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Research Article

SYNTHSIS OF NOVEL SULFONYL, ACYL AND BENZOYL DERIVATIVES OF 5-((1*H*-INDOL-3-YL) METHYLENE)-2- (4-(1H-PYRROL-1-YL) PHENYLIMINO) -3- METHYLTHIAZOLIDIN-4-ONE AND THEIR PHARMACOLOGICAL EVALUATION AS A ANTIMICROBIAL AGENTS

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ABSTRACT

A series of novel sulfonyl, acyl and benzoyl derivatives of 5-((1H-indol-3-yl) methylene)-2-(4-(1H-pyrrol-1-yl) phenylimino)-3-methylthiazolidin-4-one **(6)** were synthesized and evaluated for their antibacterial and antifungal activity. The structures of the synthesized compounds were determined by IR, ^{1}HNMR, and mass spectroscopy. They were screened for activities against bacterial and fungal strains. Some of them were found to be exhibited very good activities.

Keywords: Thiazolidin-4-one, Indole, Pyrrole, Antimicrobial, Antifungal

INTRODUCTION

Pyrrole derivatives are known to possess antimicrobial activities. It was reported in literature that PNU 171933 is a potent antibacterial compound which have substituted 1-H-Pyrrole-1-yl-phenylimino moiety [1]. One more derivative of Pyrrole BM 212 i.e. 5-diaryl-2-methyl-3-(4-methylpiperazin-1-yl)-methyl-Pyrrole is reported as a potent antimicrobial agent [2].

In continuation of our previous work presented in the research articles [3], Synthesis of novel 5-((1*H*-indol-3-yl) methylene)-2-(4-(1H-Pyrrole-1-yl) phenylimino)-3-methylthiazolidin-4-one is discussed in the present study **(Scheme 1)**. In view of the broad spectrum of biological activities and the significant applications of Indole-thiazolidin-4-one ring system, we thought it was worthwhile to explore the synthesis and evaluation of various biological activities of novel acyl, benzoyl and sulfonyl derivatives of Indole-thiazolidin-4-one having pyrrole as a side chain. In the present study, we report an efficient synthesis of different acyl, benzoyl and sulfonyl derivatives of Indole-thiazolidin-4-one. All newly synthsized compounds were tested for their antibacterial, antifungal as well as antioxidant activity. The structure of these compunds were elucidated by ^{1}HNMR, IR and mass spectroscopy.

These types of derivative are not yet reported in the literature. These observations led to the conception that sulfonyl, acyl and benzoyl derivatives of Indole-thiazolidin-4-one would possess potential biological properties. The efforts toward the synthesis of compound **(6)** are presented in **Scheme.1** The synthesis of various derivatives was carried out as per **Scheme 2** and **Scheme 3**. All newly synthesized compounds (**7a-7l) & (8a-8j)** were screened for their biological evaluation.

In literature there are many methods reported for the N-sulfonylation [4] and N-acylation [5] of Indole, In the present work, we have prepared various derivatives of Indole-thiazolidin-4-one by using the same methodology of catalytic use of DMAP [3b].

MATERIALS AND METHOD

The newly synthesized compounds were characterized on the basis of IR, ^{1}HNMR and mass spectroscopy method. IR spectrums were recorded on Schimadzu 8201 PC, FTIR spectrophotometer in KBr phase. Proton NMR spectrum were recorded on Bruker Advance II 400 & 200 MHz NMR Ultra Shield Spectrometer using DMSO-d_6/$CDCl_3$ as a solvent and tetramethyl silane (TMS) as internal standard. Chemical shift values are expressed in parts per million (ppm). Melting points were determined with Buchi B-545 melting point apparatus in degree celsius and are uncorrected. Mass spectra were recorded on either Buker daltanoics Micro TOFQ or Quattro Primer XE. All the reactions were monitored by using precoated silica gel plates, followed by UV detection at 254nm, exposure to iodine vapors.

General procedure

Synthesis of 1-(4-nitrophenyl)-1H-Pyrrole (2)

To a solution of 4-nitroaniline **(1)** (10 gm, 0.072 mol.) in 1,2-dichloroethane (DCE), AcOH and water (3:2:1 vol. ratio), cis-2,5-dimethoxy THF (11.9 gm, 0.090 mol.) was added and reaction mixture was heated at 80^{o}C for 3 hours. After completion of the reaction (TLC check; 1:1 Hexane:EtOAc), reaction mixture was cooled to rt, poured in water (500 ml) and stirred for 15 minutes. Aqueous layer was extracted with EtOAc (3×50 ml) and combine organic layer was dried and evaporated to get sticky yellow solid. Crude yellow solid was stirred in 250 ml hexane for 15 min, filtered and dried under vaccume to get 12.5 gm of 1-(4-nitrophenyl)-1H-Pyrrole **(2)**.

Yellow solid, (91% yield), EI-MS (m/z) : 187.3 [M-1]

Synthesis of 4-(1H-Pyrrole) benzamine (3)

To a solution of 1-(4-nitrophenyl)-1H-Pyrrole **(2)** (10 gm, 0.053 mol.) in MeOH (50 ml) ammonium formate (13.6 gm, 0.21mol.) and Pd/C (1 gm, 10% w/w) was added and reaction mixture was heated at 80-85 ^{o}C for 3 hours. After completion of reaction (TLC check 1:1 Hexane:EtOAc), reaction mixture cooled and filtered through a pad of celite and filtrate was evaporated to get reddish residue. The residue was partitioned between water and EtOAc. It was then extracted with EtOAc (3×50 ml), organic layer was evaporated to get sticky reddish solid. Crude reddish solid was stirred in 250 ml hexane for 15 min, filtered and dried under vacuum to get 6.1 gm 4-(1H-Pyrrole) benzamine **(3)**.

Reddish solid, (72.6% yield), EI-MS (m/z) : 156.95 [M-1]

Synthesis of 1-(4-(1H-Pyrrole-1-yl)phenyl)-3-methylthiourea (4)

To a solution of 4-(1H-Pyrrole) benzamine **(3)** (5 gm, 0.032 mol.) in EtOH (30 ml) was added methylisothiocynate (2.84 gm, 0.039 mol.) and reaction mixture was heated at 80-85^{o}C for 6 hour, after completion of reaction (TLC check; 1:1 Hexane: EtOAc), reaction mixture cooled to rt and EtOH was removed under vacuum. Water (30 ml) was added to the residue and stirred for 15 min. The solid was filtered and triturated with 50% EtOH in water (20 ml) filtered to gives 6.2 gm of 1-(4-(1H-Pyrrole-1-yl) phenyl)-3-methylthiourea **(4)** as off white solid.

Off-white solid, (86% yield), EI-MS (m/z) : 232.1 [M+1]

Synthesis of (3-ethyl -2-(4-(1H- Pyrrole -1-yl-phenylimino) thiazolidin-4-ones (5)

To a solution of 1-(4-(1H-Pyrrole-1-yl) phenyl)-3-methylthiourea **(4)** (6 gm, 0.026 mole) in EtOH (90 ml) ethylbromoacetate (4.68 gm, 0.027 mol.) and DIPEA (6.3 gm, 0.045 mol.) was added and reaction mixture was heated at 80-85°C for 6 hour. After completion of reaction (TLC check 1:1 Hexane:EtOAc), reaction mixture was cooled to rt and EtOH was removed under vacuum. Water (90 ml) was added to the residue and stirred for 15 min and extracted with EtOAc (3×60 ml). The organic layer seperated and evaporated to get sticky reddish solid. It was then recrystalised using EtOH to give 5.10 gm of (3-ethyl -2-(4-(1H- Pyrrole -1-yl-phenylimino) thiazolidin-4-ones **(5)** as off white solid.

Off-white solid, (72% yield), Mp: 132-134 °C; EI-MS (m/z) : 272.05 [M+1], IR (cm^{-1}, KBr) : 1732 (C=O), 1627 (C=N), 673 (C-S-C) cm^{-1}, ^{1}HNMR (DMSO-d_6, 400 MHz) : 3.18 (s, 3H), 4.05 (s, 2H), 6.26 (s, 2H), 7.02-7.04 (d, *J* = 8Hz, 2H), 7.35 (s, 2H), 7.56-7.58 (d, *J* = 8Hz, 2H)

Synthesis of 5-((1H-indol-3-yl) methylene)-2-(4-(1H-Pyrrole-1-yl) phenylimino)-3-methyl thiazolidin-4-one (6)

A solution of (3-ethyl -2-(4-(1H- Pyrrole -1-yl-phenylimino) thiazolidin-4-ones **(5)** (5.0 gm, 0.018 mol.) in 80 ml of EtOH, Piperidine (0.44 gm 0.0052 mol.), AcOH (0.32 gm, 0.0054 mol.) and Indole-3-carboxaldehyde (2.59 gm, 0.018 mol.) was refluxed till (5-7 hrs) the completion of the reaction, monitored by TLC. The reaction mixture was then cooled to rt and solid collected by filtration to give 6.0 gm **(6)** as yellow solid.

Yellow solid, (81.6% yield), Mp: 228-230 °C; EI-MS (m/z) : 399.3 [M+1], IR (cm^{-1}, KBr) : 3313 (N-H), 1685 (C=O), 1635 (C=C), 1600 (C=N), 673 (C-S-C) cm^{-1}, ^{1}HNMR (DMSO-d_6, 400 MHz) : 3.17 (s,3H), 6.27-6.28 (d, *J* = 4Hz, 2H), 7.13-7.15 (d, *J* = 8Hz,2H), 7.17-7.22 (m,2H), 7.39-7.40 (d, *J* = 4Hz, 2H), 7.47-7.49 (d, 2H), 7.61-7.63 (d, *J* = 8Hz, 2H), 7.85-7.87 (d, 1H), 8.02 (s,1H), 12.06 (bs,1H,exchangeable with D_2O), ^{13}C NMR (DMSO-d_6, 100 MHz) 29.95, 110.86, 112.83, 114.53, 118.72, 119.38, 120.77, 121.33, 122.83, 123.12, 123.39, 127.20, 128.69, 136.58, 137.17, 145.83, 151.41, 166.48

General procedure for synthesis of (7a-7l)

A solution of 5-((1*H*-indol-3-yl) methylene)-2-(4-(1H-Pyrrole-1-yl) phenylimino)-3-methyl thiazolidin-4-one **(6)** (0.25 gm, 0.00063 mol.) in DCM (2.5 ml), TEA (0.13 gm, 0.00126 mol.), DMAP (0.0076 gm, 0.000063 mol.) and appropriate sulfonyl chloride (0.00066 mol.) was stirred at rt over different period, till the completion of the reaction (monitored by TLC). After completion of reaction, the reaction mixture was concentrated under vacuum to get oil/solid, which further recrystallized using EtOH to get **(7a-7l)**

2-(4-(1H-Pyrrole-1-yl)phenylimino)-3-methyl-5-((1-tosyl-1H-indol-3-yl)methylene) thiazolidin-4-one (7a)

Yellow solid, (72% yield), Mp: 237-239 °C; EI-MS (m/z) : 553.6 [M+1], IR (cm^{-1}, KBr) : 1689 (C=O), 1640 (C=C), 1607 (C=N), 1373 & 1179 (SO_2) cm^{-1}

2-(4-(1H-Pyrrole-1-yl)phenylimino)-3-methyl-5-((1-(4-nitrophenyl sulfonyl)-1H-indol-3-yl) methylene) thiazolidin-4-one (7b)

Yellow solid, (61% yield), Mp: 248-250 °C; EI-MS (m/z) : 584.6 [M+1], IR (cm^{-1}, KBr) : 1710 (C=O), 1639 (C=C), 1609 (C=N), 1380 & 1188 (SO_2) cm^{-1}

2-(4-(1H-Pyrrole-1-yl)phenylimino)-3-methyl-5-((1-(methyl sulfonyl)-1H-indol-3-yl) methylene) thiazolidin-4-one (7c)

Yellow solid, (75% yield), Mp: 240-242 °C; EI-MS (m/z) : 477.5 [M+1], IR (cm^{-1}, KBr) : 1698 (C=O), 1639 (C=C), 1600 (C=N), 1369 & 1168 (SO_2) cm^{-1}, ^{1}HNMR (DMSO-d_6, 400 MHz) : 2.50 (s,3H), 3.38 (s,3H), 6.25 (d,2H), 6.99-7.05 (m,2H), 7.22-7.24 (m,4H), 7.34-7.38 (m,3H), 7.48-7.51 (d,1H), 7.73-7.77 (d.1H), 8.05 (s,1H)

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-(4-ethoxyphenylsul fonyl)-1H-indol-3-yl) methylene)-3-methylthiazolidin-4-one (7d)

Yellow solid, (68% yield), Mp: 245-247 °C; EI-MS (m/z) : 583.7 [M+1], IR (cm^{-1}, KBr) : 1689 (C=O), 1639 (C=C), 1609 (C=N), 1379 & 1178 (SO_2) cm^{-1}

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-(4-fluorophenyl sulfonyl)-1H-indol-3-yl) methylene)-3-methylthiazolidin-4-one (7e)

Yellow solid, (64% yield), Mp: 258-260 °C; EI-MS (m/z) : 557.2 [M+1], IR (cm^{-1}, KBr) : 1708 (C=O), 1637(C=C), 1612 (C=N), 1371 & 1178 (SO_2) cm^{-1}, ^{1}HNMR (DMSO-d_6, 400 MHz) : 3.51 (s, 3H), 6.39 (s, 2H), 7.12-7.18 (m, 6H), 7.36-7.41 (m, 2H), 7.49-7.51 (d, J=8Hz, 2H), 7.67 (s.1H), 7.76-7.78 (d, 1H) 7.90-7.98 (m,4H)

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-(4-chlorophenyl sulfonyl)-1H-indol-3-yl) methylene)-3-methylthiazolidin-4-one (7f)

Yellow solid, (66% yield), Mp: 255-257 °C; EI-MS (m/z) : 574.0 [M+1], IR (cm^{-1}, KBr) : 1695(C=O), 1639(C=C), 1600 (C=N), 1364 & 1166 (SO_2) cm^{-1}

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-(4-bromophenyl sulfonyl)-1H-indol-3-yl) methylene)-3-methylthiazolidin-4-one (7g)

Yellow solid, (64% yield), Mp: 252-253 °C; EI-MS (m/z) : 618.5 [M+1], IR (cm^{-1}, KBr) : 1690 (C=O), 1634 (C=C), 1602 (C=N), 1370 & 1177 (SO_2) cm^{-1}

2-(4-(1H-Pyrrole-1-yl) phenylimino)-5-((1-(4-iodophenylsulfo nyl)-1H-indol-3-yl) methylene)-3-methylthiazolidin-4-one (7h)

Yellow solid, (68% yield), Mp: 260-261 °C; EI-MS (m/z) : 665.5 [M+1], IR (cm^{-1}, KBr) : 1688(C=O), 1633(C=C), 1600 (C=N), 1368 & 1178 (SO_2) cm^{-1}

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-(4-methoxyphenyl sulfonyl)-1H-indol-3-yl) methylene)-3-methylthiazolidin-4-one (7i)

Yellow solid, (64% yield), Mp: 242-243 °C; EI-MS (m/z) : 569.1 [M+1], IR (cm^{-1}, KBr) : 1712 (C=O), 1647(C=C), 1612 (C=N), 1367 & 1166 (SO_2) cm^{-1}, ^{1}HNMR ($CDCl_3$, 400 MHz) : 3.51 (s,3H), 3.79 (s,3H), 6.39 (s,2H), 6.88-6.90 (d,J=8Hz,2H), 7.14-7.18 (m,4H), 7.28-7.43 (m,2H), 7.50-7.52 (d,J=8Hz,2H), 7.71 (s.1H), 7.75-7.77 (d,1H) 7.83-7.85 (d,2H) 7.94-7.98 (m,2H)

2-(4-(1H-Pyrrole-1-yl)phenylimino)-3-methyl-5-((1-(phenylsulfo nyl)-1H-indol-3-yl) methylene) thiazolidin-4-one (7j)

Yellow solid, (78% yield), Mp: 233-235 °C; EI-MS (m/z) : 539.4 [M+1], IR (cm^{-1}, KBr) : 1691(C=O), 1640(C=C), 1608 (C=N), 1377 & 1169 (SO_2) cm^{-1}

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-(4-ethylphenylsulfo nyl)-1H-indol-3-yl) methylene)-3-methylthiazolidin-4-one (7k)

Yellow solid, (73% yield), Mp: 238-240 °C; EI-MS (m/z) : 567.5 [M+1], IR (cm^{-1}, KBr) : 1685(C=O), 1635(C=C), 1603(C=N), 1375 & 1168 (SO_2) cm^{-1}

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-(benzylsulfonyl)-1H-indol-3-yl)methylene)-3-methylthiazolidin-4-one (7l)

Yellow solid, (72% yield), Mp: 241-243 °C; EI-MS (m/z) : 553.5 [M+1], IR (cm^{-1}, KBr) : 1688 (C=O), 1640(C=C), 1610 (C=N), 1380 & 1179 (SO_2) cm^{-1}

General procedure for synthesis of (8a-8j)

A solution of 5-((1*H*-indol-3-yl) methylene)-2-(4-(1H-Pyrrole-1-yl) phenylimino)-3-methylthiazolidin-4-one **(6)** (0.25 gm, 0.00063 mol.) in DCM (2.5 ml), TEA (0.13 gm, 0.00126 mol.), DMAP (0.0076 gm, 0.000063 mol.) and appropriate acyl/benzoyl chloride (0.00066 mol.) was stirred at rt over different period, till the completion of the reaction (monitored by TLC). After completion of reaction, the reaction mixture was concentrated under vacuum to get oil/solid, which further recrystallized using EtOH to get **(8a-8j)**.

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-acetyl-1H-indol-3-yl)methylene)-3-methyl thiazolidin-4-one (8a)

Yellow solid, (73% yield), Mp: 249-250 °C; EI-MS (m/z) : 441.2 [M+1], IR (cm^{-1}, KBr) : 1725 (C=O), 1708 (C=O), 1645(C=C), 1606 (C=N) cm^{-1}, ^{1}HNMR ($CDCl_3$, 400 MHz) : 2.67 (s,3H), 3.52 (s,3H), 6.40

(s,2H), 7.11-7.15 (m,4H), 7.40-7.48 (m,4H), 7.53 (s,1H), 7.80-7.82 (d,1H), 8.01 (s,1H), 8.41-8.42 (d,1H)

2-(4-(1H-Pyrrole-1-yl)phenylimino)-3-methyl-5-((1-propionyl-1H-indol-3-yl)methylene) thiazolidin-4-one (8b)

Yellow solid, (72% yield), Mp: 241-243 °C; EI-MS (m/z) : 455.5 [M+1], IR (cm^{-1}, KBr) : 1716 (C=O), 1693 (C=O), 1645 (C=C), 1608 (C=N) cm^{-1}

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-benzoyl-1H-indol-3-yl)methylene)-3-methyl thiazolidin-4-one (8c)

Yellow solid, (77% yield), Mp: 222-223 °C; EI-MS (m/z) : 503.4 [M+1], 504.3 [M+1], IR (cm^{-1}, KBr) : 1716 (C=O), 1693 (C=O), 1639(C=C), 1600 (C=N) cm^{-1}, ^{1}HNMR ($CDCl_3$, 400 MHz) : 3.50 (s,3H), 6.45 (s,2H), 7.05-7.07 (d,J=8Hz,2H), 7.17-7.18 (s,2H) 7.31-7.38 (m,3H), 7.42 (m.5H), 7.70-7.72 (d,J=8Hz,2H), 7.82-7.84 (d,1H), 7.97 (s,1H), 8.31-8.33 (d,1H)

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-(4-chlorobenzoyl)-1H-indol-3-yl)methylene)-3-methylthiazolidin-4-one (8d)

Yellow solid, (67% yield), Mp: 228-230 °C; EI-MS (m/z) : 538.0 [M+1], IR (cm^{-1}, KBr) : 1719 (C=O), 1695 (C=O), 1639 (C=C), 1605(C=N) cm^{-1}

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-(4-bromobenzoyl)-1H-indol-3-yl)methylene)-3-methylthiazolidin-4-one (8e)

Yellow solid, (64% yield), Mp: 210-212 °C; EI-MS (m/z) : 582.4 [M+1], IR (cm^{-1}, KBr) : 1716 (C=O), 1694 (C=O), 1634(C=C), 1606 (C=N) cm^{-1}

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-(4-iodobenzoyl)-1H-indol-3-yl)methylene)-3-methylthiazolidin-4-one (8f)

Yellow solid, (66% yield), Mp: 229-231 °C; EI-MS (m/z) : 629.1 [M+1], IR (cm^{-1}, KBr) : 1710 (C=O), 1690 (C=O), 1632(C=C), 1601 (C=N) cm^{-1}

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-(4-fluorobenzoyl)-1H-indol-3-yl)methylene)-3-methylthiazolidin-4-one (8g)

Yellow solid, (68% yield), Mp: 237-239 °C; EI-MS (m/z) : 521.6 [M+1], IR (cm^{-1}, KBr) : 1720 (C=O), 1699 (C=O),1640 (C=C), 1609 (C=N) cm^{-1}

2-(4-(1H-Pyrrole-1-yl)phenylimino)-3-methyl-5-((1-(4-nitro benzoyl)-1H-indol-3-yl) methylene) thiazolidin-4-one (8h)

Yellow solid, (61% yield), Mp: 254-256 °C; EI-MS (m/z) : 521.6 [M+1], IR (cm^{-1}, KBr) : 1725(C=O), 1699 (C=O), 1646 (C=C), 1616 (C=N) cm^{-1}

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-(4-methoxybenzoyl)-1H-indol-3-yl) methylene)-3-methylthiazolidin-4-one (8i)

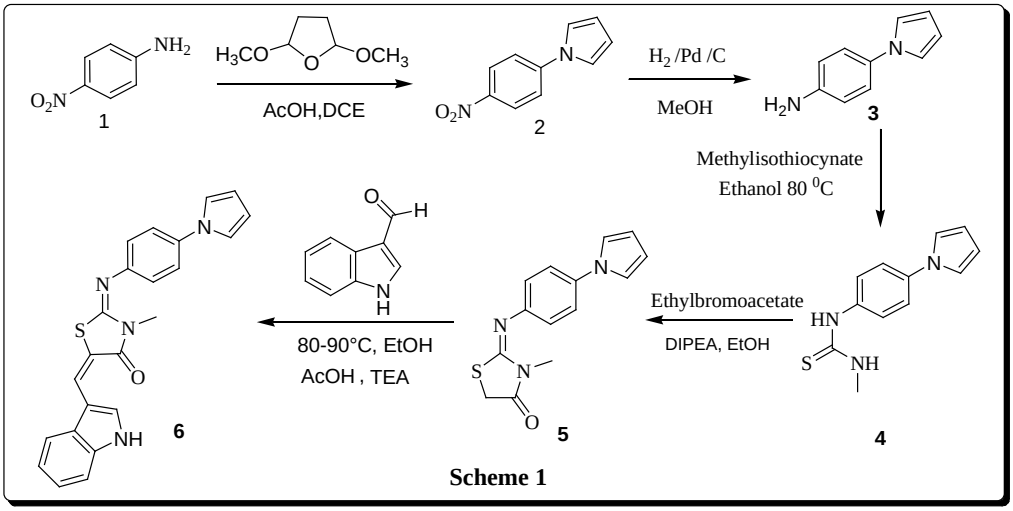
Yellow solid, (62% yield), Mp: 241-243 °C; EI-MS (m/z) : 533.5 [M+1], IR (cm^{-1}, KBr) : 1716(C=O), 1694 (C=O), 1639 (C=C), 1606 (C=N) cm^{-1}

2-(4-(1H-Pyrrole-1-yl)phenylimino)-5-((1-(4-ethoxybenzoyl)-1H-indol-3-yl)methylene)-3-methylthiazolidin-4-one (8j)

Yellow solid, (64% yield), Mp: 235-237 °C; EI-MS (m/z) : 547.3 [M+1], IR (cm^{-1}, KBr) : 1712 (C=O), 1693 (C=O), 1634 (C=C), 1605 (C=N) cm^{-1}

RESULTS AND DISCUSSION

The synthesis starts with reaction of 4-nitroaniline **(1)** with cis-2,5-dimethoxy-THF in AcOH and 1,2-dichloroethane (DCE) at 95-100°C afforded 1-(4-nitrophenyl)-1H-Pyrrole **(2)**. The product was confirmed by mass spectroscopy, it shows *m/z* at 187.3 for [M-1]. The 1-(4-nitrophenyl)-1H-Pyrrole **(2)** on catalytic reduction by using H_2, Pd/C in MeOH afforded 4-(1H-Pyrrole) benzamine **3**. The resulting product shows the *m/z* at 156.95 [M-1]**,** which confirmed the formation of 4-(1H-Pyrrole)-benzamine **(3)** The 4-(1*H*-Pyrrole)-benzamine **(3)** was further treated with methylisothiocyanate in EtOH at 80 °C to afford the 1-(4-(1H-Pyrrole-1-yl) phenyl)-3-methylthiourea **(4)**. The formation of product was confirmed by the mass spectroscopy it shows m*/z* at 246.1 for [M+1] for **(4)**. The 1-(4-(1H-Pyrrole-1-yl)phenyl)-3-methylthiourea **(4)** were treated with ethylbromoacetate in presence of DIPEA in refluxing EtOH respectively gives the key intermediate (3-methyl-2-(4-(1H-Pyrrole-1-yl)-phenyl imino)-thiazolidin-4-ones **(5)** with 76 % yield.



Scheme 1

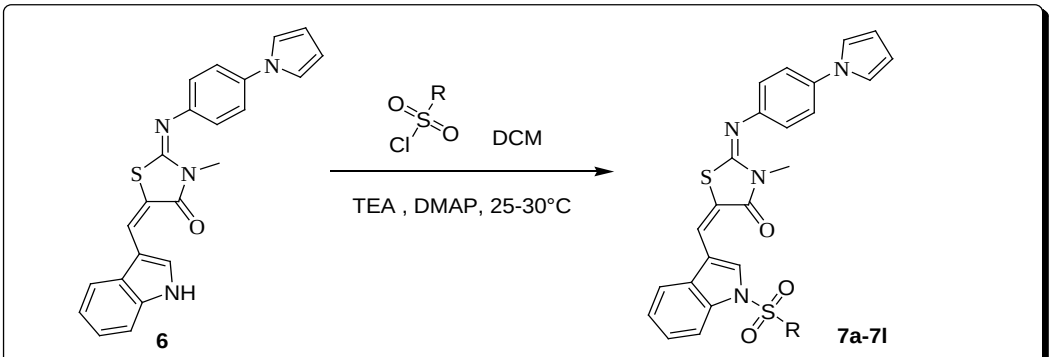
The IR spectrum of the compound **(5)** shows the strong absorption bands at 1732 cm^{-1} (C=O), 1627 cm^{-1} (C=N) and 673 cm^{-1} (C-S-C) confirmed the presence of C=O, C=N and C-S-C functional groups respectively. The ^{1}HNMR spectrum of compound **(5)** shows a singlet at 3.18 ppm for three protons for methyl group attached to nitrogen. A singlet at 4.05 ppm integrating for two protons was due to the methylene group attached to S-atom of imino thiazolidin-4-one ring. The protons of Pyrrole shows two singlets at 6.26 and 7.35 ppm each integrating for two protons. Remaining aromatic protons shows two multiplets between 7.02- 7.04 and 7.56- 7.58 ppm each integrating for two protons with J=8.0 Hz. The mass spectrum shows a peak at m/z = 272.05 [M +1] was in accordance with the molecular formula $C_{14}H_{13}N_3OS$. All these spectral values and analysis data confirmed the structure of the key intermediate (3-methyl -2-(4-(1H-Pyrrole-1-yl)-phenylimino)-thiazolidin-4-ones **(5)**. The IR spectrum of the compound **(6)** shows the strong absorption bands at 3313 cm^{-1} (N-H), 1685 cm^{-1} (C=O), 1635 cm^{-1} (C=C), 1600 cm^{-1} (C=N), 673 cm^{-1} (C-S-C) confirmed the presence of N-H, C=O,C=C, C=N and C-S-C functional groups respectively. In ^{13}CNMR spectra, methyl group attached to nitrogen observed at 29.95 ppm. Imino

carbon of thiazolidin-4-one observed at 151.41 ppm. The bridgehead olefinic carbon observed at 145.83 ppm. The carbonyl carbon of thiazolidin-4-one ring observed at 166.48 ppm. The mass spectrum shows a peak at m/z = 399.3 [M +1] was in accordance with the molecular formula $C_{23}H_{18}N_4OS$. The ^{1}HNMR spectrum of compound **(6)** shows a singlet at 3.17 ppm for three protons for methyl group attached to nitrogen. The Pyrrole protons shows two doublets at 6.27-6.28 and 7.39-7.40 each integrating for two protons. Two doublets observed at 7.13-7.15 and 7.61-7.63 ppm each integrating for two protons with a coupling constant of 8.0 Hz. A multiplet observed for two aromatic protons of phenyl ring of Indole at 7.17-7.22. A proton shows doublet at 7.47-7.49 ppm while another proton shows a doublet at 7.85-7.87 ppm. A sharp singlet observed was due to olefinic proton at 8.02 ppm while Indole –NH shows broad singlet at 12.06 ppm. All these spectral values and analysis data confirms the structure of the key intermediate (3-methyl -2-(4-(1H-Pyrrole-1-yl)-phenylimino)-thiazolidin-4-ones **(6)**.

The title compound **(6)** reacted with sulfonyl/acyl/benzoyl chlorides in presence of TEA and DMAP in a catalytic amount at rt to afford (**7a-7l)** & (**8a-8j)** in excellent yields **(Scheme 2)**. Interestingly, all above reaction gives product in excellent yields. Furthermore all the reaction has been done at rt in shortest period of time (**Table 1**). The novel thiazolidin-4-one derivatives were prepared by reaction of **(6)** with various sulfonyl/acyl/benzoyl chlorides in DCM as a solvent in presence of TEA and DMAP as a catalyt at rt to afforted the compounds (**7a-7l)** & (**8a-8j)** with excellent yields. (**Table 1**). The crude product obtained was recrystallised in EtOH. The yields obtained and the time required to complete conversion is presented in the **Table 1**. All compounds obtained are solid and having colour in the range of pale yellow to dark yellow. The yields and melting points are summerised in the **Table 1.** All the newly synthesized compounds were characterized by ^{1}HNMR, IR and mass spectroscopy.

Table 1: Physical data of synthesized compounds

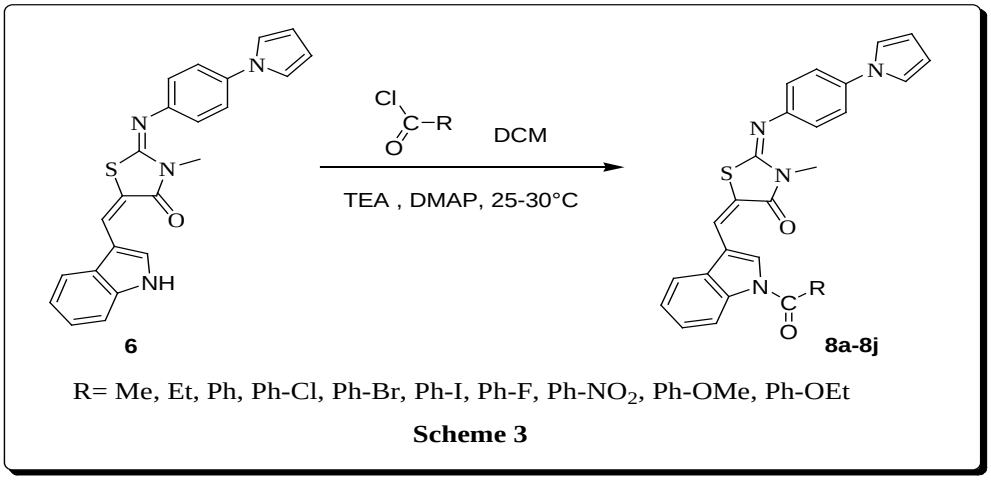
S. No.	Sulfonyl/acyl/benzoyl chloride	Product	Yield (%)	Time (Min)	M.P (°C)
1	4-Methyl phenyl	7a	72	45	237-239
2	4-Nitro phenyl	7b	61	50	248-250
3	Methyl	7c	75	35	240-242
4	4-Ethoxy phenyl	7d	68	45	245-247
5	4-Flouro phenyl	7e	64	50	258-260
6	4-Chloro phenyl	7f	66	55	255-257
7	4-Bromo phenyl	7g	64	60	252-253
8	4-Iodo phenyl	7h	68	60	260-261
9	4-Methoxy phenyl	7i	64	50	242-243
10	Phenyl	7j	78	50	233-235
11	4-Ethyl phenyl	7k	73	35	238-240
12	Benzyl	7l	72	45	241-243
13	Acetyl	8a	73	55	249-250
14	Propionyl	8b	72	30	241-243
15	Benzoyl	8c	77	45	222-223
16	4-Chlorobenzoyl	8d	67	55	228-230
17	4-Bromobenzoyl	8e	64	60	210-212
18	4-Iodobenzoyl	8f	66	50	229-231
19	4-Flourobenzoyl	8g	68	45	237-239
20	4-Nitrobenzoyl	8h	61	60	254-256
21	4-Methoxybenzoyl	8i	62	40	241-243
22	4-Ethoxybenzoyl	8j	64	35	235-237



R= Ph-Me, Ph-NO_2, Me, Ph-OEt, Ph-F, Ph-Cl, Ph-Br, Ph-I, Ph-OMe, Ph, Ph-Et, CH_2-Ph

Scheme 2

In IR spectrum of the compound **(7e)** shows the strong absorption bands at 1708 cm^{-1} (C=O), 1637 cm^{-1} (C=C), 1612 cm^{-1} (C=N), 1371 & 1178 cm^{-1} (SO_2) confirmed the presence of C=O, C=C, C=N and SO_2 functional groups respectively. The ^{1}HNMR spectrum of compound **(7e)** shows a singlet at 3.51 ppm for three protons of N-methyl group. A singlet at 6.39 integrating for two protons was due to Pyrrole protons. Multiplet at 7.12-7.18 ppm was due to six aromatic protons. Another multiplet at 7.36-7.41 ppm integrating for two protons was due to remaining two protons of Pyrrole. A doublet for two aromatic protons at 7.49-7.51 ppm with J=8Hz was due to aromatic ring attached to Pyrrole ring. A sharp singlet observed was due to olefinic proton at 7.67 ppm. A doublet for one aromatic proton at 7.76-7.78 ppm was due to aromatic proton. A multiplet observed for four aromatic protons of phenyl ring attached to sulfonyl group at 7.90-7.98 ppm. The mass spectrum shows a peak at m/z = 557.2 [M+1]. All the spectral values and analysis data confirmed the structure of the **(7e)**.



Scheme 3

In IR spectrum of the compound **(8a)** shows the strong absorption bands at 1725 cm^{-1} (C=O), 1708 cm^{-1} (C=O), 1645 cm^{-1} (C=C) and 1606 cm^{-1} (C=N) confirmed the presence of C=O, C=C and C=N functional groups respectively. The ^{1}HNMR spectrum of compound **(8a)** shows a sharp singlet at 2.67 ppm for three methyl protons was due to acetyl group. Another sharp singlet at 3.51 ppm for three protons of N-methyl group. A singlet at 6.40 integrating for two protons was due to Pyrrole protons. Multiplet at 7.11-7.15 ppm was due to four aromatic protons. Another multiplet at 7.40-7.48 ppm integrating for four protons was due to remaining two protons of Pyrrole and two aromatic protons. A singlet observed was due to one aromatic proton at 7.53 ppm. A doublet observred for one aromatic proton at 7.80-7.82 ppm. A sharp singlet observed was due to olefinic proton at 8.01 ppm. A doublet for one aromatic proton observed at 8.41-8.42 ppm. The mass spectrum shows a peak at m/z = 441.2 [M+1]. All the spectral values and analysis data confirmed the structure of the **(8a)**.

Antimicrobial activity

The various sulfonyl, acyl and benzoyl derivatives of Indole-thiazolidin-4-one were tested for their potential to inhibit growth of different bacterial and fungal species at doses of 100 µg/ml in DMSO as a solvent, against bacterial and fungal cultures. All the compounds were found to have antimicrobial activities against different species of bacteria and fungi in our studies.

Antimicrobial activity of sulfonyl derivatives (7a-7l)

Synthesized compounds **(7a-7l)** were tested to evaluate their antibacterial and antifungal activity. The newly synthesized compounds were found to exhibit good antibacterial and antifungal activity against different species of bacteria and fungi. From the activity data **(Table 2)**, it was observed that compound **(7e) & (7i)** shows good activity against all the tested bacteria and fungi. Among all tested bacteria and fungi compound **(7e)** shows good activity against *Staphylococcus aureus*, (inhibition 9 mm, standard shows 12 mm), *Bacillus subtillis* (inhibition 8 mm, standard shows 10 mm). Whereas compound **(7i)** shows good activity against *Staphylococcus aureus*, (inhibition 12 mm, standard shows 12 mm), *Bacillus subtillis* (inhibition 10 mm, standard shows 10 mm) and against *Escherichia coli* bacteria (inhibition 11 mm, standard shows 12 mm).

From the activity data **(Table 2)**, compounds (**7a), (7b), (7c), (7d), (7f), (7g), (7h), (7j), (7k) & (7l)** shows moderate activity against *Staphylococcus aureus* bacteria, *Bacillus subtillis* bacteria and *Escherichia coli* bacteria as well as against *Aspergillius Niger* and *Rhizopus Ostoyae* fungi.

Table 2: Antimicrobial activities of sulfonyl derivatives 7a-7l

Compound Code	Zone of Inhibition (mm)				
	Bacteria			Fungi	
	S. A. *NCLM No.2602*	*B. S.* *NCLM No.2458*	*E. C.* *NCLM No.2809*	*A. N.* *NCLM No.617*	*R.O.* *NCLM No.1299*
7a	4	3	5	3	3
7b	4	5	6	6	5
7c	4	3	4	2	2
7d	7	7	8	7	5
7e	9	8	7	7	6
7f	7	6	4	4	3
7g	7	5	5	5	4
7h	6	4	4	5	4
7i	12	10	11	9	8
7j	7	6	7	5	5
7k	7	6	7	4	4
7l	6	6	5	6	5
Standard	12	10	12	10	10

S.A.- Staphylococcus aureus, B.S.- Bacillus subtilis, E.C.- Escherichia coli, A.N.- Aspergillius Niger, R. O.- Rhizopus Ostoyae.

These results are average results of three experiments.

These compounds were used at concentration of 100 µg/mL.

Streptomycin for bacteria and Nystain for fungi were used as standard at concentration of 30 µg.

Antimicrobial activity of acyl & benzoyl derivatives (8a-8j)

Synthesized compounds **(8a-8j)** were tested to evaluate their antibacterial and antifungal activity. The newly synthesized compounds were found to exhibit good antibacterial and antifungal activity against different species of bacteria and fungi. From the activity data **(Table 3)**, it was observed that compound **(8g) & (8i)** shows good activity against all the tested bacteria and fungi. Among all tested bacteria and fungi compound **(8g)** shows good activity against *Staphylococcus aureus*, (inhibition 8 mm, standard shows 12 mm), *Bacillus subtillis* (inhibition 8 mm, standard shows 10 mm). Whereas compound **(8i)** shows good activity against *Staphylococcus aureus*, (inhibition 10 mm, standard shows 12 mm), *Bacillus subtillis* (inhibition 9 mm, standard shows 10 mm) and against *Escherichia coli* bacteria (inhibition 12 mm, standard shows 12 mm).

From the activity data **(Table 3)**, compounds **(8a), (8b), (8c), (8d), (8e), (8f), (8h) & (8j),** shows moderate activity against *Staphylococcus aureus* bacteria, *Bacillus subtillis* bacteria and *Escherichia coli* bacteria as well as against *Aspergillius Niger* and *Rhizopus Ostoyae* fungi.

Table 3: Antimicrobial activities of acyl and benzoyl derivatives 8a-8j

Compound Code	Zone of Inhibition (mm) Bacteria			Fungi	
	***S. A.* NCLM No.2602**	***B. S.* NCLM No.2458**	***E. C.* NCLM No.2809**	***A. N.* NCLM No.617**	***R.O.* NCLM No.1299**
8a	5	3	4	3	3
8b	5	2	5	3	3
8c	7	6	7	5	5
8d	3	3	3	2	3
8e	3	2	3	4	4
8f	2	2	3	3	2
8g	8	8	7	7	6
8h	5	5	6	4	5
8i	10	9	10	8	8
8j	7	6	6	4	5
Standard	**12**	**10**	**12**	**10**	**10**

S.A.- Staphylococcus aureus, B.S.- Bacillus subtilis, E.C.- Escherichia coli, A.N.- Aspergillius Niger, R. O.- Rhizopus Ostoyae.

These results are average results of three experiments.

These compounds were used at concentration of 100 µg/mL

Streptomycin for bacteria and Nystain for fungi were used as standard at concentration of 30 µg.

CONCLUSION

In the present study all synthesized compounds reported first time and describe the simple route of their synthesis in mild condition with good yield.The present study showed that all the title compounds were exhibiting significant antibacterial and antifungal activities. However, further studies are required to establish the mechanism of action of the title compounds. From the screening data it was found that (7e), (7i), (8g) and (8i) derivative have encouraging antibacterial and antifungal activity, which need to be further investigation to get better antibacterial and antifungal agents. We herein also reported the synthesis of series of novel sulfonyl, acyl and benzoyl derivatives of 5-((1H-indol-3-yl) methylene)-2-(4-(1H-Pyrrole-1-yl) phenylimino)-3-methylthiazolidin-4-one.

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