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Synthesis and Biological Importance of 6-Nitroindazole linked Thiazolidines

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Abstract: *New series of N[1]-2-[-{2-substitutedphenyl-4-oxo-5-(substitutedbenzylidene)-1, 3-thiazolidine}-imino]-ethyl-6-nitroindazole, compound **5(a-m)** have been synthesized from 6-nitroindazole as a starting material by conventional method. All the synthesized compound **4(a-m)** were screened for their antibacterial and antifungal activities against some selected bacteria and fungi with their MIC values and antitubercular activity screened against M. tuberculosis. Antiinflammatory activity screened against albino rats (either sex). The structure of all the synthesized compounds were confirmed by chemical and spectral analyses such as IR, [1]H NMR, [13]C NMR and FAB-Mass.*

Keywords: *Synthesis, 6-nitroindazole, thiazolidinone, antimicrobial, antitubercular, anti-inflammatory activity.*

1. INTRODUCTION

The chemistry and pharmacology of indazole derivatives have been of great interest to medicinal chemistry, because the indazole nucleus is a pharmaceutically important and emerging heterocycle with a broad spectrum of activities such as biological evaluation [1], antiproliferative [2], antibacterial [3], nitric oxide synthases [4], protein kinase inhibitors [5], anesthesia [6]. The indazole ring system is also present in many other compounds such as herbicides, dyes or sweeteners like guanidine-1-indazole. Despite the many useful applications of indazole derivatives, indazole chemistry remains less study compared to other heterocyclic compounds. A large number of drugs and biologically relevant molecules contain heterocyclic systems. Often the presence of heteroatom or groupings imparts preferential specificities in their biological responses.

Amongst the heterocyclic systems, thiazolidine is a biologically important scaffold known to be associated with several biological activities. Some of prominent biological responses attributed to this skeleton are antimicrobial [7], antifungal [8], antiviral [9], anti-inflammatory [10], neuroprotective agents [10], herbicidal activity [11], calcium channel blockers [12] activities. The diversity in biological response profiles of thiazolidine has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities.

2. EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. Progress of reaction was monitored by silica gel-G coated TLC plates in MeOH: $CHCl_3$ system (1:9). The spot was visualized by exposing dry plate in iodine vapours. IR spectra were recorded in KBr disc on a Schimadzu 8201 PC, FTIR spectrophotometer (ν_{max} in cm^{-1}) and ^1H and ^{13}C NMR spectra were measured on a Brucker DRX-300 spectrometer in $CDCl_3$ at 300 MHz using TMS as an internal standard. All chemical shifts were reported on δ scales. The FAB-Mass spectra were recorded on a Jeol SX–102 mass spectrometer. Elemental analyses were performed on a Carlo Erba–1108 analyzer. The analytical data of all the compounds were highly satisfactory. For column

chromatographic purification of the products, Merck silica Gel 60 (230-400 Mesh) was used. The reagent grade chemicals were purchased from the commercial sources and further purified before use.

2.1. Procedure for the Synthesis of the Compound 1

A mixture of 6-nitroindazole and 1-bromo-2-chloroethane (1:1 mole) was dissolved in methanol at room temperature. The reaction mixture was continuously stirred on a magnetic stirrer for about 7.45 hrs. The product was filtered and purified over a column chromatography. The purified product was recrystallized from ethanol at room temperature to yield compound **1**.

2.1.1. Synthesis of N^1-(2-chloroethyl)-6-nitroindazole 1

Yield: 60%, m.p. 153-155 ºC; Anal. Calcd for $C_9H_8N_3O_2Cl$: C,47.90, H,3.57, N,18.62%; found C,47.85, H,3.52, N,18.60%; IR (cm^{-1}): 761 (C-Cl), 1320 (N-CH_2), 1538 (NO_2), 1564 (C=C), 2842, 3032, (CH); ^{1}H NMR (δ): 3.40 (t, 2H, J = 7.50 Hz, $\underline{CH_2}$-Cl), 3.86 (t, 2H, J = 7.50 Hz, N-$\underline{CH_2}$), 6.86-8.15 (m, 4H, Ar-H); ^{13}C NMR (δ): 47.8 ($\underline{CH_2}$-Cl), 54.5 (N-$\underline{CH_2}$), 111.3, 114.8, 121.9, 126.3, 134.8, 138.8, 145.9 (7C, Ar); Mass (FAB): 226M^+.

2.2. Procedure for the Synthesis of the Compound 2

A mixture of compound **1** and hydrazine hydrate (1:1 mole) was dissolved in methanol at room temperature. The reaction mixture was continuously stirred on a magnetic stirrer for about 6.30 hrs. The product was filtered and purified over a column chromatography. The purified product was recrystallized from ethanol at room temperature to yield compound **2**.

2.2.1. Synthesis of N1-{2-(hydrazino)-ethyl}-6-nitroindazole 2

Yield: 72%, m.p. 136-138 ºC; Anal. Calcd for $C_9H_{11}N_5O_2$: C,48.86, H,5.01, N,31.65%; found C,48.82, H,5.00, N,31.61%; IR: 1335 (C-N), 1528 (NO_2), 3342 (NH), 3428 (NH_2); ^{1}H NMR (δ): 3.39 (t, 2H, J = 7.55 Hz, $\underline{CH_2}$-NH), 3.89 (t, 2H, J = 7.55 Hz, N-$\underline{CH_2}$), 6.69 (s, 1H, NH), 5.74 (s, 2H, NH_2), 6.69-8.02 (m, 4H, Ar-H); ^{13}C NMR (δ): 45.7 ($\underline{CH_2}$-NH), 54.9 (N-$\underline{CH_2}$), 109.6, 114.8, 122.9, 126.8, 134.7, 137.8, 146.9 (7C, Ar); Mass (FAB): 221M^+.

2.3. General Method for the Synthesis of Compound 3(A-M)

A mixture of compound **2** and substituted benzaldehydes (1:1 mole) was dissolved in methanol at room temperature and allowed to react. The reaction mixture was first continuously stirred on a magnetic stirrer for about 2.00-3.30 hrs. Then kept on a steam bath for about 1.30-2.30 hrs. The products were cooled and filtered. The products were purified over a column chromatography and recrystallized from ethanol at room temperature to yield compound **3(a-m)**.

2.3.1. Synthesis of N1-{2-(benzylidenimino)-ethyl}-6-nitroindazole 3a

Yield: 61%, m.p. 136-137 ºC; Anal. Calcd for $C_{16}H_{15}N_5O_2$(309.32): C,62.12, H,4.88, N,22.64%; found C,62.07, H,4.80, N,22.61%; IR: 1559 (N=CH), 3358 (NH); ^{1}H NMR (δ): 3.36 (t, 2H, J = 7.55 Hz, $\underline{CH_2}$-N), 3.89 (t, 2H, J = 7.55 Hz, N-$\underline{CH_2}$), 6.79 (s, 1H, NH), 7.88 (s, 1H, N=CH), 6.70-8.11 (m, 12H, Ar-H); ^{13}C NMR (δ): 46.8 ($\underline{CH_2}$-N), 54.6 (N-$\underline{CH_2}$), 151.8 (N=CH), 108.6, 121.8, 125.8, 126.7, 127.8, 127.8, 128.7, 129.8, 130.9, 134.8, 137.7, 138.8, 147.7 (13C, Ar); Mass (FAB): 309M^+.

2.3.2. Synthesis of N1-{2-(4-chlorobenzylidenimino)-ethyl}-6-nitroindazole 3b

Yield: 63%, m.p. 169-170ºC; Anal. Calcd for $C_{16}H_{14}N_5O_2Cl$(343.78): C,55.90, H,4.10, N,20.37%; found C,55.82, H,4.02, N,20.31%; IR: 750 (C-Cl), 1552 (N=CH), 3378 (NH); ^{1}H NMR(δ): 3.44 (t, 2H, J = 7.60 Hz, $\underline{CH_2}$-N), 4.10 (t, 2H, J = 7.60 Hz, N-$\underline{CH_2}$), 6.95 (s, 1H, NH), 7.98 (s, 1H, N=CH), 6.78-8.18 (m, 8H, Ar-H); ^{13}C NMR (δ): 49.5 ($\underline{CH_2}$-NH), 59.8 (N-$\underline{CH_2}$), 158.9 (N=CH), 110.8, 115.9, 123.7, 126.8, 127.7, 128.6, 128.9, 129.8, 134.9, 135.7, 138.2, 139.4, 145.9 (13C, Ar); Mass (FAB): 344M^+.

2.3.3. Synthesis of N1-{2-(3-chlorobenzylidenimino)-ethyl}-6-nitroindazole 3c

Yield: 65%, m.p. 166-168ºC; Anal. Calcd for $C_{16}H_{14}N_5O_2Cl$(343.78): C,55.90, H,4.10, N,20.37%; found C,55.83, H,4.02, N,20.35%; IR: 755 (C-Cl), 1568 (N=CH), 3367 (NH); ^{1}H NMR (δ): 3.45 (t, 2H, J = 7.60 Hz, $\underline{CH_2}$-N), 4.08 (t, 2H, J = 7.60 Hz, N-$\underline{CH_2}$), 6.98 (s, 1H, NH), 7.97 (s, 1H, N=CH), 6.75-8.23 (m, 8H, Ar-H); ^{13}C NMR (δ): 48.9 ($\underline{CH_2}$-N), 58.9 (N-$\underline{CH_2}$), 157.2 (N=CH),

109.7, 117.8, 123.5, 124.8, 126.7, 127.9, 128.8, 129.7, 134.6, 135.2, 137.8, 138.9, 146.9 (13C, Ar); Mass (FAB): 344M^+.

2.3.4. Synthesis of N1-{2-(2-chlorobenzylidenimino)-ethyl}-6-nitroindazole 3d

Yield: 65%, m.p. 168-169ºC; Anal. Calcd for $C_{16}H_{14}N_5O_2Cl$(343.78): C,55.90, H,4.10, N,20.37%; found C,55.84, H,4.01, N,20.30%; IR: 755 (C-Cl), 1560 (N=CH), 3374 (NH); ^{1}H NMR (δ): 3.40 (t, 2H, J = 7.55 Hz, $\underline{CH_2}$-NH), 4.01 (t, 2H, J = 7.55 Hz, N-$\underline{CH_2}$), 6.88 (s, 1H, NH), 8.04 (s, 1H, N=CH), 6.69-8.19 (m, 8H, Ar-H); ^{13}C NMR (δ): 47.8 ($\underline{CH_2}$-NH), 59.6 (N-$\underline{CH_2}$), 159.6 (N=CH), 111.3, 115.4, 123.7, 126.8, 127.7, 128.7, 129.8, 131.9, 134.8, 135.7, 136.8, 139.8, 147.9 (13C, Ar); Mass(FAB): 344M^+.

2.3.5. Synthesis of N1-{2-(4-bromobenzylidenimino)-ethyl}-6-nitroindazole 3e

Yield: 68%, m.p. 163-165ºC; Anal. Calcd for $C_{16}H_{14}N_5O_2Br$(388.22): C,49.50, H,3.63, N18.03%; found C,49.45, H,3.60, N,18.00%; IR: 645 (C-Br), 1568 (N=CH), 3366 (NH); ^{1}H NMR (δ): 3.45 (t, 2H, J = 7.65 Hz, $\underline{CH_2}$-NH), 3.96 (t, 2H, J = 7.65 Hz, N-$\underline{CH_2}$), 6.88 (s, 1H, NH), 8.03 (s, 1H, N=CH), 6.69-8.18 (m, 8H, Ar-H); ^{13}C NMR (δ): 48.4 ($\underline{CH_2}$-NH), 59.7 (N-$\underline{CH_2}$), 157.6 (N=CH), 109.8, 116.8, 123.7, 124.6, 126.7, 127.9, 128.7, 129.5, 133.4, 134.8, 137.2, 138.7, 146.5 (13C, Ar); Mass (FAB): 488M^+.

2.3.6. Synthesis of N1-{2-(3-bromobenzylidenimino)-ethyl}-6-nitroindazole 3f

Yield: 65%, m.p. 164-166ºC; Anal. Calcd for $C_{16}H_{14}N_5O_2Br$(388.22): C,49.50, H,3.63, N18.03%; found C,49.42, H,3.56, N,18.01%; IR: 641 (C-Br), 1560 (N=CH), 3362 (NH); ^{1}H NMR (δ): 3.41 (t, 2H, J = 7.60 Hz, $\underline{CH_2}$–NH), 3.98 (t, 2H, =7.60 Hz, N-$\underline{CH_2}$), 6.85 (s, 1H, NH), 7.99 (s, 1H, N=CH), 6.73-8.17 (m, 8H, Ar-H); ^{13}C NMR (δ): 46.9 ($\underline{CH_2}$-NH), 58.7 (N-$\underline{CH_2}$), 156.6 (N=CH), 111.8, 115.7, 122.2, 126.4, 127.9, 127.7, 129.9, 132.5, 134.8, 134.7, 137.7, 138.6, 146.5 (13C, Ar); Mass (FAB): 488M^+.

2.3.7. Synthesis of N1-{2-(2-bromobenzylidenimino)-ethyl}-6-nitroindazole 3g

Yield: 66%, m.p. 167-168ºC; Anal. Calcd for $C_{16}H_{14}N_5O_2Br$(388.22): C,49.50, H,3.63, N18.03%; found C,49.40, H,3.55, N,17.97%; IR: 652 (C-Br), 1562 (N=CH), 3367 (NH); ^{1}H NMR (δ): 3.40 (t, 2H, J = 7.55 Hz, $\underline{CH_2}$-NH), 3.95 (t, 2H, J = 7.55 Hz, N-$\underline{CH_2}$), 6.89 (s, 1H, NH), 7.94 (s, 1H, N=CH), 6.68-8.13 (m, 8H, Ar-H); ^{13}C NMR (δ): 47.8 ($\underline{CH_2}$-NH), 59.4 (N-$\underline{CH_2}$), 157.8 (N=CH), 111.3, 115.8, 122.9, 125.8, 125.7, 127.7, 128.5, 132.8, 133.4, 135.8, 138.8, 142.7, 147.5 (13C, Ar); Mass (FAB): 388M^+.

2.3.8. Synthesis of N1-{2-(4-nitrobenzylidenimino)-ethyl}-6-nitroindazole 3h

Yield: 64%, m.p. 162-163ºC; Anal. Calcd for $C_{16}H_{14}N_6O_4$(354.32): C,54.23, H,3.98, N,23.71%; found C,54.21, H,3.95, N,23.70%; IR: 1051 (C-N), 1544 (N=O), 1568 (N=CH), 3356 (NH); ^{1}H NMR (δ): 3.42 (t, 2H, J = 7.50 Hz, $\underline{CH_2}$-NH), 3.88 (t, 2H J = 7.50 Hz, N-$\underline{CH_2}$), 6.85 (s, 1H, NH), 8.07 (s, 1H, N=CH), 6.76-8.21 (m, 8H, Ar-H); ^{13}C NMR (δ): 48.8 ($\underline{CH_2}$-N), 55.3 (N-$\underline{CH_2}$), 155.9 (N=CH), 113.6, 119.8, 121.8, 123.9, 127.7, 128.9, 129.8, 132.5, 134.7, 137.8, 138.9, 145.7, 148.8 (13C, Ar); Mass (FAB): 354M^+.

2.3.9. Synthesis of N1-{2-(3-nitrobenzylidenimino)-ethyl}-6-nitroindazole 3i

Yield: 62%, m.p. 156-158ºC; Anal. Calcd for $C_{16}H_{14}N_6O_4$(354.32): C,54.23, H,3.98, N,23.71%; found C,54.15, H,3.90, N,23.65%; IR: 1040 (C-N), 1531 (N=O), 1569 (N=CH), 3367 (NH); ^{1}H NMR (δ): 3.40 (t, 2H, J = 7.60 Hz, $\underline{CH_2}$-NH), 3.89 (t, 2H, J = 7.60 Hz, N-$\underline{CH_2}$), 6.89 (s, 1H, NH), 7.92 (s, 1H, N=CH), 6.73-8.26 (m, 8H, Ar-H); ^{13}C NMR (δ): 48.2 ($\underline{CH_2}$-NH), 58.9 (N-$\underline{CH_2}$), 158.7 (N=CH), 111.8, 117.9, 122.9, 125.9, 126.8, 127.9, 128.8, 133.9, 135.6, 136.8, 139.8, 145.7, 151.6 (13C,Ar); Mass (FAB): 354M^+.

2.3.10. Synthesis of N1-{2-(2-nitrobenzylidenimino)-ethyl}-6-nitroindazole 3j

Yield: 62%, m.p. 161-163ºC; Anal. Calcd for $C_{16}H_{14}N_6O_4$(354.32): C,54.23, H,3.98, N,23.71%; found C,54.20, H,3.92, N,23.64%; IR: 1060 (C-N), 1538 (N=O), 1564 (N=CH), 3360 (NH); ^{1}H NMR (δ): 3.34 (t, 2H, J = 7.55 Hz, $\underline{CH_2}$-NH), 3.87 (t, 2H, J = 7.55 Hz, N-$\underline{CH_2}$), 6.83 (s, 1H, NH), 8.07 (s, 1H, N=CH), 6.76-8.17 (m, 8H, Ar-H); ^{13}C NMR (δ) 47.7 ($\underline{CH_2}$-N), 58.8 (N-$\underline{CH_2}$), 156.8 (N=CH), 109.7, 119.6, 121.7, 122.8, 125.8, 127.9, 130.9, 133.8, 134.9, 136.7, 138.8, 147.8, 150.9 (13C, Ar); Mass (FAB): 354M^+.

2.3.11. Synthesis of N1-{2-(4-methoxybenzylidenimino)-ethyl}-6-nitroindazole 3k

Yield: 60%, m.p. 149-151ºC; Anal. Calcd for $C_{17}H_{17}N_5O_3$(339.35): C,60.16, H,5.05, N,20.63%; found C,60.11, H,5.01, N,20.53%; IR: 1560 (N=CH), 2959 (OCH_3), 3360 (NH); ^{1}H NMR (δ): 3.28 (t, 2H, J = 7.65 Hz, $\underline{CH_2}$-NH), 3.73 (s, 3H, OCH_3), 3.79 (t, 2H, J = 7.65 Hz, N-$\underline{CH_2}$), 6.81 (s, 1H, NH), 7.84 (s, 1H, N=CH), 6.54-7.94 (m, 8H, Ar-H); ^{13}C NMR (δ): 46.6 ($\underline{CH_2}$-NH), 53.7 (OCH_3), 54.9 (N-$\underline{CH_2}$), 155.2 (N=CH), 108.4, 113.5, 115.7, 118.8, 119.8, 129.7, 131.9, 133.8, 135.8, 136.7, 137.9, 148.6, 161.9 (13C, Ar); Mass (FAB): 339M^+.

2.3.12. Synthesis of N1-{2-(4-methylbenzylidenimino)-ethyl}-6-nitroindazole 3l

Yield: 61%, m.p. 140-142ºC; Anal. Calcd for $C_{17}H_{17}N_5O_2$(323.35): C,63.14, H,5.29, N,21.65%; found C,63.10, H,5.22, N,21.60%; IR: 1557 (N=CH), 2924 (CH_3), 3340 (NH); ^{1}H NMR (δ): 2.67 (s, 3H, CH_3), 3.24 (t, 2H, J = 7.50 Hz, $\underline{CH_2}$-NH), 3.72 (t, 2H, J = 7.50 Hz, N-$\underline{CH_2}$), 6.78 (s, 1H, NH), 7.90 (s, 1H, N=CH), 6.59-7.99 (m, 8H, Ar-H); ^{13}C NMR (δ): 26.9 (CH_3), 45.3 ($\underline{CH_2}$-NH), 53.7 (N-$\underline{CH_2}$), 153.2 (N=CH), 108.5, 114.5, 122.7, 124.9, 126.7, 127.6, 129.9, 131.8, 133.9, 134.8, 138.6, 141.8, 147.2 (13C, Ar); Mass (FAB): 323M^+.

2.3.13. Synthesis of N1-{2-(4-hydroxybenzylidenimino)-ethyl}-6-nitroindazole 3m

Yield: 64%, m.p. 153-155ºC; Anal. Calcd for $C_{16}H_{15}N_5O_3$(325.32): C,59.07, H,4.64, N,21.52%; found C,59.01, H,4.60, N,21.48%; IR: 1545 (N=CH), 3380 (NH), 3477 (OH); ^{1}H NMR (δ): 3.37 (t, 2H, J = 7.55 Hz, $\underline{CH_2}$-NH), 3.91 (t, 2H, J = 7.55 Hz, N-$\underline{CH_2}$), 4.22 (s, 1H, OH), 6.92 (s, 1H, NH), 8.01 (s, 1H, N=CH), 6.72-7.98 (m, 8H, Ar-H); ^{13}C NMR (δ): 47.8 ($\underline{CH_2}$-NH), 59.6 (N-$\underline{CH_2}$), 157.3 (N=CH), 112.5, 114.8, 118.9, 120.8, 123.8, 125.8, 127.9, 130.7, 133.8, 136.9, 136.7, 141.5, 145, 156.9 (13C, Ar); Mass (FAB): 325M^+.

2.4. General Method for the Synthesis of Compound 4(A-M)

A mixture of compound **3(a-m)** and thioglycolic acid (1:1 mole) dissolved in acetone was allow to react in the presence of catalytic amount of $ZnCl_2$. The reaction mixture was first continuous stirred on a magnetic stirrer for about 2.00-3.30 hrs then kept on steam bath for about 2.45-3.45 hrs at 80-90 ^{0}C. The products were cooled and filtered at room temperature. The filtered products were purified over column chromatography and recrystallized from acetone at room temperature to yield compound **4(a-m).**

2.4.1. Synthesis of N^1-2-[-{- (2-phenyl-4-oxo-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (4a)

Yield: 64%, m.p. 161-163ºC; Anal. Calcd for $C_{18}H_{17}N_5O_3S$(383.43): C,56.38, H,4.46, N,18.26%; found C,56.30, H,4.41, N,18.22%; IR: 668 (C-S-C), 1319 (C-N), 1710 (CO cyclic), 2970 (S-CH_2); ^{1}H NMR: 3.22 (s, 2H, S-CH_2), 4.72 (s, 1H, N-CH), 6.74-7.91 (m, 9H, Ar-H); ^{13}C NMR: 36.5 (S-CH_2), 62.3 (N-CH), 172.8 (CO cyclic), 111.2, 115.8, 121.8, 123.9, 126.2, 127.5, 128.6, 129.7, 134.9, 136.8, 138.5, 139.6, 144.8 (13C, Ar); Mass (FAB): 383M^+.

2.4.2. Synthesis of N1-[-{2-(4-chlorophenyl)-4-oxo-1,3-thiazolidine-imino}-ethyl-6-nitroindazole (4b)

Yield: 65%, m.p. 188-190ºC; Anal. Calcd for $C_{18}H_{16}N_5O_3SCl$(417.87): C,51.73, H,3.85, N,16.75%; found C,51.70, H,3.82, N,16.71%; IR: 675 (C-S-C), 740 (C-Cl) 1328 (C-N), 1757 (CO cyclic), 2980 (S-CH_2); ^{1}H NMR: 3.44 (s, 2H, S-CH_2), 4.92 (s, 1H, N-CH), 8.75-7.98 (m, 8H, Ar-H); ^{13}C NMR: 41.2 (S-CH_2), 64.2 (N-CH), 176.5 (CO cyclic), 113, 118.6, 121.7, 123.5, 125.4, 126.5, 127.3, 131.6, 135.8, 136.2, 137.5, 138.6, 147.8, (13C, Ar); Mass (FAB): 418M^+.

2.4.3. Synthesis of N1-2-[-{2-(3-chlorophenyl)-4-oxo-1,3-thiazolidine-imino}-ethyl-6-nitroindazole (4c)

Yield: 67%, m.p. 185-187ºC; Anal. Calcd for $C_{18}H_{16}N_5O_3SCl$(417.87): C,51.73, H,3.85, N,16.75%; found C,51.68, H,3.80, N,16.72%; IR: 665 (C-S-C), 740 (C-Cl), 2979 (S-CH_2), 1322 (C-N), 1752 (CO cyclic); ^{1}H NMR: 3.42 (s, 2H, S-CH_2), 4.94 (s, 1H, N-CH), 6.80-8.09 (m, 8H, Ar-H); ^{13}C NMR: 42.6 (S-CH_2), 64.8 (N-CH), 176.8 (CO cyclic), 112.7, 119.8, 123.6, 125.7, 126.8, 128.6, 131.6, 133.8, 136.7, 138.4, 139.8, 141.9, 145.8, (13C, Ar); Mass (FAB): 418M^+.

2.4.4. Synthesis of N1-2-[-{2-(2-chlorophenyl-4-oxo-1,3-thiazolidine}-imino]-ethyl-6 nitroindazole (4d)

Yield: 68%, m.p. 180-182ºC; Anal. Calcd for $C_{18}H_{16}N_5O_3SCl$(417.87): C,51.73, H,3.85, N,16.75%; found C,51.67, H,3.79, N,16.69%; IR: 656 (C-S-C), 748 (C-Cl), 1332 (C-N), 1748 (CO cyclic), 2975 (S-CH_2); ^{1}H NMR 3.48 (s, 2H, S-CH_2), 4.98 (s, 1H, N-CH), 6.76-8.14 (m, 8H, Ar-H); ^{13}C NMR: 39.8 (S-CH_2), 64.1 (N-CH), 175.7 (CO cyclic), 117.8, 119.9, 122.7, 126.8, 129.7, 130.8, 131.8, 134.8, 137.7, 138.9, 139.8, 141.9, 149.7, (13C, Ar); Mass (FAB): 418M^+.

2.4.5. Synthesis of N1-2-[-{2-(4-bromophenyl-4-oxo-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (4e)

Yield: 61%, m.p. 184-185ºC; Anal. Calcd for $C_{18}H_{16}N_5O_3SBr$(462.32): C,46.76, H,3.48, N,15.44%; found C,46.72, H,3.44, N,15.40%; IR: 676 (C-S-C), 745 (C-Cl), 1328 (C-N), 1744 (CO cyclic), 2976 (S-CH_2); ^{1}H NMR: 3.44 (s, 2H, S-CH_2), 4.92 (s, 1H, N-CH), 6.68-8.13 (m, 8H, Ar-H); ^{13}C NMR: 38.3 (S-CH_2), 62.8 (N-CH), 174.8 (CO cyclic), 113.2, 116.4, 122.7, 125.7, 126.8, 129.4, 130.8, 133.8, 133.6, 138.7, 142.2, 146.4, 149.3 (13C, Ar); Mass (FAB): 462M^+.

2.4.6. Synthesis of N1-2-[-{2-(3-bromophenyl-4-oxo-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (4f)

Yield: 63%, m.p. 178-180ºC; Anal. Calcd for $C_{18}H_{16}N_5O_3SBr$(462.32): C,46.76, H,3.48, N,15.44%; found C,46.71, H,3.42, N,15.40%; IR: 673 (C-S-C), 741 (C-Cl), 1317 (C-N), 1740 (CO cyclic), 2969 (S-CH_2); ^{1}H NMR: 3.39 (s, 2H, S-CH_2), 4.90 (s, 1H, N-CH), 6.64-8.19 (m, 8H, Ar-H); ^{13}C NMR: 37.8 (S-CH_2), 62.9 (N-CH), 174.8 (CO cyclic), 117.5, 120.8, 123.7, 125.9, 127.8, 129.7, 130.9, 133.7, 138.8, 141.8, 142.8, 145.7, 148.6, (13C, Ar); Mass (FAB): 462M^+.

2.4.7. Synthesis of N1-2-[-{2-(2-bromophenyl-4-oxo-1,3-thiazolidine}-imino]-ethyl-6 nitroindazole (4g)

Yield: 65%, m.p. 184-186ºC; Anal. Calcd for $C_{18}H_{16}N_5O_3SBr$(462.32): C,46.76, H,3.48, N,15.44%; found C,46.74, H,3.43, N,15.42%; IR: 670 (C-S-C), 748 (C-Cl), 1332 (C-N), 1754 (CO cyclic), 2962 (S-CH_2); ^{1}H NMR: 3.41 (s, 2H, S-CH_2), 4.97 (s, 1H, N-CH), 6.76-8.17 (m, 8H, Ar-H); ^{13}C NMR: 36.6 (S-CH_2), 63.9 (N-CH), 175.2 (CO cyclic), 114.5, 118.5, 123.7, 126.8, 129.9, 131.6, 135.5, 133.8, 136.7, 137.9, 139.9, 142.7, 147.8, (13C, Ar); Mass (FAB): 462M^+.

2.4.8. Synthesis of N1-2-[-{2-(4-nitrophenyl-4-oxo-1, 3-thiazolidine}-imino]-ethyl-6-nitroindazole (4h)

Yield: 62%, m.p. 177-179ºC; Anal. Calcd for $C_{18}H_{16}N_6O_5S$(428.42): C,50.46, H,3.76, N,19.61%; found C,50.42, H,3.71, N,19.60%; IR: 678 (C-S-C), 868 (C-NO), 1324 (C-N), 1478 (N=O), 1745 (CO cyclic), 2978 (S-CH_2); ^{1}H NMR: 3.49 (s, 2H, S-CH_2), 4.86 (s, 1H, N-CH), 6.69-8.18 (m, 8H, Ar-H); ^{13}C NMR: 38.7 (S-CH_2), 62.8 (N-CH), 176.8 (CO cyclic), 111.5, 113.8, 119.7, 122.9, 126.7, 128.7, 131.6, 132.8, 136.7, 139.8, 143.7, 145.8, 148.8, (13C, Ar); Mass (FAB): 428M^+.

2.4.9. Synthesis of N1-[-{2-(3-nitrophenyl-4-oxo-1, 3-thiazolidine}-imino]-ethyl-6-nitroindazole (4i)

Yield: 61%, m.p. 182-183ºC; Anal. Calcd for $C_{18}H_{16}N_6O_5S$(428.42): C,50.46, H,3.76, N,19.61%; found C,50.40, H,3.70, N,19.56%; IR: 682 (C-S-C), 860 (C-NO), 1332 (C-N), 1490 (N=O), 1745 (CO cyclic), 2981 (S-CH_2); ^{1}H NMR: 3.47 (s, 2H, S-CH_2), 4.81 (s, 1H, N-CH), 6.81-8.28 (m, 8H, Ar-H); ^{13}C NMR: 38.9 (S-CH_2), 62.5 (N-CH), 175.6 (CO cyclic), 115.7, 118.5, 124.8, 126.7, 129.8, 131.6, 132.7, 133.5, 136.8, 140.7, 143.8, 145.6, 148.9, (13C, Ar); Mass (FAB): 428M^+.

2.4.10. Synthesis of N1-2-[-{2-(2-nitrophenyl-4-oxo-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (4j)

Yield: 62%, m.p. 177-178ºC; Anal. Calcd for $C_{18}H_{16}N_6O_5S$(428.42): C,50.46, H,3.76, N,19.61%; found C,50.38, H,3.69, N,19.51%; IR: 670 (C-S-C), 878 (C-NO), 1328 (C-N), 1498 (N=O), 1748 (CO cyclic), 2967 (S-CH_2); ^{1}H NMR: 3.49 (s, 2H, S-CH_2), 4.82 (s, 1H, N-CH), 6.74-8.29 (m, 8H, Ar-H); ^{13}C NMR: 37.8 (S-CH_2), 62.3 (N-CH), 174.2 (CO cyclic), 109.7, 117.8, 120.6, 124.7, 126.5, 127.6, 128.5, 132.7, 136.6, 139.8, 141.5, 142.7, 145.6, 148.5, (13C, Ar); Mass (FAB): 428M^+.

2.4.11. Synthesis of N1-2-[-{2-(4-methoxyphenyl-4-oxo-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (4k)

Yield: 65%, m.p. 172-174ºC; Anal. Calcd for $C_{19}H_{19}N_5O_4S$(413.45): C,55.19, H,4.63, N,16.93%; found C,55.17, H,4.60, N,16.91%; IR: 667 (C-S-C), 1136 (C-O), 1330 (C-N), 1748 (CO cyclic), 2978 (S-CH_2), 2955 (OCH_3); ^{1}H NMR: 3.28 (s, 2H, S-CH_2), 3.63 (s, 3H, OCH_3), 4.80 (s, 1H, N-CH), 6.86-8.25 (m, 8H, Ar-H); ^{13}C NMR: 35.7 (S-CH_2), 53.6 (OCH_3), 59.1 (N-CH), 171.5 (CO cyclic), 110.4, 116.6, 119.5, 121.5, 124.5, 126.8, 127.2, 128.4, 130.8, 131.7, 135.9, 146.5, 161.5 (13C, Ar); Mass (FAB): 413M^+.

2.4.12. Synthesis of N1-2-[-{2-(4-methylphenyl-4-oxo-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (4l)

Yield: 63%, m.p. 163-164ºC; Anal. Calcd for $C_{19}H_{19}N_5O_3S$(397.45): C,57.41, H,4.81, N,17.62%; found C,57.36, H,4.75, N,17.55%; IR: 661 (C-S-C), 1330 (C-N), 1748 (CO cyclic), 2981 (S-CH_2); ^{1}H NMR: 2.34 (s, 3H, CH_3), 3.24 (s, 2H, S-CH_2), 4.70 (s, 1H, N-CH), 6.86-7.92 (m, 8H, Ar-H); ^{13}C NMR: 26.6 (CH_3), 35.8 (S-CH_2), 60.4 (N-CH), 171.8 (CO cyclic), 115.6, 118.7, 120.8, 123.9, 125.8, 126.6, 128.5, 129.7, 131.7, 133.8, 139.9, 141.7, 148.6, (12C, Ar); Mass (FAB): 497M^+.

2.4.13. Synthesis of N1-2-[-{2-(4-hydroxyphenyl-4-oxo-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (4m)

Yield: 66%, m.p. 181-183ºC; Anal. Calcd for $C_{18}H_{17}N_5O_4S$(399.43): C,54.12, H,4.28, N,17.53%; found C,54.10, H,4.24, N,17.50%; IR: 677 (C-S-C), 1132 (C-O), 1339 (C-N), 1750 (CO cyclic), 2984 (S-CH_2), 3582 (OH); ^{1}H NMR: 3.41 (s, 2H, S-CH_2), 4.18 (s, 1H, OH) 4.96 (s, 1H, N-CH), 6.86-8.02 (m, 8H, Ar-H); ^{13}C NMR: 38.5 (S-CH_2), 63.5 (N-CH), 175.7 (CO cyclic), 113.3, 115.8, 118.8, 120.6, 122.7, 126.6, 128.4, 129.5, 132.8, 135.7, 140.5, 147.3, 159.5 (13C, Ar); Mass (FAB): 499M^+.

2.5. General Methods for the Synthesis of Compound 5(A-M)

A mixture of compound **4(a-m)** and substituted benzaldehydes (1:1 mole) was dissolved in acetone in the presence of sodiumethoxide (C_2H_5ONa) and allow to react. The reaction mixture was first continuous stirred on a magnetic stirrer for about 2.00-3.30 hrs then kept on steam bath for about 2.45-3.45 hrs at 80-90 ^{0}C. The products were cooled and filtered at room temperature. The filtered products were purified over column chromatography and recrystallized from acetone at room temperature to yield final products compound **5(a-m).**

2.5.1. Synthesis of N^1-2-[-{2-phenyl-4-oxo-5-benylidene-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (5a)

Yield: 66%, m.p. 145-147 ºC; Anal. Calcd for $C_{25}H_{21}N_5O_3S$(471.54): C,63.67, H,4.48, N,14.85%; found C,63.63, H,4.45, N,14.82%; IR: 1565 (C=CH), 2850 (C=CH); ^{1}H NMR: 6.45 (C=CH), 6.86-7.98 (m, 14H, Ar-H); ^{13}C NMR: 134.8 (C=CH), 142.2 (C=CH), 110.2, 112.6, 115.8, 118.7, 120.5, 122.8, 123.9, 124.7, 125.8, 126.8, 128.9, 129.7, 130.8, 131.7, 132.9, 134.8, 135.9, 140.6, 147.6 (19C, Ar); Mass (FAB): 471M^+.

2.5.2. Synthesis of N1-2-[-{2-(4-chlorophenyl)-4-oxo-5-(4-chlorobenzylidene)-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (5b)

Yield: 64%, m.p. 177-178ºC; Anal. Calcd for $C_{25}H_{19}N_5O_3SCl_2$(540.42): C,55.56, H,3.54, N,12.95%; found C,55.54, H,3.51, N,12.92%; IR: 736 (C-Cl), 1478 (C=CH), 2860 (C=CH); ^{1}H NMR: 6.71 (s, 1H, C=CH), 6.80-8.06 (m, 12H, Ar-H); ^{13}C NMR: 140.2 (C=CH), 148.2 (C=CH), 111.2, 114.6, 118.7, 119.6, 120.5, 122.8, 125.6, 126.7, 128.8, 129.7, 130.9, 131.7, 132.6, 133.7, 137.7, 138.6, 140.8, 143.6, 149.9 (19C, Ar); Mass (FAB): 540M^+.

2.5.3. Synthesis of N1-2-[-{-5-(3-chlorobenzylidene)-2-(3-chlorophenyl)-4-oxo-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (5c)

Yield: 62%, m.p. 172-173ºC; Anal. Calcd for $C_{25}H_{19}N_5O_3SCl_2$(540.42): C,55.56, H,3.54, N,12.95%; found C,55.52, H,3.52, N,12.90%; IR: 745 (C-Cl), 1470 (C=CH), 2868 (C=CH); ^{1}H NMR: 6.82 (s, 1H, C=CH), 6.86-8.11 (m, 12H, Ar-H); ^{13}C NMR: 141.3 (C=CH), 148 (C=CH), 112.9, 115.8, 118.8, 119.7, 121.8, 123.7, 124.8, 125.8, 126.8, 127.7, 128.8, 129.6, 130.7, 132.5, 135.8, 137.7, 138.5, 143.8, 148.9 (19C, Ar); Mass (FAB) 540M^+.

2.5.4. Synthesis of N1-2-[-{2-(2-chlorophenyl-4-oxo-5-(2-chlorobenzylidene)-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (5d)

Yield: 64%, m.p. 176-178ºC; Anal. Calcd for $C_{25}H_{19}N_5O_3SCl_2$(540.42): C,55.56, H,3.54, N,12.95%; found C,55.49 H,3.50, N,12.91%; IR: 748 (C-Cl), 1579 (C=CH), 2862 (C=CH); ^{1}H NMR: 6.78 (s, 1H, C=CH), 6.86-7.99 (m, 12H, Ar-H); ^{13}C NMR: 138.8 (C=CH), 147.8 (C=CH), 110.8, 116.8, 119.7, 120.8, 124.9, 125.8, 126.7, 127.8, 128.9, 129.7, 131.8, 132.8, 133.7, 134.7, 135.6, 136.7, 138.8, 144.9, 147.3 (19C, Ar); Mass (FAB): 540M$^+$.

2.5.5. Synthesis of N1-2-[-{2-(4-bromophenyl-4-oxo-5-(4-bromobenzylidene)-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (5e)

Yield: 62%, m.p. 170-172ºC; Anal. Calcd for $C_{25}H_{19}N_5O_3SBr_2$(629.33): C,47.71, H,3.04, N,11.12%; found C,47.65, H,3.00, N,11.05%; IR: 569 (C-Br), 1478 (C=CH), 2862 (C=CH); ^{1}H NMR: 6.79 (s, 1H, C=CH), 6.84-8.12 (m, 12H, Ar-H); ^{13}C NMR: 139.6 (C=CH), 148.2 (C=CH), 113.2, 115.8, 118.8, 121.7, 124.7, 125.8, 126.8, 128.9, 129.9, 130.6, 131.7, 132.8, 133.7, 134.8, 136.9, 138.5, 140.9, 142.9, 145.8 (19C, Ar); Mass (FAB): 629M$^+$.

2.5.6. Synthesis of N1-2-[-{2-(3-bromophenyl-4-oxo-5-(3-bromobenzylidene)-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (5f)

Yield: 66%, m.p. 169-170ºC; Anal. Calcd for $C_{25}H_{19}N_5O_3SBr_2$(629.33): C,47.71, H,3.04, N,11.12%; found C,47.61, H,3.01, N,11.08%; IR: 578 (C-Br), 1485 (C=CH), 2862 (C=CH); ^{1}H NMR: 6.68 (s, 1H, C=CH), 6.86-8.18 (m, 12H, Ar-H); ^{13}C NMR: 140.8 (C=CH), 148.7 (C=CH), 111.3, 116.7, 118.9, 122.8, 124.7, 126.6, 127.6, 128.8 129.7, 130.8, 132.9, 133.7, 134.8, 136.6, 138.8, 138.8, 139.7, 141.6, 146.8 (19C, Ar); Mass (FAB): 629M$^+$.

2.5.7. Synthesis of N1-2-[-{2-(2-bromophenyl-4-oxo-5-(2-bromobenzylidene)-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (5g)

Yield: 64%, m.p. 164-166ºC; Anal. Calcd for $C_{25}H_{19}N_5O_3SBr_2$(629.33): C,47.71, H,3.04, N,11.12%; found C,47.68, H,2.96, N,11.07%; IR: 560 (C-Br), 1478 (C=CH), 2854 (C=CH); ^{1}H NMR: 6.79 (s, 1H, C=CH), 6.78-8.02 (m, 12H, Ar-H); ^{13}C NMR: 141.3 (C=CH), 149.2 (C=CH), 112.9, 116.3, 118.8, 120.9, 122.7, 124.9, 125.8, 126.8, 127.7, 128.8, 130.7, 131.6, 132.8, 135.6, 137.9, 138.8, 140.7, 143.6, 147.8 (19C, Ar); Mass (FAB): 629M$^+$.

2.5.8. Synthesis of N1-2-[-{2-(4-nitrophenyl)-4-oxo-5-(4-nitrobenzylidene)-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (5h)

Yield: 62%, m.p. 165-168ºC; Anal. Calcd for $C_{25}H_{19}N_7O_7S$(561.53): C,53.47, H,3.41, N,17.46%; found C,53.42, H,3.38, N,17.42%; IR: 862 (C-NO), 1490 (N=O), 1572 (C=CH), 2855 (C=CH); ^{1}H NMR: 6.71 (s, 1H, C=CH), 6.81-8.10 (m, 12H, Ar-H); ^{13}C NMR: 140.3 (C=CH), 149.6 (C=CH), 111.7, 112.6, 115.8, 117.7, 122.6, 123.7, 124.6, 125.8, 126.7, 128.8, 129.9, 131.7, 133.8, 134.8, 137.6, 141.5, 145.8, 147.7, 148.7 (19C, Ar); Mass (FAB): 561M$^+$.

2.5.9. Synthesis of N1-2-[-{2-(3-nitrophenyl-4-oxo-5-(3-nitrobenzylidene)-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (5i)

Yield: 66%, m.p. 160-162ºC; Anal. Calcd for $C_{25}H_{19}N_7O_7S$(561.53): C,53.47, H,3.41, N,17.46%; found C,53.44, H,3.40, N,17.43%; IR: 863 (C-NO), 1498 (N=O), 1480 (C=CH), 2864 (C=CH); ^{1}H NMR: 6.76 (s, 1H, C=CH), 6.79-8.18 (m, 12H, Ar-H); ^{13}C NMR: 140.7 (C=CH), 148.7 (C=CH), 111.8, 115.7, 117.8, 119.7, 121.7, 122.2, 123.5, 124.5, 125.3, 126.7, 128.6, 130.4, 132.2, 133.2, 136.2, 139.3, 144.3, 147.5, 150.5 (19C, Ar); Mass (FAB): 561M$^+$.

2.5.10. Synthesis of N1-2-[-{2-(2-nitrophenyl-4-oxo-5-(2-nitrobenzylidene)-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (5j)

Yield: 60%, m.p. 159-160ºC; Anal. Calcd for $C_{25}H_{19}N_7O_7S$(561.53): C,53.47, H,3.41, N,17.46%; found C,53.40, H,3.37, N,17.42%; IR: 862 (C-NO), 1472 (N=O), 1482 (C=CH), 2874 (C=CH); ^{1}H NMR: 6.68 (s, 1H, C=CH), 6.89-8.15 (m, 12H, Ar-H); ^{13}C NMR: 141.4 (C=CH), 147.9 (C=CH), 111.9, 115.8, 118.9, 120.8, 122.6, 124.7, 125.8 126.7, 127.8, 128.6, 130.8, 133.6, 134.7, 135.8, 136.8, 140.9, 142.7, 147.5, 148.9 (19C, Ar); Mass (FAB): 561M$^+$.

2.5.11. Synthesis of N1-2-[-{2-(4-methoxyphenyl-4-oxo-5-(4-methoxybenzylidene)-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (5k)

Yield: 67%, m.p. 154-156ºC; Anal. Calcd for $C_{27}H_{25}N_5O_5S$(531.69): C,61.00, H,4.74, N,13.17%; found C,60.95, H,4.70, N,13.15%; IR: 1144 (C-O), 1478 (C=CH), 2872 (C=CH), 2849 (OCH_3); ^{1}H NMR: 3.65 (s, 3H, OCH_3), 6.71 (s, 1H, C=CH), 6.71-7.88 (m, 12H, Ar-H); ^{13}C NMR: (OCH_3), 139.9 (C=CH), 145.3 (C=CH), 109.7, 115.3, 116.6, 118.6, 119.8, 123.7, 124.7, 125.6, 128.9, 127.8, 128.6, 130.7, 132.8, 137.9, 138.7, 139.8, 144.7, 147.6, 155.8 (19C, Ar); Mass (FAB) 532M^+.

2.5.12. Synthesis of N1-2-[-{2-(4-methylphenyl-4-oxo-5-(4-methylbenzylidene)-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (5l)

Yield: 60%, m.p. 150-152ºC; Anal. Calcd for $C_{27}H_{25}N_5O_3S$(499.59): C,64.91, H,5.04, N,14.01%; found C,64.89, H,5.00, N,14.97%; IR: 1482 (C=CH), 2878 (C=CH), 2862 (CH_3); ^{1}H NMR: 2.46 (s, 3H, CH_3), 6.68 (s, 1H, C=CH), 6.82-7.95 (m, 12H, Ar-H); ^{13}C NMR: 25.8 (CH_3), 138.7 (C=CH), 146.1 (C=CH), 107.9, 116.8, 119.6, 122.7, 124.6, 126.5, 127.8, 128.9, 129.6, 130.7, 131.8, 132.8, 134.9, 134.7, 136.8, 137.8, 140.7, 145.8, 148.8 (19C, Ar); Mass (FAB) 499M^+.

2.5.13. Synthesis of N1-2-[-{2-(4-hydroxyphenyl-4-oxo-5-(4-hydroxybenzylidene)-1,3-thiazolidine}-imino]-ethyl-6-nitroindazole (5m)

Yield: 61%, m.p. 175-176ºC; Anal. Calcd for $C_{25}H_{21}N_5O_5S$(503.53): C,59.63, H,4.20, N,13.90%; found C,59.60, H,4.12, N,13.85%; IR: 1134 (C-O), 1480 (C=CH), 2862 (C=CH), 3578 (OH); ^{1}H NMR: 4.16 (s, 1H, OH), 6.62 (s, 1H, C=CH), 6.78-7.90 (m, 12H, Ar-H); ^{13}C NMR: 142.7 (C=CH), 149.8 (C=CH), 111.5, 112.6, 114.7, 117.6, 120.6, 122.8, 124.6, 125.8, 126.8, 127.6, 128.9, 129.8, 130.6, 131.8, 134.7, 136.5, 144.6, 148.7, 154.6 (19C, Ar); Mass (FAB) 503M^+.

2.6. Biological Activity

A series of newly synthesized compounds were active against selected microorganisms. The minimal inhibition values were determined using the filter paper disc diffusion method and the concentrations have been used in ppm. All the final synthesized compounds **5(a-m)** have been screened in vitro for their antibacterial activity against B. *subtilis*, E. *coli*, S. *aureus* and K. *pneumoniae* and antifungal activity against A. *niger*, A. *flavus*, F. *oxisporium* and C. *albicans*. Standards for antibacterial and antifungal activity Streptomycin and Griseofulvin were used respectively. Standards also screened under the similar conditions for comparison. The antitubercular activity screened against the M. *tuberculosis*. For the antitubercular activity Isoniazid and Rifampicin were used as standard and also screened under the similar conditions.

2.6.1. Antibacterial Activity

The above synthesized compound **5(a-m)** were screened against some selected bacteria and examined for the inhibition of growth of the organism. The concentrations of the compounds were given in µg/mL. The MIC results were given in Table 1.

2.6.2. Antifungal Activity

The above synthesized compound **5(a-m)** were screened against selected fungi and determined their minimal inhibition concentration presented in Table 1 and concentrations of the compounds were given in µg/mL.

2.6.3. Antitubercular Activity

The above synthesized compound **5(a-m)** were screened against M. *tuberculosis* (H37Rv strain) using L. J. medium (Conventional) method. The results showed in table 1. Antitubercular drugs Isoniazid and Rifampicin were taken as standards.

Table 1. *Antibacterial, antifungal and antitubercular activity of compound **5(a-m)** with MIC value (µg/mL).*

	Antibacterial activity				Antifungal activity				Antitubercular activity
Comp.	B. *subtilis*	E. *coli*	S. *aureus*	K. *pneumoniae*	A. *niger*	A. *flavus*	F. *oxisporium*	C. *albicans*	M. *tuberculosis*
5a	12.5	>6.25	12.5	6.25	>25	>25	>25	>25	>12.5
5b	>3.25	6.25	3.25	>3.25	>25	>12.5	>25	>25	>2.5
5c	6.25	>3.25	6.25	3.25	>12.	25	>12.5	>12.5	>2.5

					5				
5d	>3.25	6.25	3.25	6.25	>12.5	>25	>12.5	>12.5	2.5
5e	6.25	>3.25	3.25	>3.25	>12.5	25	25	>25	>2.5
5f	6.25	3.25	6.25	>3.25	>12.5	>12.5	>12.5	>12.5	>2.5
5g	>3.25	6.25	>3.25	6.25	25	>12.5	>12.5	25	6.25
5h	3.25	>3.25	3.25	3.25	25	>12.5	>12.5	>25	2.5
5i	3.25	3.25	>3.25	3.25	>12.5	>12.5	>12.5	>12.5	2.5
5j	3.25	>3.25	3.25	3.25	>12.5	>12.5	>12.5	>12.5	>2.5
5k	>12.5	6.25	>12.5	6.25	25	25	>25	>25	12.5
5l	>12.5	>12.5	>12.5	>12.5	>25	>25	>25	>25	>12.5
5m	>3.25	>3.25	>6.25	>6.25	>25	25	>12.5	>12.5	6.25

The mic values of standard streptomycin for all bacteria strain and griseofulvin for all fungi strain were in the range of 1.25-3.25 and 6.25-12.5 μg/ml respectively.

isoniazid and rifampicin were used as standards, mic values in the range of 1.25-2.50 μg/ml for m. *tuberculosis.*

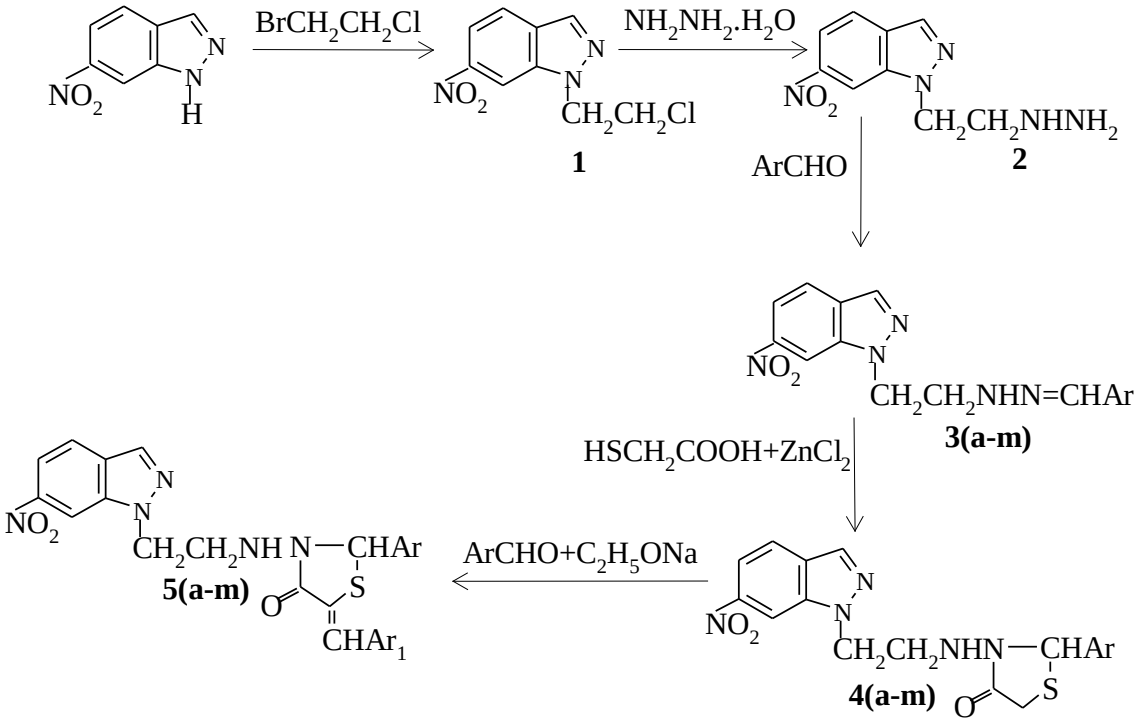
2.6.4. Anti-inflammatory Activity

Carageenan induced rat paw oedema method was employed for evaluating the antiinflammatory activity of compounds at a dose 50 mg/ kg bw in albino rats (weighing 80-110 gm, each group contain 5 animal) using phenylbutazone as a standard drug for comparison at a dose 30 mg/ kg bw. The percentage inhibition of inflammation was calculated by applying Newbould formula. Results of some active compounds were given in Table 2.

Table 2. *Anti-inflammatory activity of compounds* ***5(a-m)***.

Compound Code	**Before carageenan administration (mean ± SEM)**	**Total increase in paw volume after 5 hours (mean ± SEM)**	**Percent inhibition**
5a	0.60 ± 0.02	0.16± 0.02	50.00
5b	0.64 ± 0.02	0.14± 0.02	56.25
5c	0.66 ± 0.02	0.13 ± 0.01	59.38
5d	0.68 ± 0.02	0.13 ± 0.02	59.38
5e	0.66 ± 0.03	0.14 ± 0.02	56.25
5f	0.65 ± 0.02	0.12 ± 0.01	62.50
5g	0.67 ± 0.02	0.13 ± 0.01	59.38
5h	0.64 ± 0.03	0.12 ± 0.01	62.50
5i	0.65 ± 0.02	0.10 ± 0.03	68.75
5j	0.67 ± 0.03	0.11 ± 0.02	65.63
5k	0.64 ± 0.02	0.15± 0.02	51.13
5l	0.63 ± 0.02	027± 0.02	46.88
5m	0.65 ± 0.02	0.14 ± 0.01	56.25
Control	0.66 ± 0.02	0.32 ± 0.01	-
Standard; phenylbutazone	0.68 ± 0.03	0.08 ± 0.02	75.00

3. RESULTS AND DISCUSSION



Ar = Ar_1 = substituted phenyl ring

Scheme 1

Comp.	Ar=Ar_1	Comp.	Ar=Ar_1
3a, 4a, 5a	C_6H_5	3h, 4h, 5h	4-$NO_2C_6H_4$
3b, 4b, 5b	4-ClC_6H_4	3i, 4i, 5i	3-$NO_2C_6H_4$
3c, 4c, 5c	3-ClC_6H_4	3j, 4j, 5j	2-$NO_2C_6H_4$
3d, 4d, 5d	2-ClC_6H_4	3k, 4k, 5k	4-$CH_3OC_6H_4$
3e, 4e, 5e	4-BrC_6H_4	3l, 4l, 5l	4-$CH_3C_6H_4$
3f, 4f, 5f	3-BrC_6H_4	3m, 4m,5m	4-HOC_6H_4
3g, 4g, 5g	2-BrC_6H_4		

The reaction of 1-bromo-2-chloroethane with 6-nitroindazole was carried out in the methanol to afford a product compound **1.** The spectroscopic analyses of compound **1** showed absorption peaks for N-CH and C-Cl at 1320 cm^{-1} and 761 cm^{-1} in the IR spectrum. In the IR spectrum confirms the formation of compound **1**. This fact also supported by the disappearance of NH absorption of the 6-nitroindazole. The compound **1** on the reaction with hydrazine hydrate yielded compound **2**. In the spectroscopic analyses of compound **2** we have found two absorption peaks in IR spectrum for NH and NH_2 at 3342 and 3428 cm^{-1} respectively while absorption of C-Cl has been disappeared. This fact was also supported by ^1H and ^{13}C NMR spectra because two signals appeared in the ^1H NMR spectrum for NH and NH_2 at δ 6.69 and δ 5.74 ppm respectively. All the facts together were strong evidence for the synthesis of compound **2**. Substituted benzaldehydes give the condensation reaction with compound **2** resulting the production of Schiff bases N=CH which was confirmed by IR, ^1H NMR and ^{13}C NMR spectra of compound **3(a-m)**. In the IR spectra an absorption found in the range of 1545-1569 cm^{-1} while a strong signal appeared in the range of δ 7.84-8.07 and δ 151.8-159.6 ppm in the ^1H NMR and ^{13}C NMR spectra for N=CH of compound **3(a-m)** respectively. The facts also supported by the disappearance of the signal of NH_2 in the ^1H NMR spectra. The compound **3(a-m)** on reaction with of thioglycolic acid in the presence of $ZnCl_2$ gave the cycloaddition reaction and produced a five membered thiazolidinone ring, compound **4(a-m)**. The compound **4(a-m)** showed a characteristic absorption of the cyclic carbonyl group in the range of 1710-1757 cm^{-1} in the IR spectra. The ^1H NMR spectra of compound **4(a-m)** aroused our attention and clearly indicate the presence of the active methylene group in the thiazolidine ring in the range of δ 3.22-3.49 ppm. The ^{13}C NMR spectra of compound

4(a-m) also supported the fact that cyclic carbonyl group present a signal appeared in the range of δ 176.8-171.5 ppm. These all fact also supported by the two evidences that are (a) disappearance of N=CH proton and (b) appearance of N-CH proton in the range of δ 4.70-4.98 ppm in the ^{1}H NMR spectra of compound **4(a-m)**. The compound **4(a-m)** underwent the Knoevenagel condensation reaction with substituted benzaldehydes in the presence of C_2H_5ONa to afford compound **5(a-m)**. In the ^{1}H NMR spectra of the compound **5(a-m)**, we have found the disappearance of two methylene protons of compound **4(a-m)** and an appearance of a new signal for C=CH in the range of δ 6.45-6.82 ppm. In the ^{13}C NMR spectra two new signals for C=CH and C=CH appeared in the range of δ 134.8-142.7 and δ 142.2-149.6 ppm respectively in the spectra of the compound **5(a-m)**. These all above facts clearly confirmed the synthesis of all final products. Antimicrobial and antitubercular data (as shown in Table 1) revealed that all the synthesized compound **5(a-m)** have a structure activity relationship (SAR) because activity of compounds varies with substitution. Nitro group containing compounds **(5h, 5i** and **5j)** showed higher activity than chloro **(5c, 5d),** or bromo group containing compounds **(5e, 5f).** Chloro and bromo derivatives also have higher activity than other rested compounds**.** On the basis of SAR, concluded that the activity of compounds depends on electron withdrawing nature of the substituted groups.

4. CONCLUSION

Concluded that antimicrobial and antitubercular data shown in Table 1 revealed that the compounds **(5c), (5d), (5e), (5f), (5h), (5i)** and **(5j)** displayed highly active compounds of the series, compounds **(5b), (5g)** and **(5m)** showed moderate activity and rest compounds showed less activity against all the strains compared with standard drugs but incase of anti-inflammatory activity in Table 2 compounds **(5c), (5e), (5f), (5h), (5i)** and **(5j)** showed high activity.

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