 1638 (C=N), 1598 (C=C), 1258, 1066 (C-S-C), 1124 (C-N), 715 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.25 (t, 2H, *J* = 5.11 Hz, CH_2), 3.42 (s, 2H, N-CH_2-CO), 3.62 (t, 2H, *J* = 5.66 Hz, CH_2), 4.63 (s, 1H, C_3-H), 5.27 (d, 1H, *J* = 5.05 Hz, CH-Ar), 5.51 (d, 1H, *J* = 4.95 Hz, CH-Cl of azetidinone ring), 7.05-7.48 (m, 8H, ArH), 8.28 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 41.7, 47.1, 59.2, 59.3, 61.3, 67.8, 100.1, 106.1, 109.2, 125.8, 126.0, 126.1, 135.5, 139.2, 149.3, 150.1, 162.0, 169.1, 170.1. Anal. Calcd. for $C_{21}H_{18}N_5O_4SCl$: C, 53.45; H, 3.84; N, 14.84; S, 6.79%. Found: C, 53.41; H, 3.80; N, 14.79; S, 6.73%.

RESULTS AND DISCUSSION

In this study, we have prepared new 2-azetidinone derivatives and related Schiff bases from (R)-3-phenyl-2,3,6,7-tetrahydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazole 1. Compound 1 was condensed with ethylchloro acetate in refluxing absolute ethanol to give ethyl (R) 2-(3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazole-2(3H)-yl) acetate 2. In the IR spectra of compound 2, the absence of the absorption pertaining to the NH group and the appearance of the absorption at 1636-1649 cm^{-1}, the characteristic absorption of the carbonyl group, are good evidence of the expected reaction. In addition, in the ^{1}H NMR spectrum of compound 2, additional signals derived from the ester group were observed at 1.25 (COOCH$_2$<u>CH$_3$</u>=3H), 4.20 (COO<u>CH$_2$</u>CH$_3$=2H) and 3.57 (N-CH_2-CO) ppm. (R) 2-(3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetohydrazide 3 was prepared from compound 2 and hydrazine hydrate in ethanol. The IR spectrum of 3 showed the absorption bands

Table 1. Compounds 4a-j and 5a-j Derivatives

Comp.	Substitution R	M.W.	M.P. (°C)	Yield (%)
2	-	331.39	138-140	75
3	-	317.37	153-155	65
4a	C_6H_5	405.48	145-147	57
4b	4-$CH_3C_6H_4$	419.50	165-167	61
4c	3-$OCH_3C_6H_4$	435.50	181-183	54
4d	3-ClC_6H_4	439.92	171-173	55
4e	3-BrC_6H_4	484.37	186-188	53
4f	2-OHC_6H_4	421.48	175-177	68
4g	2-$NO_2C_6H_4$	450.47	203-205	60
4h	3-$NO_2C_6H_4$	450.47	196-198	54
4i	4-$NO_2C_6H_4$	450.47	164-166	68
4j	C_4H_3O (Furyl)	395.44	171-173	51
5a	C_6H_5	471.92	223-225	62
5b	4-$CH_3C_6H_4$	485.94	199-201	55
5c	3-$OCH_3C_6H_4$	501.94	238-240	53
5d	3-ClC_6H_4	506.36	270-272	58
5e	3-BrC_6H_4	550.81	254-256	56
5f	2-OHC_6H_4	487.92	249-251	61
5g	2-$NO_2C_6H_4$	516.91	261-263	63
5h	3-$NO_2C_6H_4$	516.91	278-280	55
5i	4-$NO_2C_6H_4$	516.91	286-288	62
5j	C_4H_3O (Furyl)	461.88	230-232	53

of NH_2NH_2 group at 3345-3371 cm^{-1}. ^1H NMR spectrum of compound 3 exhibited signals at 7.80 and 4.47 ppm for -NH and -NH_2 (D_2O exchangeable) of hydrazide, respectively. In the next step, Schiff bases 4a-j were prepared by the condensation of (R) 2-(3-phenyl-6,7-dihydroimidazo [2', 1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetohydrazide 3 with various aromatic aldehydes. The reaction of compounds 4a-j with chloroacetyl chloride in the presence of triethylamine underwent dehydrative annulation to afford N-((3S,4S)-3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-((R)-3-(aryl)-6,7-dihydroimidazo [2',1':2,3] thiazolo [5,4-d] isoxazol-2(3H)-yl) acetamide 5a-j. The IR spectra of the

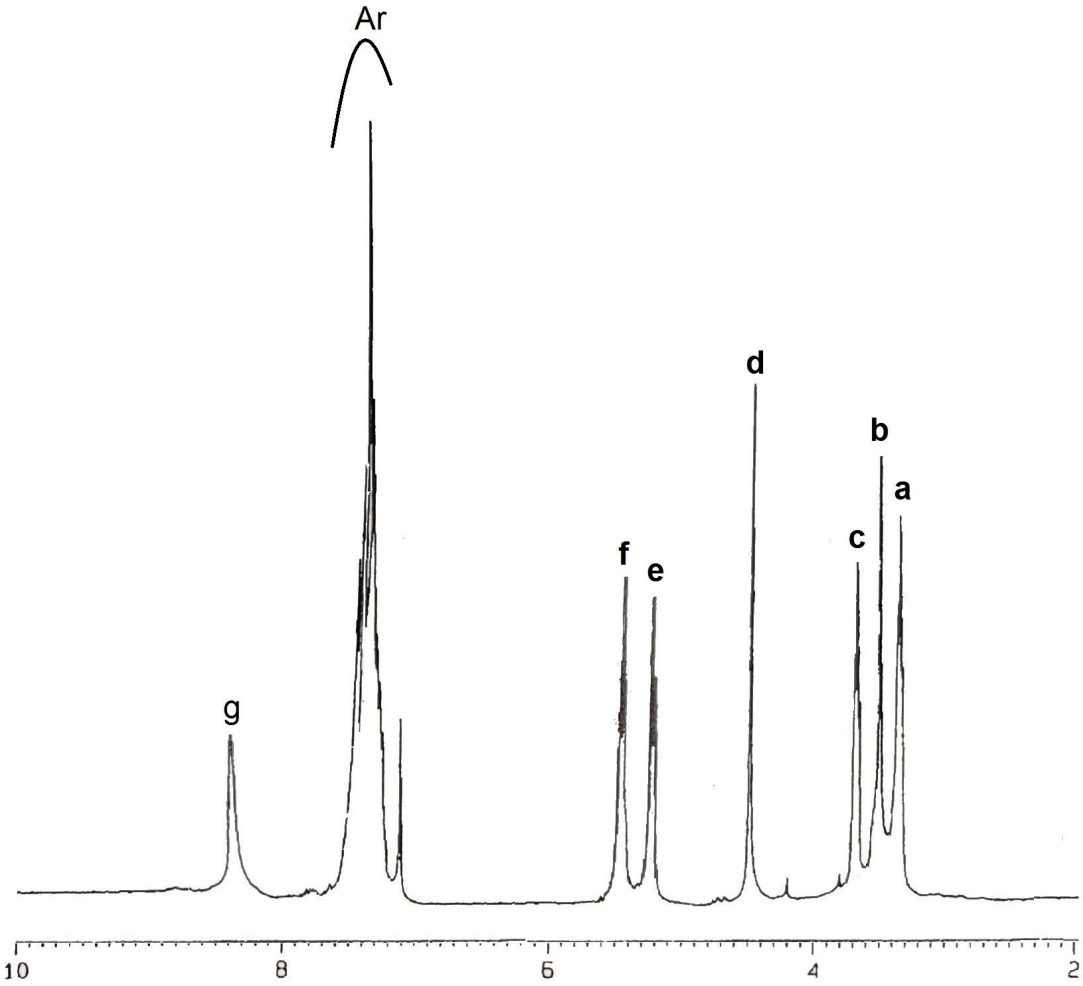

Fig. 1. N-((3S, 4S)-3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-((R)-3-phenyl-6,7-dihydroimidazo [2',1':2,3] thiazolo [5, 4-d] isoxazol-2(3H)-yl) acetamide.

compounds 5a-j showed strong absorption band in the region of 1748-1757 cm^{-1} characteristic of the β-lactam group. For example, ^{1}H NMR spectrum of compound 5a is shown in Fig. 1. Assignments of each proton are also presented in the figure, and the spectrum agrees well with the proposed compound 5a structure. These reactions are summarized in Scheme 1. In the present work the formulas of all compounds were found by elemental analysis and their structures were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra data. The yields of all products after recrystallization from appropriate solvent are shown in Table 1.

CONCLUSIONS

In succinct, a series of novel 2-azetidinone derivatives were synthesized *via* a sequence involving coupling of Schiff base derivatives with chloroacetyl chloride and triethylamine. The structure of all new compounds was proved using spectral methods. It can be concluded that this class of compounds certainly holds great promise towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress. We hope that our research work assists all those interested in this promising class of

heterocyclic compounds to make decision in the choice of targets and tasks for further investigations.

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