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An expeditious green synthesis of Schiff bases and azetidinones derivatised with 1,2,4-triazoles

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Abstract. An efficient green approach to the synthesis of Schiff bases (**11**–**21**) of 1-amino-2-aryl-3-oxo-1,2,4-triazoles (**1**–**3**) have been reported under $Mg(ClO_4)_2$ as catalyst followed by the reaction with chloroacetyl chloride in solvent-free conditions to yield the azetidinones (**22**–**32**) with excellent yields. The synthesized compounds were evaluated for the extent of penetration into biological membranes (*clogP*), drug-likeliness and finally drug score was calculated and also screened for antitubercular and antimicrobial activities.

Keywords. 1,2,4-Triazole; Schiff base; $Mg(ClO_4)_2$; azetidinone; solvent-free; drug score; MIC.

1. Introduction

Sydnones are extensively studied mesoionic compounds which have gained importance due to their use as synthons for heterocyclic systems.[1–4] Recent years have witnessed a great deal of interest in the synthesis and characterization of Schiff bases.[5] Several reports have shown that the presence of a lone pair of electrons in sp^2 hybridized orbital of nitrogen atom of the azomethine group has considerable chemical and biological importance.[6–12] Since the advent of penicillin, β-lactam antibiotic has been the subject of much discussion. The primary biological targets of the β-lactam antibacterial drugs are the penicillin binding proteins. A large number of 3-chloro monocyclic β-lactams possess powerful antibacterial, antimicrobial, antiinflammatory, anticonvulsant, antitubercular and enzyme inhibition activity.[13–19] Synthesis of Schiff bases have been described in variant conditions using sulphuric acid[20] and glacial acetic acid.[21] The need for effective β-lactams has motivated synthetic organic and medicinal chemists to design new functionalized 2-azetidinones.

Azetidinone synthesis has been described with various conditions of temperature and reaction durations.[22,23] The ring transformation of *N*-arylsydnones to 1,2,4-triazoles appended to azetidinone ring has not been attempted so far. Hence, it was thought of to study such type of moieties as shown in scheme 1. The demand for environmental friendly chemistry for organic transformations is increasingly popular. Lewis acid catalyst can interact with reagents containing a functional group having donor atom with non-bonded pairs of electrons. Depending on the substrates, the reaction gives rise to positively polarized complexes (tight ion pair) which then react with electron donor reagent (nucleophile). Reactions that are catalysed by protonic acids viz., sulphuric acid, phosphoric acid, PPA, HF may also be catalysed by Lewis acids. Magnesium perchlorate has been found to be an efficient catalyst for the synthesis of imines and phenylhydrazones from carbonyl compounds with amines and phenylhydrazine in high yields at room temperatures in short times. Especially, the condensation of less electrophilic carbonyl compounds with poorly nucleophilic amines afford the imines in excellent yields.[24] Therefore, we have reported the use of various Lewis acids in the synthesis of Schiff bases and their effect on the yields. Design of benign experimental method for the synthesis of azetidinones in solvent and solvent-free conditions is also reported in the present work. Further, the antibacterial and antitubercular activity analyses were carried out and MIC values were determined for the title compounds (**22**–**32**).

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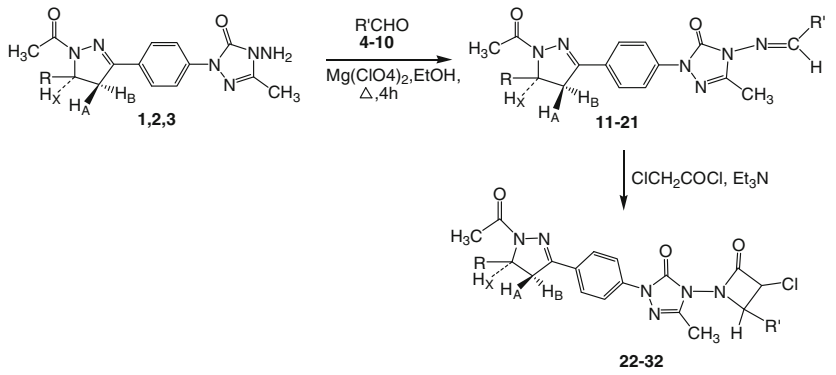

1; R = Ph, **2**; R = 4-HOC_6H_4 **3**; R = 4-$NO_2C_6H_4$ **4**; R′ = CH_3 **5;** R′ = C_6H_5 **6**; R′ = 2-HOC_6H_4 **7**; R′ = 4-HOC_6H_4 **8**; R′ = 4-$MeOC_6H_4$ **9**; R′ = 4-$NO_2C_6H_4$ **10**; R′ = 2-ClC_6H_4 **11**; R = Ph, R' = CH_3 **12**; R = Ph, R' = Ph; **13**; R = Ph, R' = 2-HOC_6H_4 **14**; R = Ph, R' = 4-HOC_6H_4 **15**; R = Ph, R' = 4-$MeOC_6H_4$ **16**; R = Ph, R' = 4-$NO_2C_6H_4$ **17**; R = Ph, R' = 2-ClC_6H_4 **18;** R = 4-OHC_6H_4,R' = CH_3 **19**; R = 4-HOC_6H_4, R' = 2-ClC_6H_4 **20**; R=4-$NO_2C_6H_4$, R' = CH_3 **21**; R = 4-$NO_2C_6H_4$, R' = 2-ClC_6H_4 **22**; R = Ph, R' = CH_3 **23;** R = Ph, R' = Ph; **24**; R=Ph, R'=2-HOC_6H_4 **25**; R = Ph, R' = 4-HOC_6H_4 **26**; R = Ph, R' = 4-$MeOC_6H_4$ **27**; R = Ph, R' = 4-$NO_2C_6H_4$ **28**; R = Ph, R' = 2-ClC_6H_4 **29**; R = 4-HOC_6H_4,R' = CH_3 **30**; R = 4-HOC_6H_4, R' = 2-ClC_6H_4 **31**; R = 4-$NO_2C_6H_4$, R' = CH_3, **32**; R = 4-$NO_2C_6H_4$, R' = 2-ClC_6H_4

Scheme 1. Formation of Schiff bases (**11–21**) and azetidinones (**22–32**).

2. Experimental

2.1 *Materials, methods and instruments*

Melting points were determined in open capillaries. The IR spectra were recorded on Nicolet Impact 5200 USA FT IR spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on Bruker 300 MHz FT NMR spectrometer with TMS as an internal standard. Mass spectra were recorded on Shimadzu Japan QP2010 S model spectrometer and elemental analyses were carried out using Heraus CHN rapid analyzer. The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plate using hexane and ethyl acetate as eluent. The pharmacological evaluation was carried out at the Department of Microbiology and Immunology, NGH college of Dental sciences, Belgaum, Karnataka, India. The OSIRIS property explorer was used to evaluate mutagenicity, tumorigenicity, irritability, reproductive effects, *clogP* values, drug-likeliness and drug score of the title compounds.

2.2 *General method for the synthesis of 2-[4-(1-acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-4-alkyl/arylamino-5-methyl-3-oxo-2,4-dihydro-[1,2,4]-triazoles* **(11–21)**

Method 1: A mixture of the compound (**1–3**, 1 mmol), aldehyde (**4–10**, 1 mmol), conc. H_2SO_4 (2 drops) in ethanol (5 ml) were refluxed for 4 h on water bath. The reaction progress was monitored by TLC using hexane and ethyl acetate as eluents (8:2 v/v). After completion of the reaction, the reaction mixture was poured into water to get yellow solid which on recrystallisation gave Schiff bases (**11–21**) in poor yields.

Method 2: A mixture of the compound (**1–3**, 1 mmol), aldehyde (**4–10**, 1 mmol) in dichloroethane (5 ml) and magnesium perchlorate (0.005 mol%) was refluxed for 3 h on water bath. The progress of reaction was monitored by TLC using hexane and ethyl acetate (9:1 v/v) as eluent. Magnesium perchlorate was removed by filtration and the solvent was removed *in vacuo* and the residue was recrystallized using solvents as indicated below to get the Schiff bases (**11–21**) in excellent yields.

2.2a *2-[4-(1-Acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-4-ethylidene amino-5-methyl-3-oxo-2,4-dihydro-[1,2,4]-triazole* **(11)**: $C_{22}H_{22}N_6O_2$, yield 65%, m.p. 190–1°C, Brown crystals (methanol), IR (KBr) ν_{max}: C=O 1709, 1662, C=N 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.23 (3H, d, CH_3), 2.14 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.44 (dd, 1H, CH_2, J = 12.05 Hz), 3.50 (dd, 1H, CH_2, J = 12.45 Hz), 3.74 (m, 1H, CH, J_{XA} = 3 Hz, J_{XB} = 9 Hz), 7.22–8.00 (m, 9H, Ar-H), 8.03 (s, 1H, N=CH); MS: m/z 402 (10), 376 (15), 361 (90), 334 (25), 319 (100), 304 (20), 279 (25), 263 (25), 242 (60), 235 (30), 216 (35), 201 (30), 191(25), 178 (25), 165 (25), 149 (20), 131 (40), 120 (35), 104 (35), 91 (35), 71 (40), 57 (50), 44 (80).

2.2b *2-[4-(1-Acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-4-(benzylidene-amino)-5-methyl-3-oxo-2, 4-dihydro-[1,2,4]-triazole* **(12)**: $C_{27}H_{24}N_6O_2$, yield 70%, m.p. 180–1°C, Brown solid (ethanol), IR (KBr) ν_{max}: C=O 1690, 1662, C=N 1604 cm^{-1}; ^1H NMR ($CDCl_3$): 2.54 (s, 3H, CH_3), 3.48 (dd, 1H, CH_2, $J = 10.88$ Hz), 3.71 (dd, 1H, CH_2 $J = 11.00$ Hz), 3.84 (m, 1H, CH, $J_{XA} = 4.38$ Hz, $J_{XB} = 11.31$ Hz), 7.25–8.09 (m, 14H, Ar-H), 9.88–9.93 (s, 1H, N=CH); MS: m/z 464 (15), 438 (10), 411 (80), 396 (20), 381 (100), 356 (20), 340 (25), 319 (25), 298 (65), 281 (30), 262 (35), 247 (40), 237 (30), 224 (25), 208 (25), 192 (25), 181 (20), 163 (42), 137 (35), 103 (30), 90 (35), 71 (45), 57 (50), 44 (80).

2.2c *2-[4-(1-Acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-4-[(2-hydroxy-benzylidene)-amino]-5-methyl-2-oxo-2,4-dihydro-[1,2,4]-triazole* **(13)**: $C_{27}H_{24}N_6O_3$, yield 75%, 185–6°C, Pale green crystals (methanol), IR (KBr) ν_{max}: OH 3400, C=O 1706, 1664, C=N 1602 cm^{-1}; ^1H NMR ($CDCl_3$): 2.20 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.48 (dd, 1H, CH_2, $J = 14.95$ Hz), 3.71 (dd, 1H, CH_2, $J = 15.10$ Hz), 3.84 (m, 1H, CH, $J_{XA} = 4.42$ Hz, $J_{XB} = 11.38$ Hz), 7.20–8.05 (m, 13H, Ar-H), 11.03 (s, 1H, OH, D_2O exchangeable), 9.89–10.06 (s, 1H, N=CH); MS: m/z 480 (100), 474 (60), 460 (10), 438 (90), 432 (25), 413 (25), 395 (70), 381 (30), 376 (50), 361 (55), 339 (20), 334 (55), 318 (100), 315 (40), 305 (40), 289 (10), 277 (15), 263 (90), 240 (40), 235 (35), 216 (30), 210 (25), 186 (40), 180 (60), 165 (25), 150 (45), 146 (60), 131 (50), 119 (80), 104 (55), 91 (95), 77 (60), 63 (70), 44 (50).

2.2d *2-[4-(1-Acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-4-[(4-hydroxy-benzylidene)-amino]-5-methyl-2-oxo-2,4-dihydro-[1,2,4]-triazole* **(14)**: $C_{27}H_{24}N_6O_3$, yield 75%, m.p. 176–7°C, Dark brown crystals (ethanol), IR (KBr) ν_{max}: OH 3414, C=O 1710, 1662, C=N 1604 cm^{-1}; ^1H NMR ($CDCl_3$): 2.25 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.47 (dd, 1H, CH_2, $J = 12.69$ Hz), 3.70 (dd, 1H, CH_2, $J = 12.89$ Hz), 3.90 (m, 1H, CH, $J_{XA} = 3.60$ Hz, $J_{XB} = 10.44$ Hz), 7.22–8.09 (m, 13H, Ar-H), 8.00 (s, 1H, N=CH), 11.00 (s, 1H, OH, D_2O exchangeable); MS: m/z 480 (100), 474 (60), 460 (10), 438 (90), 432 (25), 413 (25), 395 (70), 381 (30), 376 (50), 361 (55), 339 (20), 334 (55), 318 (100), 315 (40), 305 (40), 289 (10), 277 (15), 263 (90), 240 (40), 235 (35), 216 (30), 210 (25), 186 (40), 180 (60), 165 (25), 150 (45), 146 (60), 131 (50), 119 (80), 104 (55), 91 (95), 77 (60), 63 (70), 44 (50).

2.2e *2-[4-(1-Acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-4-[(4-anisylidene)-amino]-5-methyl-2-oxo-2,4-dihydro-[1,2,4]-triazole* **(15)**: $C_{27}H_{24}N_6O_2$, yield 60%, m.p. 180–1°C, Brown crystals (ethanol), IR (KBr) ν_{max}: C=O 1710, 1674, C=N 1604 cm^{-1}; ^1H NMR ($CDCl_3$): 2.19 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.42 (dd, 1H, CH_2, $J = 15.12$ Hz), 3.51 (dd, 1H, CH_2, $J = 15.35$ Hz), 3.70 (s, 3H, OCH_3), 3.81 (m, 1H, CH, $J_{XA} = 4.50$ Hz, $J_{XB} = 10.68$ Hz), 6.99–8.08 (m, 14H, Ar-H) 8.64 (s, 1H, N=CH); MS: m/z 494 (20), 468 (10), 441 (70), 396 (20), 426 (100), 411 (20), 386 (25), 370 (25), 349 (60), 328 (30), 311 (35), 292 (40), 277 (30), 267 (25), 254 (25), 238 (20), 222 (20), 211 (40), 193 (35), 167 (30), 133 (35), 120 (45), 101 (60), 87 (50) 74 (40) 71 (40), 57 (40), 43 (70).

2.2f *2-[4-(1-Acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-5-methyl-4-[(4-nitro benzylidene)-amino]-2-oxo-2,4-dihydro-[1,2,4]-triazole* **(16)**: $C_{27}H_{23}N_7O_4$, yield 75%, m.p. 185–6°C, Pale brown crystals (ethanol), IR (KBr) ν_{max}: C=O 1710, 1653, C=N 1605 cm^{-1}; ^1H NMR ($CDCl_3$): 2.40 (s, 3H, CH_3), 3.52 (dd, 1H, CH_2, $J = 14.89$ Hz), 3.76 (dd, 1H, CH_2, $J = 15.01$ Hz), 4.36 (m, 1H, CH, $J_{XA} = 4.80$ Hz, $J_{XB} = 8.25$ Hz), 7.27–8.29 (m, 13H, Ar-H), 8.75 (s, 1H, N=CH); MS: m/z 509 (M^+, 0.3), 504 (10), 489 (10), 464 (20), 460 (35), 445 (37), 412 (15), 383 (10), 376 (40), 361 (90), 345 (45), 332 (50), 319 (92), 304 (10), 277 (15), 257 (25), 242 (40), 233 (25), 216 (30), 201 (45), 216 (30), 201 (35), 178 (25), 152 (20), 131 (35), 104 (42), 91 (45), 83 (60), 57 (70), 43 (100).

2.2g *(E)-4-(2-Chlorobenzylideneamino)-2-(4-(1-acetyl-5-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-phenyl)-5-methyl-2-oxo-2,4,dihydro-[1,2,4]-triazole* **(17)**: $C_{24}H_{26}N_6O_2$, yield 50%, m.p. 175–6°C, Dark brown crystals (pet ether), IR (KBr) ν_{max}: OH 3415, C=O 1710, 1662, C=N 1605, cm^{-1}; ^1H NMR ($CDCl_3$): 2.40 (s, 3H, CH_3), 3.52 (dd, 1H, CH_2, $J = 15.06$ Hz), 3.76 (dd, 1H, CH_2, $J = 15.68$ Hz), 4.36 (m, 1H, CH, $J_{XA} = 3.60$ Hz, $J_{XB} = 10.44$ Hz), 5.15 (s, 1H, Ar-OH, D_2O exchangeable), 7.20–8.20 (m, 9H, Ar-H), 8.54 (s, 1H, N=CH); MS: m/z 432 (M^{+2}, 05), 430 (M^+, 15),

425 (0.3), 410 (10), 385 (10), 381 (20), 366 (35), 333 (37), 304 (15), 297 (10), 291 (10), 235 (30), 222 (25), 193 (25), 181 (20), 165 (15), 150 (25), 139 (30), 125 (30), 120 (30), 99 (30), 91 (25), 77 (25), 64 (40), 55 (42), 44 (100).

2.2h *(E)-2-(4-(1-Acetyl-5-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-4-(ethylideneamino)-5-methyl-2-oxo-2,4,dihydro-[1,2,4]-triazole* **(18)**: $C_{22}H_{22}N_6O_3$, yield 62%, m.p. 180–1°C, Brown crystals (methanol), IR (KBr) ν_{max}: OH 3440, C=O 1715, 1662, C=N 1604 cm^{-1}; ^1H NMR ($CDCl_3$): 1.25 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.42 (dd, 1H, CH_2, J = 12.03 Hz), 3.52 (dd, 1H, CH_2, J = 12.46 Hz), 4.90 (m, 1H, CH, J_{XA} = 4.50 Hz, J_{XB} = 8.70 Hz), 4.89 (s, 1H, Ar-OH, D_2O exchangeable), 6.55–7.45 (m, 8H, Ar-H), 7.50 (s, 1H, N=CH); MS: m/z: 418 (M^+, 74), 403 (15), 377 (15), 360 (90), 333 (25), 319 (100), 304 (20), 278 (25), 262 (30), 242 (60), 235 (30), 213 (33), 201 (30), 191(25), 178 (25), 165 (25), 149 (20), 135 (40), 120 (35), 104 (35), 90 (35), 71 (40), 57 (50), 43 (70).

2.2i *(E)-4-(2-Chlorobenzylideneamino)-2-(4-(1-acetyl-5-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-5-methyl-2-oxo-2H-[1,2,4]-triazole* **(19)**: $C_{27}H_{23}N_6ClO_3$, yield 72%, m.p. 180–1°C, Brown crystals (pet ether), IR (KBr) ν_{max}: C=O 1710, 1662, C=N 1605 cm^{-1}; ^1H NMR ($CDCl_3$): 2.21 (s, 3H,CH_3), 2.40 (s, 3H,CH_3), 3.20 (s, 1H, CH), 3.39 (dd, 1H, CH_2, J = 12.13 Hz), 3.52 (dd, 1H, CH_2, J = 12.78 Hz), 4.36 (m, 1H, CH, J_{XA} = 4.80 Hz, J_{XB} = 9.00 Hz), 5.00 (s, 1H, Ar-OH, D_2O exchangeable), 6.68–7.65 (m, 9H, Ar-H), 8.10 (s, 1H, N = CH); MS: m/z: 516 (M^{+2}, 28), 514 (M^+, 90), 516.15 (32), 515.16 (29), 517.15 (10), 516.16 (48), 515.15 (22), 518.16 (14), 500 (20), 470 (66), 455 (40), 430 (15), 425 (0.3), 410 (10), 385 (10), 381 (20), 366 (35), 333 (37), 304 (15), 297 (10), 291 (10), 235 (30), 222 (25), 193 (25), 181 (20), 165 (15), 150 (25), 139 (30), 125 (30), 120 (30), 99 (30), 91 (25), 77 (25), 64 (40), 55 (42), 44 (100).

2.2j *(E)-2-(4-(1-Acetyl-5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-4-(ethylideneamino)-5-methyl-2-oxo-2H-[1,2,4]-triazole* **(20)**: $C_{22}H_{21}N_7O_4$, yield 70%, m.p. 185–6°C, Brown crystals (methanol), IR (KBr) ν_{max}: C=O 1725, 1665, C=N 1610 cm^{-1}; ^1H NMR ($CDCl_3$): 1.32 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.45 (dd, 1H, CH_2, J = 11.93 Hz), 3.57 (dd, 1H, CH_2, J = 12.87 Hz), 4.92 (m, 1H, CH, J_{XA} = 3.60 Hz, J_{XB} = 8.43 Hz), 7.60–8.14 (m, 8H, Ar-H), 8.20 (s, 1H, N=CH); MS: m/z: 447 (M^+, 25), 418 (30), 405 (15), 378 (15), 362 (90), 333 (25), 320 (100), 304 (20), 278 (25), 262 (30), 242 (60), 235 (30), 213 (33), 201 (30), 191(25), 178 (25), 165 (25), 149 (20), 135 (40), 120 (35), 104 (35), 91 (35), 71 (40), 57 (50), 44 (70).

2.2k *(E)-4-(2-Chlorobenzylideneamino)-2-(4-(1-acetyl-5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-5-methyl-2-oxo-2H-[1,2,4]-triazole* **(21)**: $C_{27}H_{22}N_7ClO_4$, yield 70%, m.p. 210–1°C, Dark Brown crystals (pet ether), IR (KBr) ν_{max}: C=O 1717, 1665, C=N 1610 cm^{-1}; ^1H NMR ($CDCl_3$): 2.25 (s, 3H, CH_3), 3.45 (dd, 1H, CH_2, J = 11.98 Hz), 3.55 (dd, 1H, CH_2, J = 12.75 Hz), 4.80 (m, 1H, CH, J_{XA} = 3.30 Hz, J_{XB} = 11.4 Hz), 7.20–8.16 (m, 9H, Ar-H), 8.18 (s, 1H, N=CH); MS: m/z: 545 (M^{+2}, 07), 543 (M^+, 25), 516 (32), 517 (10), 515 (29), 500 (20), 470 (66), 455 (40), 430 (15), 425 (0.3), 410 (10), 385 (10), 382 (20), 366 (35), 335 (37), 304 (15), 300 (10), 291 (10), 235 (30), 222 (25), 193 (25), 181 (20), 165 (15), 150 (25), 139 (30), 125 (30), 120 (30), 99 (30), 91 (25), 77 (25), 64 (40), 55 (42), 43 (100).

2.3 *General method for the synthesis of 2-[4-(1-acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-alkyl/aryl]-4-(3-chloro-2-methyl-4-oxo-azetidin-1-yl)-5-methyl-3-oxo-2,4-dihydro-[1,2,4]-triazoles* **(15–25)**

Method 1: A mixture of compound (**11–21**) (1 mmol) and chloroacetyl chloride (1 mmol) in dioxane and triethylamine were stirred at 0–5°C for 3 h. The progress of reaction was monitored by TLC using hexane and methanol (8:2, v/v) mixture as eluent. The solvent was evaporated under pressure and the residue was recrystallised to get the azetidinone (**22–32**) in moderate yields.

Method 2: A paste of (**11–21**) (1 mmol), chloroacetyl chloride (1 mmol) and triethylamine were stirred at RT for 4 h in nitrogen. The progress of reaction was monitored by TLC (hexane and methanol, 8:2, v/v). The formed product was then extracted with dichloromethane and the organic layer was washed with $NaHCO_3$ (10%), HCl (10%) and dried over an. Na_2SO_4. Dicholoromethane was then evaporated under vacuo and crude product was then recrystallized to get azetidinone derivative (**22–32**) in excellent yield.

2.3a *2-[4-(1-Acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-4-(3-chloro-2-methyl-4-oxo-azetidin-1-yl)-5-methyl-3-oxo-2,4-dihydro-[1,2,4]-triazole* **(22)**: $C_{24}H_{23}N_6ClO_3$, yield 60%, m.p. 200–1°C, Dark brown crystals (ethanol), IR (KBr) ν_{max}: C=O 1758, 1714, 1662, C=N 1606 cm^{-1}; ^1H NMR ($CDCl_3$): 1.23 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.71 (dd, 1H, CH_2, J = 11.10 Hz), 4.08 (dd, 1H, CH_2, J = 11.98 Hz), 4.23 (d, 1H, CHCl), 4.71 (m, 1H, CH, J_{XA} = 3.32 Hz, J_{XB} = 9.43 Hz), 5.62 (m, 1H, N-CH), 7.20–8.00 (m, 9H, Ar-H); MS: m/z 476 (M^{+2}, 03), 474 (M^+,10), 441 (30), 418 (20), 402 (10), 376 (15), 361 (90), 334 (25), 319 (100), 304 (20), 279 (25), 263 (25), 242 (60), 235 (30), 216 (35), 201 (30), 191(25), 178 (25), 165 (25), 149 (20), 131 (40), 120 (35), 104 (35), 91 (35), 71 (40), 57 (50), 44 (80).

2.3b *2-[4-(1-Acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-4-(3-chloro-2-oxo-4-phenyl-azetidin-1-yl)-5-methyl-3-oxo-2,4-dihydro-[1,2,4]-triazole* **(23)**: $C_{29}H_{25}N_6ClO_3$, yield 55%, m.p. 214–5°C, Brown crystals (chloroform), IR (KBr) ν_{max}: C=O, 1776, 1690, 1662, C=N 1604 cm^{-1}; ^1H NMR ($CDCl_3$): 2.25 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.50 (dd, 1H, CH_2, J = 12.90 Hz), 3.70 (dd, 1H, CH_2, J = 13.05 Hz), 3.78 (d, 1H, CHCl), 4.40 (m, 1H, CH, J_{XA} = 4.35 Hz, J_{XB} = 11.29 Hz), 5.64 (m, 1H, NCH), 7.20–8.00 (m, 14H, Ar-H); MS: m/z 542 (M^{+2}, 05), 540 (M^+, 15), 536 (15), 503 (15), 480 (25), 464 (15), 438 (10), 411 (80), 396 (20), 381 (100), 356 (20), 340 (25), 319 (25), 298 (65), 281 (30), 262 (35), 247 (40), 237 (30), 224 (25), 208 (25), 192 (25), 181 (20), 163 (42), 137 (35), 103 (30), 90 (35), 71 (45), 57 (50), 44 (80).

2.3c *2-[4-(1-Acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-4-[3-chloro-2-(2-hydroxyphenyl)-4-oxo-azetidin-1-yl]-5-methyl-3-oxo-2,4-dihydro-[1,2,4]-triazole* **(24)**: $C_{29}H_{25}N_6ClO_4$, yield 60%, m.p. 219–0°C, Dark brown crystals (methanol), IR (KBr) ν_{max}: OH 3400, C=O 1750, 1706, 1664, C=N 1602 cm^{-1}; ^1H NMR ($CDCl_3$): 2.40 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.78 (dd, 1H, CH_2, J = 14.05 Hz), 4.12 (dd, 1H, CH_2, = 13.90 Hz), 4.62 (d, 1H, CHCl), 4.76 (m, 1H, CH, J_{XA} = 4.48 Hz, J_{XB} = 11.42 Hz), 5.63 (m, 1H, NCH), 7.00–8.20 (m, 13H, Ar-H), 11.00 (s, 1H, OH, D_2O exchangeable); MS: m/z 558 (M^{+2}, 06), 556 (M^+, 20), 552 (15), 519 (30), 496 (35),480 (100), 474 (60), 460 (10), 438 (90), 432 (25), 413 (25), 395 (70), 381 (30), 376 (50), 361 (55), 339 (20), 334 (55), 318 (100), 315 (40), 305 (40), 289 (10), 277 (15), 263 (90), 240 (40), 235 (35), 216 (30), 210 (25), 186 (40), 180 (60), 165 (25), 150 (45), 146 (60), 131 (50), 119 (80), 104 (55), 91 (95), 77 (60), 63 (70), 44 (50).

2.3d *2-[4-(1-Acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-4-[3-chloro-2-(4-hydroxyphenyl)-4-oxo-azetidin-1-yl]-5-methyl-3-oxo-2,4-dihydro-[1,2,4]-triazole* **(25)**: $C_{29}H_{25}N_6ClO_4$, yield 55%, Dark brown semisolid (ethanol), IR (KBr) ν_{max}: OH 3414, C=O 1753, 1710, 1636, C=N 1610 cm^{-1}; ^1H NMR ($CDCl_3$): 2.40 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.09 (dd, 1H, CH_2, J = 17.01 Hz), 3.45 (dd, 1H, CH_2, J = 17.23 Hz), 4.05 (m, 1H, CHCl,), 4.70 (m, 1H, CH_2, J_{XA} = 4.56 Hz, J_{XB} = 10.72 Hz), 5.54 (d, 1H, NCH), 7.00–8.09 (m, 13H, Ar-H), 11.00 (s, 1H, OH, D_2O exchangeable); MS: m/z 558 (M^{+2}, 06), 556 (M^+, 20), 552 (15), 519 (30), 496 (35), 480 (100), 474 (60), 460 (10), 438 (90), 432 (25), 413 (25), 395 (70), 381 (30), 376 (50), 361 (55), 339 (20), 334 (55), 318 (100), 315 (40), 305 (40), 289 (10), 277 (15), 263 (90), 240 (40), 235 (35), 216 (30), 210 (25), 186 (40), 180 (60), 165 (25), 150 (45), 146 (60), 131 (50), 119 (80), 104 (55), 91 (95), 77 (60), 63 (70), 44 (50).

2.3e *2-[4-(1-Acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-4-[3-chloro-2-(4-anisyl)-4-oxo-azetidin-1-yl]-5-methyl-3-oxo-2,4-dihydro-[1,2,4]-triazole* **(26)**: $C_{30}H_{27}N_6ClO_4$, yield 45%, 230–1°C, Dark brown crystals (methanol), IR (KBr) ν_{max}: C=O 1744, 1710,1674, 1650, C=N 1604 cm^{-1}; ^1H NMR ($CDCl_3$): 2.35 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.47 (dd, 1H, CH_2, J = 14.02 Hz), 3.75 (dd, 1H, CH_2, J = 14.21 Hz), 3.91 (s, 3H, OCH_3), 4.12 (d, 1H, CHCl), 4.88 (m, 1H, CH, J_{XA} = 4.58 Hz, J_{XB} = 10.75 Hz), 4.91 (m, 1H, NCH), 6.99–8.00 (m, 14H, Ar–H); MS: m/z 572 (M^{+2}, 05), 570 (M^+,15), 566 (20), 533 (25), 510 (30), 494 (20), 468 (10), 441 (70), 396 (20), 426 (100), 411 (20), 386 (25), 370 (25), 349 (60), 328 (30), 311 (35), 292 (40), 277 (30), 267 (25), 254 (25), 238 (20), 222 (20), 211 (40), 193 (35), 167 (30), 133 (35), 120 (45), 101 (60), 87 (50) 74 (40) 71 (40), 57 (40), 43 (70).

2.3f *2-[4-(1-Acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-4-[3-chloro-2-(4-nitrophenyl)-4-oxo-azetidin-1-yl]-5-methyl-3-oxo-2,4-dihydro-[1,2,4]-triazole* **(27)**: $C_{29}H_{24}N_7ClO_5$, yield 75%, m.p. 185–6°C, Orange solid (ethanol), IR (KBr) ν_{max}: C=O 1756,

1707, 1653, C=N 1605 cm^{-1}; ^1H NMR (CDCl3): 2.40 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.78 (s, 1H, CH), 4.14 (dd, 1H, CH_2, J = 15.25 Hz), 4.20 (d, 1H, CHCl), 4.77 (dd, 1H, CH, J = 15.40 Hz), 4.85 (m, 1H, CH, J_{XA} = 4.75 Hz, J_{XB} = 8.45 Hz), 7.25–8.25 (m, 13H, Ar-H); MS: m/z 588 (M^{+2}, 06), 586 (M^{+1}, 20), 551 (10), 509 (0.3), 504 (10), 489 (10), 464 (20), 460 (35), 445 (37), 412 (15), 383 (10), 376 (40), 361 (90), 345 (45), 332 (50), 319 (92), 304 (10), 277 (15), 257 (25), 242 (40), 233 (25), 216 (30), 201 (45), 216 (30), 201 (35), 178 (25), 152 (20), 131 (35), 104 (42), 91 (45), 83 (60), 57 (70), 43 (100).

2.3g *2-(4-(1-Acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-4-(3-chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl)-5-methyl-3-oxo-2H-1,2,4-triazole* **(28)**: $C_{26}H_{27}N_6ClO_3$, yield 50%, m.p. 175–6°C, Dark brown solid (pet ether), IR (KBr) ν_{max}: C=O 1765, 1710, 1662, C=N 1605 cm^{-1}; ^1H NMR ($CDCl_3$): 2.20 (s, 1H, CH), 2.30 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.56 (1H, s, CH), 3.25 (s, 1H, CH), 3.55 (dd, 1H, CH_2, J = 11.86 Hz), 3.77 (d, 1H, CHCl), 3.90 (dd, 1H, CH_2, J = 12.25 Hz), 4.36 (m, 1H, CH, J_{XA} = 3.65 Hz, J_{XB} = 10.52 Hz), 5.60 (m, 1H, NCH), 7.20–8.20 (m, 9H, Ar-H); MS: m/z: 576 (M^{+2}, 03), 574 (M^+, 10), 551 (20), 524 (20), 504 (10), 489 (15), 464 (25), 460 (40), 445 (55), 376 (50), 361 (80), 345 (30), 332 (60), 319 (80), 305 (10), 277(10), 257 (20), 257 (10), 242 (40), 233 (20), 216 (25), 201 (30), 191 (32), 165 (30), 145 (20), 131 (35), 115 (40), 104 (45), 91 (45), 77 (47), 57 (60), 43 (100).

2.3h *2-(4-(1-Acetyl-5-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-4-(3-chloro-2-methyl-4-oxoazetidin-1-yl)-5-methyl-3-oxo-2H-[1,2,4]-triazole* **(29)**: $C_{24}H_{23}N_6ClO_{4,}$, yield 73%, m.p. 205–6°C, Dark brown crystals (ethanol), IR (KBr) ν_{max}: OH 3415, C=O 1749, 1714, 1662, C=N 1606 cm^{-1}; ^1H NMR ($CDCl_3$): 1.30 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 3.44 (dd, 1H, CH_2, J = 15.25 Hz), 3.52 (dd, 1H, CH_2, J = 15.95 Hz), 4.25 (d, 1H, CHCl), 4.90 (m, 1H, CH, J_{XA} = 4.62 Hz, J_{XB} = 8.80 Hz), 5.10 (m, 1H, NCH), 6.68–7.78 (m, 8H, Ar-H) 8.85 (s, 1H, Ar-OH, D_2O exchangeable); MS: m/z: 497 (M^{+2}, 07), 495 (M^+, 26), 494 (60), 478 (10), 474 (10), 441 (30), 418 (20), 402 (10), 376 (15), 361 (90), 334 (25), 319 (100), 304 (20), 279 (25), 263 (25), 242 (60), 235 (30), 216 (35), 201 (30), 191(25), 178 (25), 165 (25), 149 (20), 131 (40), 120 (35), 104 (35), 91 (35), 71 (40), 57 (50), 44 (80).

2.3i *2-(4-(1-Acetyl-5-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-phenyl)-4-(3-chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl)-5-methyl-3-oxo-2H-[1,2,4]-triazole* **(30)**: $C_{29}H_{24}N_6Cl_2O_4$, yield 68, m.p. 181–2°C, Brown solid (pet ether), IR (KBr) ν_{max}: C=O 1750, 1710, 1662, C=N 1605 cm^{-1}; ^1H NMR ($CDCl_3$): 2.30 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.55 (dd, 1H, CH_2, J = 15.05 Hz), 3.90 (dd, 1H, CH_2, J = 15.45 Hz), 4.00 (d, 1H, CHCl), 4.36 (m, 1H, CH, J_{XA} = 4.77 Hz, J_{XB} = 9.30 Hz), 5.15 (m, 1H, NCH), 7.20–8.20 (m, 9H, Ar–H); MS: m/z: 622 (M^{+2}, 10), 620 (M^+, 30), 610 (25), 590 (12) 589 (64), 506 (20), 502 (20), 469 (30), 446 (40), 435 (15), 425 (0.3), 410 (10), 385 (10), 381 (20), 366 (35), 333 (37), 304 (15), 297 (10), 291 (10), 235 (30), 222 (25), 193 (25), 181 (20), 165 (15), 150 (25), 139 (30), 125 (30), 120 (30), 99 (30), 91 (25), 76 (25), 64 (40), 55 (42), 43 (100).

2.3j *2-(4-(1-Acetyl-5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-phenyl)-4-(3-chloro-2-methyl-4-oxoazetidin-1-yl)-5-methyl-3-oxo-2H-[1,2,4]-triazole* **(31)**: $C_{24}H_{22}N_7ClO_5$, yield 66%, m.p. 210–1°C, Dark brown crystals (ethanol), IR (KBr) ν_{max}: C=O 1772, 1715, 1660, C=N 1607 cm^{-1}; ^1H NMR ($CDCl_3$): 1.32 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 3.46 (dd, 1H, CH_2, J = 17.04 Hz), 3.51 (dd, 1H, CH_2, J= 16.98 Hz), 4.22 (d, 1H, CHCl), 4.92 (m, 1H, CH, J_{XA} = 3.70 Hz, J_{XB} = 8.52 Hz), 5.50 (m, 1H, NCH), 7.38–8.14 (m, 8H, Ar-H); MS: m/z: 525 (M^{+2}, 15), 523 (M^+, 45), 497 (26), 490 (60), 480 (10), 475 (10), 441 (30), 418 (20), 402 (10), 375 (15), 365 (90), 335 (25), 320 (100), 305 (20), 280 (25), 260 (25), 245 (60), 235 (30), 216 (35), 201 (30), 190 (25), 178 (25), 169 (25), 149 (20), 131 (40), 120 (35), 106 (35), 91 (35), 71 (40), 57 (50), 43 (80).

2.3k *2-(4-(1-Acetyl-5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-phenyl)-4-(3-chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl)-5-methyl-3-oxo-2H-[1,2,4]-triazole* **(32)**: $C_{29}H_{23}N_7Cl_2O_5$, yield 65%, m.p. 162–3°C, Brown solid (pet ether), IR (KBr) ν_{max}: C=O 1742, 1712, 1662, C=N 1605 cm^{-1}; ^1H NMR ($CDCl_3$): 2.30 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.25 (dd, 1H, CH_2, J = 12.45 Hz), 3.55 (dd, 1H, CH_2, J = 13.05 Hz), 3.90 (d, 1H, CHCl), 4.36 (m, 1H, CH, J_{XA} = 3.35 Hz, J_{XB} = 11.34 Hz), 5.64 (m, 1H, NCH), 7.20–8.20 (m, 9H, Ar-H); MS: m/z: 622 (M^{+2}, 10), 620 (M^+, 30), 610 (25), 590 (12) 589 (64), 506 (20), 502 (20), 469 (30), 446 (40), 435 (15), 425 (0.3), 410 (10), 385 (10), 381 (20), 366 (35), 333 (37), 304 (15), 297 (10), 291 (10), 235 (30), 222 (25), 193 (25),

181 (20), 165 (15), 150 (25), 139 (30), 125 (30), 120 (30), 99 (30), 91 (25), 76 (25), 64 (40), 55 (42), 43 (100).

3. Biological evaluation

3.1 *Antimicrobial assay*

The protocol for the antimicrobial activity assay was as follows.[25] Dimethylformamide was used as solvent control. The bacterial cultures were inoculated on Mueller Hinton Agar (Merck), media (20 ml) were poured into each sterilized Petri dish (99 mm) and inoculated with liquid cultures homogeneously by spread plate method. All the compounds were dissolved in dimethylsulfoxide (DMSO) to get a concentration of 100 μg. Each sample (100 μl) was loaded into the wells of agar plates directly. Plates inoculated with bacteria were incubated at 37°C for 24 h. All the determinations were done in triplicates. The standard ampicillin (100 μg/ml) was used as positive control and 100 μl of DMSO was used as negative control, zone of inhibition were recorded in mm. Preliminary screening was conducted for all compounds at 100 μg/ml concentration, against above mentioned microorganisms. Different series of dilutions of compounds were made (0.5, 1.0,.... 10.0 μg/ml) to determine the MIC.

3.2 *Antitubercular assay*[26]

The antitubercular activity of the test compounds were evaluated against standard strain of *Mycobacterium tuberculae* H37Rv. Antibiotic standards used were streptomycin and pyrazinamide. The procedure followed for antitubercular activity involved the use of Middlebrook 7H-9 broth and standard strain of *M. tuberculae* H37Rv. The basal medium was prepared according to manufacturer's instructions (Hi- Media) and sterilized by autoclaving. Then broth (4.5 ml) was poured into each one of the sterile bottles. To this, ADC (0.5 ml) supplement was added. The supplement consisted of catalase, dextrose and BSA fraction v. A stock solution was prepared (10 mg/ml) and from this appropriate amount of the solution was transferred to media bottles to achieve final concentrations of 25, 50, 100 μg/ml. Finally, 10 μl suspension of *M. tuberculae* H37Rv strain (1 lakh organisms/ml adjusted by McFarmland's turbidity standard) was transferred to each of the tubes and incubated at 37°C. Along with this, one growth control without compound and drug controls were also set-up. The bottles were inspected for growth twice a week for a period of three weeks. The appearance of the turbidity indicated the growth and infers the resistance to the compound. The growth was confirmed by making a smear from each bottle and performing a ZN stain.

4. Results and discussion

4-Amino-3-oxo-1,2,4-triazole derivatives (**1**–**3**) were prepared from 1,3,4-oxadiazoles by the method reported.[27] Earlier methods described for Schiff base synthesis involved the use of few drops of glacial acetic acid or sulphuric acid to trigger the reaction. Under these conditions Schiff bases were obtained only in 30% yield. This is probably because of the presence of the electron withdrawing carbonyl group of the 1,2,4-triazole ring (**1**–**3**). Hence, we planned to use Lewis acid catalyst for the formation of Schiff base derivatives. Initially, we tried the reaction with series of Lewis acids such as $ZnCl_2$, $AlCl_3$, $FeCl_3$, $MgBr_2$ and $Mg(ClO_4)_2$. The range of yield observed were 50–55, 45–47, 45–48, 40–42 and 50–75% respectively. Thus, $Mg(ClO_4)_2$ was found to be highly efficient catalyst for the synthesis of imines. The uncatalysed reaction gave yields in the range 31–41% where as the catalysed reaction gave yields in the range of 50–75%. Using equimolar quantities of 1,2,4-triazole and aldehyde with DCE as solvent and magnesium perchlorate (0.005 mol%) gave Schiff base in excellent yield. The advantage of this reaction include mild reaction condition, high yield and use of catalytic amounts of $Mg(ClO_4)_2$. The title compounds (**22**–**32**) were obtained by reacting equimolar quantity of Schiff base with chloroacetylchloride and triethylamine in dioxan with stirring at 0–5°C temperature for 3 h. This method gave yield in the range of 40–51%. The reaction was also carried out in solvent-free condition at RT with yields in the range of 65–77%. The structure of the title compounds was confirmed by IR and ^{1}H NMR spectral studies. IR spectra of Schiff base (**11**–**21**) revealed sharp bands for carbonyl in the range of 1690–1725 cm^{-1} for five-membered ring, medium intensity acetyl carbonyl in the range of 1653–1675 cm^{-1} and another medium intensity band around 1601–1615 cm^{-1} due to C=N stretching frequencies of pyrazoline ring. Compounds **13**, **14**, **18**, **19** have shown a broad band for OH group in the range 3400–3440 cm^{-1}. IR spectra of the title compounds revealed sharp carbonyl band for four-membered ring around 1730–1754 cm^{-1}. Another carbonyl group present in the 1,2,4-triazoline ring appeared around 1695–1717 cm^{-1}. A medium intensity

band for acetyl carbonyl was observed around 1640–1670 cm^{-1} and 1600–1615 cm^{-1} due to C=N stretching frequencies of pyrazoline ring. Compounds **24**, **25**, **29**, **30** have exhibited a broad band responsible for OH group around 3400–3440 cm^{-1}.

The ^1H NMR spectra substantiated the results of the IR analysis. ^1H NMR spectra of Schiff bases depicted a singlet around δ 2.12–2.45 ppm, for methyl protons of N-acetyl group in all the compounds. Another singlet for three protons was observed in the range δ 2.14–2.58 ppm. due to C5- methyl protons of the 1,2,4-triazole ring. The protons of the pyrazoline ring viz., a methine proton and the diastereotopic methylene protons showed a characteristic ABX pattern. The methylene protons were assigned as H_A, H_B and the methine proton as Hx. H_A and H_B are diastereotopic and also anisochronous as they differ in chemical shifts and since this difference was not large they are identified as AB protons. The H_A and H_B protons appeared as doublet due to geminal and vicinal coupling. These H_A and H_B differ in coupling with the Hx and hence they are also anisogamous. The H_A proton appears as doublet of doublet in the range δ 3.42–3.55 ppm. with two coupling constants in the range J_{AB} = 10.88–17.04 Hz and J_{AX} = 4.5 Hz. The H_B also appeared as doublet of doublet at δ 3.55–3.70 ppm. where, J_{BA} is in the range of 12.25–17.23 Hz. The Hx always appeared as four line spectrum with J_{XA} = 3.32–4.80 Hz and J_{XB} = 8.43–11.42 Hz in the range δ 3.80–4.92 ppm. Aromatic protons appear around δ 7.20–8.20 ppm. A singlet for the OH group (D_2O exchanged) in compounds **13**, **14**, **18**, **19** resonated in the range δ 4.32–11.03 ppm. Compounds **11**, **18**, **21** showed a singlet for methyl group in line range δ 1.25–1.32 ppm. Imine protons for all the compounds appeared as singlet in a downfield range at 8.10–8.50 ppm.

Azetidinone derivatives (**22–32**) exhibited CHCl proton of β-lactam ring as doublet at δ 3.77–4.62 ppm. and NCH proton as multiplet at δ 4.85–5.64 ppm. The structures were further confirmed by the mass spectra which exhibited the molecular ion peaks at their respective molecular weights.

4.1 *Biological activity*

To qualify as a drug candidate, a new molecule has to be analysed for the parameters set by Lipinski's rule of five using Osiris property explorer.[28] Lipinski's rule of five is a thumb rule to evaluate drug-likeliness or to determine if a compound with a certain pharmacological activity has properties that would make it a likely orally active drug in humans. The molecular properties are important for drug pharmacokinetics in human body, including their absorption, distribution, metabolism and excretion (ADME). The rule is important for drug development where pharmacologically active lead structure is optimized step-wise for increased activity and selectivity, as well as drug-like properties. The modification of the molecular structure often leads to drugs with higher molecular weight, more rings, more rotatable bonds and higher lipophilicity. The rule states that in general an orally active drug has no more than 5 hydrogen bond donors, and not more than 10 hydrogen acceptors, a molecular weight under 500 and partition coefficient *clogP* less than 5 did not title compounds do not violate the Lipinski rule and they fall well in the range as mentioned when evaluated by the Osiris property explorer (table 1) which lead us to evaluate the compounds experimentally. Promising results were shown for all compounds as they are safe drug molecules without any effects as analysed by Osiris property explorer. Almost all the title compounds showed *clogP* well within the range and also certain compounds have molecular weights less than 500. The drug-likeliness ranged from −5.37 to 4.98 where as the drug score ranged from 0.15 to 0.60. The compounds **27**, **29**, **30** which have electron donating groups such as phenyl and a halogen atom exhibited varying drug scores as depicted in table 1. The compounds **31**, **32** which have electron withdrawing *nitro* group showed drug-likeliness in a negative value and also the drug score was less, and the presence of a halogen atom did not magnify the effect, where as the compounds **28** and **32** which have *chloro* substituent on the aryl group have also shown diversified effects based on drug-likeliness and drug score but *clogP* values are well within the range as mentioned by the rule.

Table 1. Pharmacological parameters for bioavailability of the compounds (**22–32**).

Entry no.	*clogP*	Mol Wt	Drug-likeliness	Drug score
22	2.57	476	5.42	0.29
23	3.60	538	4.98	0.58
24	3.30	554	5.05	0.42
25	3.30	554	5.32	0.44
26	3.50	568	5.18	0.44
27	3.47	583	5.02	0.40
28	4.21	572	5.39	0.18
29	4.21	572	5.39	0.18
30	3.17	599	−5.43	0.42
31	3.91	588	4.98	0.19
32	4.08	617	−5.37	0.15

Table 2. Antibacterial activities of the compounds (MIC μg/ml) (**22–32**).

Entry no.	*B. subtilis* (6633)[a]	*S. aureus* (25293)[a]	*E. coli* (35218)[a]	*P. aeruginosa* (10145)[a]	*E. faecalis* MMH594(21)	*K.pneumoniae*
22	256	256	256	256	256	256
23	32	24	32	32	32	32
24	24	12	12	24	24	24
25	24	12	12	6	24	12
26	12	12	12	12	12	12
27	128	128	76	76	76	128
28	256	256	256	256	256	256
29	64	32	64	32	32	64
30	128	256	128	256	256	256
31	64	128	128	128	128	256
32	32	32	76	32	64	32
Ampicillin	24	128	128	256	128	256
Control	DMSO	DMSO	DMSO	DMSO	DMSO	DMSO

4.2 *Antibacterial activity assay*

MIC values for the *in vitro* antibacterial studies of the compounds (**22–32**) and the standard are represented in table 2 which range from 12 to 256 μg/ml. The antibacterial activity of all the compounds against *S. aureus, B. subtilis, P. aeruginosa, E. coli*, *E. faecalis*, *K. pneumoniae*, showed good potencies compared to control drug ampicillin. From the results it is apparent that among the title compounds, compound **26** with methoxy substituent showed excellent activity against *B. subtilis* with MIC value 12 μg/ml. The compounds **24, 25** with hydroxy substituent, and **26** with methoxy substituent have shown good inhibition against *S. aureus* with inhibition concentration at 12 μg/ml. The compounds **25** and **26** with hydroxyl and methoxy substituent showed good activity against *P. aeruginosa* with values ranging from 6 to 12 μg/ml. The compound **26** has exhibited potent inhibition against *E. faecalis* with values of 12 μg/ml and **25**, and **26** with hydroxyl and methoxy substituent have shown excellent activity against *K. pneumoniae* with values of 12 μg/ml. Among the eleven compounds screened, all of them have shown promising inhibition against one or the other bacterial cultures compared to control drug ampicillin. The results are well in agreement with the drug scores obtained from the Osiris property explorer. MIC values of the azetidinone derivates (**22–32**) are promising because of the electron donating substituent on aryl moieties and halogen on four-membered rings which is analogous to penicillin type ring table 2.

In case of antitubercular activity studies, the compounds with electron donating and withdrawing viz., **24–26** (hydroxyl and methoxy substituent), **28** (with only phenyl), **30** (*hydroxyl* and *chloro*), **31** (*nitro* group) and **32** (*nitro* and *chloro*) have exhibited excellent inhibition (MIC) at less than 5 μg/ml concentration. The compounds **23** (phenyl group), **27** (*nitro* group) and **29** (*hydroxyl* and *methyl* group) showed moderate inhibition at a range of 10 μg/ml. The compound **22** with phenyl and methyl substituents showed activity only at 25 μg/ml concentrations as compared to standards used viz., streptomycin (7.5 μg/ml) and pyrazinamide (10 μg/ml) respectively. Encouraging activity was attributed to the presence of electron withdrawing groups, and halogen moiety on four-membered ring viz., *hydroxy*, *nitro*, *chloro* appended to 1,2,4-triazoline moiety.

5. Conclusion

In conclusion, we have developed a simple and efficient method for the preparation of Schiff bases **11–21** using $Mg(ClO_4)_2$ as catalyst, and thereby conversion into 2-chloro-3-azetidinone derivatives **22–32** in solventless condition in excellent yields. We also believe that the procedural simplicity, the efficiency and the easy accessibility of the reaction partners give access to azetidinones equipped with 1,2,4-triazoline unit. MIC values of the final compounds were evaluated respectively and promising results were obtained for the compounds as depicted by the Osiris property explorer and some compounds have exhibited excellent activity against tubercular strain H37Rv.

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