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Synthesis of Some 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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Abstract

2-Azetidinones, commonly known as β -lactams, are well-known heterocyclic compounds. Herein we described 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 3-phenyl-2, 3, 6, 7-tetrahydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazole 1 that has been synthesized in recent literature [1]. In the first, 3-phenyl-2, 3, 6, 7-tetrahydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazole 1 on condensation with ethylchloro acetate yielded ethyl 2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazole-2(3H)-yl) acetate 2, which on amination with hydrazine hydrate yielded 2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) acetohydrazide 3. Then Compound 3, on condensation with various aromatic aldehydes was converted to Schiff base derivatives 4a-j, which upon dehydrative annulation in the presence of chloroacetyl chloride and triethylamine yielded 3-chloro-4-(Aryl)-1-(2-oxo-2-(3-phenyl-5, 6-dihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) ethylamino) azetidin-2-one 5a-j. All synthesized compounds were characterized by elemental analyses, IR, ^{1}H-NMR and ^{13}C-NMR data.

Keywords: imidazo [2, 1- b] [1, 3] thiazole; heterocyclic compounds; synthesis; Schiff bases; 2-azetidinones; β-lactam

Introduction

Monocyclic β-lactams are an important class of hetero cyclic compounds because of their use in the synthesis of biologically active classical or non-classical β-lactam antibiotics [2, 3]. The activity of the famous antibiotics such as penicillins, cephalosporins and carbapenems are attributed to the presence of 2-azetidinone ring in them. Azetidinones can be prepared from Schiff's bases. 2-Azetidines have been extensively investigated by the organic chemists due to their close association with various types of biological activities [4-7]. 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 [8-11]. The β -lactams also serve as synthons for many biologically important classes of organic compounds [12]. Due to this, the chemistry and biology of these compounds continue to appeal the synthetic and medicinal organic chemists [13-15]. They also function as enzyme inhibitors and are effective on the central nervous system [16]. In this paper we turned our attention to synthesis of some new 2-azetidinones derivatives and their related Schiff bases obtained from the reaction of 2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) acetohydrazide **3**, with various aldehydes (Scheme 1).

Materials and Methods

Experimental Section

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 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DRX-300 (300 MHz) NMR instrument using DMSO-d_6 and $CDCl_3$ as solvent and TMS as internal standard. 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 2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazole-2(3H)-yl) acetate (2)

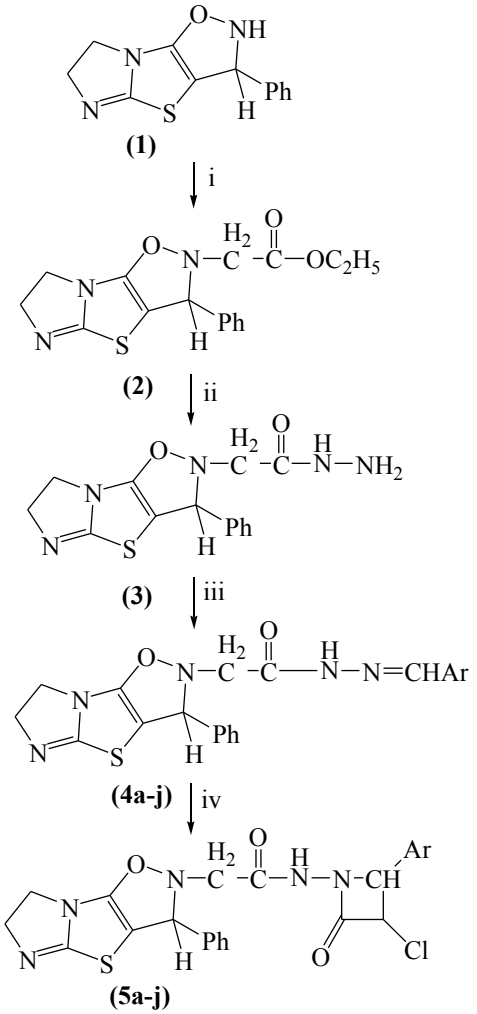
To a solution of 3-phenyl-2, 3, 6, 7-tetrahydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazole **1** (0.003 mol, 0.7359 g) in absolute ethanol (20 ml), ethyl chloroacetate (0.006 mol, 0.7355 g) was added. The mixture was refluxed under stirring for 2h in the presence of KOH (0.003 mol, 0.1683 g). Then, the reaction mixture was evaporated under reduced pressure and the residue was purified by H_2O:C_2H_5OH (1:1) to give pure products.

Yield 75%, m.p. 138-140 °C. 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= 5.11 Hz, CH_2), 3.43 (t, 2H, J= 5.85 Hz, CH_2), 3.57 (s, 2H, N-CH_2-CO), 4.20 (q, 2H, J= 3.75 Hz, -$COO\underline{CH_2}CH_3$), 4.55 (s, 1H, C_3-H), 7.42 (m, 5H, Ar-H). ^{13}C-NMR (300 MHz, DMSO-d_6) δ/ppm: 15.30, 41.10, 47.25, 57.42, 61.43, 68.38, 98.64, 126.48, 126.57, 126.86, 134.86, 149.18, 169.32, 171.04. 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 %.

Synthesis of 2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] 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 3h. 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**.

Yield 65%, m.p. 153-155 °C. 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=5.25 Hz, CH_2), 3.49 (t, 2H, J= 5.80 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 (300 MHz, DMSO-d_6) δ/ppm: 40.75, 46.07, 59.73, 67.89, 98.65, 126.91, 127.09, 127.16, 133.86, 149.26, 170.11, 170.54. 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 %.



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

Ar: C_6H_6, 4-$CH_3C_6H_5$, 3-$OCH_3C_6H_5$, 3-ClC_6H_5, 3-BrC_6H_5, 2-OHC_6H_5, 2-$NO_2C_6H_5$, 3-$NO_2C_6H_5$, 4-$NO_2C_6H_5$, C_4H_3O (2-Furyl).

Reaction condition: i: $ClCH_2COOEt$, EtOH, reflux; ii: NH_2NH_2 H_2O,reflux; iii: RCHO, reflux; iv:$ClCH_2COCl$, Et_3N,reflux

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), the appropriate aldehyde (0.0006 mol), 4-5 drops of glacial acetic acid (as a catalyst) was added. The reaction mixture was refluxed for 2-6 h. The reaction mixture was allowed to cool and was poured into water (15-20 mL). The solid substance was filtered off and crystallized from appropriate solvent to give compound **4a-j**.

N'-benzylidene-2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol 2(3H)-yl) acetohydrazide (4a)

Yield 57%, m.p. 145-147 °C. IR (KBr, cm^{-1}): υ= 3468 (NH), 1658 (C=O), 1622 (C=N), 1593 (C=C), 1540 (N=CH). ^{1}H-NMR (300 MHz, DMSO-d_6) 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 (300 MHz, DMSO-d_6) δ/ppm: 41.47, 46.68, 61.44, 69.06, 98.16, 126.25, 126.34, 126.48, 127.15, 127.35, 129.56, 131.14, 135.51, 141.53, 149.38, 169.83, 171.12. 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 %.

N'-(4-methylbenzylidene)-2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol 2(3H)-yl) acetohydrazide (4b)

Yield 61%, m.p. 165-167 °C. 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 (300 MHz, CDCl3) δ/ppm: 22.12, 40.95, 46.08, 60.81, 69.02, 98.93, 126.22, 126.31, 126.53, 128.28, 128.40, 129.06, 134.65, 138.43, 142.37, 149.86, 170.06, 170.39. 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 %.

N'-(3-methoxybenzylidene)-2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol 2(3H)-yl) acetohydrazide (4c)

Yield 54%, m.p. 181-183 °C. 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 (300 MHz, CDCl3) δ/ppm: 41.31, 46.48, 57.24, 61.36, 68.89, 99.45, 117.63, 118.12, 120.41, 126.33, 126.51, 126.68, 128.07, 132.84, 135.49, 142.39, 150.08, 158.73, 169.87, 170.95. 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 %.

N'-(3-chlorobenzylidene)-2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol 2(3H)-yl) acetohydrazide (4d)

Yield 55%, m.p. 171-173 °C. 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 (300 MHz, CDCl3) δ/ppm: 41.14, 46.33, 59.65, 68.74, 99.06, 126.34, 126.45, 126.67, 127.69, 128.33, 128.56, 128.74, 131.08, 132.42, 135.18, 141.05, 149.92, 169.82, 170.26. 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 %.

N'-(3-bromobenzylidene)-2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol 2(3H)-yl) acetohydrazide (4e)

Yield 53%, m.p. 186-188 °C. IR (KBr, cm^{-1}): υ= 3471 (NH), 1659 (C=O), 1637 (C=N), 1607 (C=C), 1540 (N=CH). ^{1}H-NMR (300 MHz, CDCl3) 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 (300 MHz, CDCl3) δ/ppm: 41.19, 46.27, 59.72, 68.59, 98.14, 125.62, 126.27, 126.35, 126.58, 126.73, 128.24, 128.46, 129.08, 132.57, 135.09, 142.25, 149.92, 169.73, 170.26. 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 %.

N'-(2-hydroxybenzylidene)-2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol 2(3H)-yl) acetohydrazide (4f)

Yield 68%, m.p. 175-177 °C. 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, CDCl3) 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 (300 MHz, CDCl3) δ/ppm: 40.76, 46.12, 60.21, 69.10, 97.89, 118.56, 119.14, 120.24, 126.31, 126.40, 126.52, 128.31, 129.14, 135.16, 141.66, 149.85, 158.69, 169.57, 170.03. 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 %.

N'-(2-nitrobenzylidene)-2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol 2(3H)-yl) acetohydrazide (4g)

Yield 60%, m.p. 203-205 °C. 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 (300 MHz, CDCl3) δ/ppm: 41.32, 45.88, 59.83, 69.26, 98.17, 125.34, 126.34, 126.48, 126.57, 127.13, 129.47, 130.16, 132.62, 134.98, 140.92, 147.23, 149.71, 169.36, 170.20. 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 %.

N'-(3-nitrobenzylidene)-2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol 2(3H)-yl) acetohydrazide (4h)

Yield 54%, m.p. 196-198 °C. IR (KBr, cm^{-1}): υ= 3345 (NH), 1667 (C=O), 1629 (C=N), 1596 (C=C), 1550 (N=CH), 1515, 1338 (NO2). ^{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 (300 MHz, CDCl3) δ/ppm: 41.20, 46.07, 60.24, 69.32, 98.76, 121.45, 125.61, 126.19, 126.27, 126.39, 128.10, 130.52, 131.84, 135.75, 141.22, 146.11, 149.69, 169.59, 170.16. 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 %.

N'-(4-nitrobenzylidene)-2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol 2(3H)-yl) acetohydrazide (4i)

Yield 68%, m.p. 164-166 °C. 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

(300 MHz, CDCl3) δ/ppm: 41.38, 46.16, 59.21, 70.02, 98.54, 125.63, 125.97, 126.17, 126.29, 128.13, 133.47, 135.64, 140.68, 148.15, 150.79, 170.12, 170.24. 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 %.

N'-(furan-2-ylmethylene)-2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol 2(3H)-yl) acetohydrazide (4j)

Yield 51%, m.p. 171-173 °C. IR (KBr, cm^{-1}): υ= 3455 (NH), 1664 (C=O), 1639 (C=N), 1607 (C=C), 1548 (N=CH). ^{1}H-NMR (300 MHz, DMSO-d_6) 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 (300 MHz, DMSO-d_6) δ/ppm: 41.63, 46.75, 61.10, 69.88, 97.91, 112.94, 113.18, 126.32, 126.45, 126.61, 130.72, 131.55, 138.97, 140.09, 149.46, 169.25, 170.22. 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 %.

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 4h 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 solid obtained was washed with water (30 mL), filtered and dried. The crude product obtained was purified by appropriate solvent to give compound **5a-j**.

3-chloro-4-phenyl-1-(2-oxo-2-(3-phenyl-5, 6-dihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) ethylamino) azetidin-2-one (5a)

Yield 62%, m.p. 223-225 °C. 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, DMSO-d_6) 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), 7.14-7.51 (m, 10H, ArH), 8.34 (s, 1H, NH). ^{13}C-NMR (300 MHz, DMSO-d_6) δ/ppm: 42.10, 47.03, 59.67, 63.78, 65.41, 68.89, 99.18, 125.76, 125.88, 126.08, 126.22, 126.35, 126.47, 135.29, 141.29, 150.03, 162.42, 169.23, 170.38. 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 %.

3-chloro-4-(4-methylphenyl)-1-(2-oxo-2-(3-phenyl-5, 6-dihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) ethylamino) azetidin-2-one (5b)

Yield 59%, m.p. 199-201 °C. 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 (300 MHz, CDCl3) δ/ppm: 23.65, 41.79, 47.33, 59.67, 62.79, 63.83, 68.47, 101.07, 126.35, 126.49, 126.66, 126.83, 127.11, 134.14, 135.07,

139.13, 150.07, 161.23, 169.35, 169.81. 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 %.

3-chloro-4-(3-methoxyphenyl)-1-(2-oxo-2-(3-phenyl-5, 6-dihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) ethylamino) azetidin-2-one (5c)

Yield 53%, m.p. 238-240 °C. 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, CDCl3) 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 (300 MHz, CDCl3) δ/ppm: 41.89, 46.74, 56.17, 60.28, 63.43, 65.68, 69.16, 99.83, 111.59, 114.15, 118.30, 125.76, 125.98, 126.10, 128.43, 135.05, 142.92, 150.29, 161.16, 162.47, 169.24, 170.22. 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 %.

3-chloro-4-(3-chlorophenyl)-1-(2-oxo-2-(3-phenyl-5, 6-dihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) ethylamino) azetidin-2-one (5d)

Yield 58%, m.p. 270-272°C. 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 (300 MHz, CDCl3) δ/ppm: 41.69, 47.34, 60.28, 62.14, 63.89, 69.13, 100.37, 125.79, 126.16, 126.25, 126.33, 126.49, 126.61, 129.23, 129.41, 134.80, 142.24, 149.64, 161.61, 169.83, 170.19. 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 %.

3-chloro-4-(3-bromophenyl)-1-(2-oxo-2-(3-phenyl-5, 6-dihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) ethylamino) azetidin-2-one (5e)

Yield 56%, m.p. 254-256°C. 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 (300 MHz, CDCl3) δ/ppm: 42.07, 47.31, 59.67, 62.57, 63.61, 69.19, 99.11, 123.26, 125.64, 126.19, 126.31, 126.46, 128.87, 129.16, 129.68, 134.16, 143.41, 150.20, 162.08, 169.64, 169.93. 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 %.

3-chloro-4-(2-hydroxyphenyl)-1-(2-oxo-2-(3-phenyl-5, 6-dihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) ethylamino) azetidin-2-one (5f)

Yield 61%, m.p. 249-251°C. 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 (300 MHz, DMSO-d_6) δ/ppm: 41.81, 47.22, 57.45, 61.12, 65.70, 68.68, 98.47, 116.65, 120.09, 126.51, 126.63, 126.79, 126.96, 127.03, 128.23, 135.08, 150.29, 152.27, 163.30, 169.48, 169.82. 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 %.

3-chloro-4-(2-nitrophenyl)-1-(2-oxo-2-(3-phenyl-5, 6-dihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) ethylamino) azetidin-2-one (5g)

Yield 63%, m.p. 261-263°C. 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 (300 MHz, CDCl3) δ/ppm: 42.06, 47.19, 58.11, 61.79, 62.78, 69.26, 100.33, 124.12, 126.46, 126.55, 126.62, 126.78, 126.89, 133.23, 135.19, 138.04, 145.36, 150.12, 160.42, 169.31, 170.09. 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 %.

3-chloro-4-(3-nitrophenyl)-1-(2-oxo-2-(3-phenyl-5, 6-dihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) ethylamino) azetidin-2-one (5h)

Yield 55%, m.p. 278-280°C. 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 (300 MHz, CDCl3) δ/ppm: 41.75, 47.06, 59.72, 60.03, 64.69, 68.76, 99.12, 123.32, 124.28, 126.32, 126.48, 126.60, 127.06, 131.18, 135.01, 143.41, 146.43, 149.64, 163.12, 169.31, 170.17. 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 %.

3-chloro-4-(4-nitrophenyl)-1-(2-oxo-2-(3-phenyl-5, 6-dihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) ethylamino) azetidin-2-one (5i)

Yield 62%, m.p. 286-288 °C. 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 (300 MHz, CDCl3) δ/ppm: 42.15, 46.89, 61.04, 62.73, 65.17, 69.11, 99.89, 124.58, 126.07, 126.18, 126.29, 126.46, 134.79, 144.51, 148.46, 150.07, 162.46, 169.22, 170.21. 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 %.

3-chloro-4-(furan-2-yl)-1-(2-oxo-2-(3-phenyl-5, 6-dihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) ethylamino) azetidin-2-one (5j)

Yield 51%, m.p. 230-232 °C. 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 (300 MHz, DMSO-d_6) δ/ppm: 41.74, 47.18, 59.22, 59.37, 61.37, 67.86, 100.17, 106.19, 109.28, 125.82, 126.05, 126.14, 135.53, 139.28, 149.39, 150.10, 162.04, 169.17, 170.13. 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 3-phenyl-2, 3, 6, 7-tetrahydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazole **1**. Compound **1** was condensed with ethylchloro acetate in refluxing absolute ethanol to give ethyl 2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazole-2(3H)-yl) acetate **2**. The IR spectra showed the absence of band ν(NH) at about 3170 cm^{-1} for **1** and the presence of bands at 1720 cm^{-1} for **2** corresponding to ν(C=O). Also, in the ^{1}H-NMR spectrum of compound **2**, additional signals derived from the ester group were observed at 1.25 ($COOCH_2CH_3$=3H), 4.20 ($COOCH_2CH_3$=2H) and 3.57 (N-CH_2-CO) ppm. 2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) acetohydrazide **3** were prepared from ethyl 2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazole-2(3H)-yl) acetate **2** and hydrazine hydrate in ethanol. The IR spectra of **3** showed the presence of broad bands in the region of 3345-3371cm^{-1} corresponding to ν($NHNH_2$). ^{1}H-NMR spectrum of compound **2** 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's bases **4a-j** were prepared by the condensation of 2-(3-phenyl-3, 6, 7-trihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) acetohydrazide **3** with various aromatic aldehydes. In the ^{1}H NMR spectra of **4a-j** the signal belonging to the NH_2 group of hydrazide structure was not appeared. Compounds **4a-j** on reaction with chloroacetyl chloride in the presence of triethylamine underwent dehydrative annulation to afford 3-chloro-4-(Aryl)-1-(2-oxo-2-(3-phenyl-5, 6-dihydroimidazo [2, 1-b] thiazolo [5, 4-d] isoxazol -2(3H)-yl) ethylamino) azetidin-2-one **5a-j**, According to the literature [18, 24]. The IR spectra of the compounds **5a-j** showed strong absorption band in the region of 1748-1757cm^{-1}characteristic of the β -lactam group. 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 determined by IR, ^{1}H-NMR and ^{13}C-NMR spectra data.

Conclusions:

In summary, a series of novel 2-Azetidinone derivatives were synthesized via a sequence involving coupling of Schiff base derivatives with chloroacetyl chloride and triethylamine. 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.

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Refereces

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