Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.47750/jptcp.2023.30.12.034

Synthesis new derivatives related to indole contains 1,3,4-thiadiazole ring tethered to β-lactam ring and study their antibacterial activity

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Submitted: 27 March 2023; Accepted: 10 April 2023; Published: 18 May 2023

ABSTRACT

Indole are important heterocyclic in medicinal compounds. We report the synthesis of some compounds related to indole, the reaction of indole-3-acetic acid (IAA) with thiosemicarbazide in the presence of POCl3 gave good yield of compound 5-((1H-indol-3-yl)methyl)-1,3,4-thiadiazol-2-amine (1). Then imine group was generated by the reaction of compound (1) with different aldehydes to give compound 2a-f in good yields. Further treating with chloroacetyl chloride produced compounds 3a-f with β-lactam in good yields. The antibacterial activities were tested against two types of bacteria; gram +ve and –ve and the results were good.

Keywords: *Indole-3-acetic acid, 1,3,4-thiadiazole, β-lactam, antibacterial*

INTRODUCTION

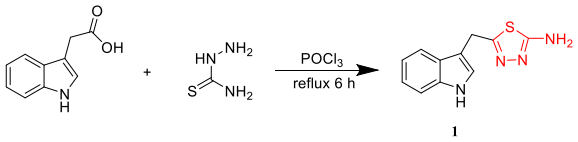
Indole derivatives have sparked significant scientific interest and remain one of the most active areas of heterocyclic chemistry, owing to their natural occurrence and pharmacological effects.[1] Several indole derivatives are emerging as pharmacologically active lead molecules for therapeutic development. Indole derivatives are also found in a variety of natural products, including those derived from plants[2], fungi , and bacteria .[3] The isolation, biological assessment, and chemical characteristics of natural compounds have caught the interest of organic chemists, medicinal chemists, biologists, and pharmacists. It has also been very difficult to advance chemical and biological research, to create innovative, inexpensive, and highly effective synthetic pathways to molecules with biological activity. Indole-3-acetic acid is an endogenous growth hormone in plants. Its scaffold is frequently found in a series of biologically active compounds such as Bunodosine 3911 and therapeutically effective drugs such as Indomethacin2, Sumatriptan3 and Rizatriptan4. Owing to its great importance in medicinal chemistry, much effort has been focused on the development of more effective synthetic methods over the past years.[4] 1,3,4-thiadiazoles and related compounds have garnered increasing attention in medicinal chemistry and technological fields in recently years because associated with diverse biological activities such as anti-microbial,[5] anti-bacterial,[6] anticancer,[7] anti-inflammatory,[8] carbonic anhydrase inhibitory, [9] anti-depressant, and antioxidant properties.[10] In the context, the synthetic program we adopted comprises the synthesis of 5-((1H-indol-3-yl) methyl)-1,3,4-thiadiazol-2-amine with four-membered ring. β-lactams, which are a cyclic structure, consists of the four-membered with nitrogen atom and three

carbon atoms, one of which is a carbonyl group and nitrogen, which called azetidine-2-on, and have an important place in both organic chemistry and pharmaceutical chemistry.[11] The azetidin-2-one ring is included in penicillins, carbapenems, cephalosporins, nocardicins, and monabactams, which are valuable medicinal chemistry structures. β-lactam also have a variety of interesting pharmacological properties, including cholesterol absorption inhibitors, human cytomegalovirus protease inhibitors,[12] thrombin inhibitors, anti-hyperglycemic, anticancer, anti-HIV, anti-inflammatory, analgesic, antimalarial, and serine-dependent enzyme inhibitors.[13]

RESULTS AND DISCUSSION

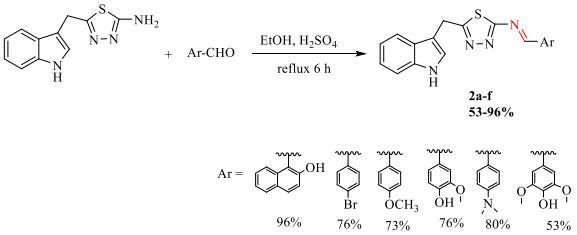
Chemistry

In the current study, 5-((1H-indol-3-yl) methyl)-1, 3, 4-thiadiazol-2-amine 1 was prepared by the reaction of IAA with thiosemicarbazide in the presence of POCl3, which gave good yield (Scheme 1).Compound 1 was confirmed by the FT-IR spectra that show absorption bands of the NH_2 at 3317 and 3294 cm^{-1}. It is also shows the stretching peak of C=N group at 1620 cm^{-1} for thiadiazole ring.[14]



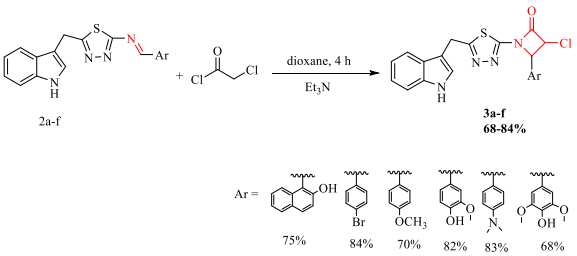
SCHEME 1: The synthesis of thiadiazole ring

The next step is the preparation of imine group by the condensation reaction. However, reaction of 1.0 equivalent of the compound 1 in ethanol with 1.0 equivalent of 2-hydroxynaphthaldehyde (a) and in the presnce of 3 drops of H_2SO_2 and heated under reflux for 6 hour, which gave compound 2a in 97% yield. Further, using the same method other substituted aldehydes; 2-naphthaldehyde, 4-bromobenzaldehyde, 4-methoxybenzaldehyde, 4-hydroxy-3-methoxybenzaldehyde, 4-(dimethylamino)benzaldehyde, and syringaldehyde have used to obtain compounds 2b-f, see (Scheme 2).



SCHEME 2: The synthesis of Schiff base product

In the FT-IR spectra of compounds 2a-f, the stretching band of the imine group C=N appeared at range (1635-1689 cm^{-1}).[15] Compounds 2a, 2d, and 2f had absorption bands in the region of (3564-3402 cm-1) related to OH group. The N-H stretching vibration could be observed as a sharp midium intensity bands at (3394-3201cm^{-1}). Towards the formation of β-lactam ring, the obtained compounds 2a-f were subjected to [2+2] cycloadditions via the reaction with chloro acetylchloride. However, the compounds 3a-f were obtained in good yields. See (Scheme 3).



SCHEME 3: The synthesis of compounds 3a-f contains β-lactam

FT-IR, ^1H, and ^{13}C NMR spectroscopy were used to characterised compounds 3a-f. The FT-IR spectra shows strong bands of the C=O group stretching vibration in the range of 1712–1774 cm^{-1}.[16] [17] The bands in the FT-IR spectra of compounds 3a-f at approximately 784 cm^{-1} can be assigned to the C-Cl stretching bonds. The ^1H NMR spectra for all synthesized compound 3a-f shows peaks for HC-Cl as a doublet in range of 4.50-4.20 ppm. Protons of H-CN gave doublet in rang of 4.35-4.07 ppm, and the methoxy group (-OCH_3) shows singlet peak at 4.28 ppm for compound 3f. Other aromatic peaks were observed between 8.79-7.10 ppm.[18] The proton of the indole ring (N-CH) appeared as

J Popul Ther Clin Pharmacol Vol 30(12):e289–e294; 18 May 2023.

singlat in the 6.70-4.13 ppm range. And singlet at 4.46-4.12 ppm is for (-CH_2) group, as well as an(-NH) and(O-H) proton gave a singlet at 11.87-8.41 and 10.65-8.12 ppm respectively,[19] while the CH_3 protons gave a singlet at 3.03 ppm for compounds 3a, 3f.

In the ^{13}C-NMR of compounds 3a, the characteristic peak of C=O group was appeared at 168 ppm. The carbon C=N in the thiadiazole ring was observed at 164 ppm, while carbon attached to C-OH was observed to peak at 138 ppm. The characteristic peak of $C_{aldehyde}$-C_{lactam} appeared at around 132 ppm. While the peak of $C_{thiadiazole}$-N_{lactam} was appeared at 112 ppm. The carbon aromatic rings showed at the rang between 129-119 ppm. Finally, the ^{13}C-NMR of the β-lactam ring, peaks of HC-Cl, HC-N respectively, were obsearved at 63 and 41 ppm.

Biological Evaluation

The synthesized compounds 3a-f were evaluated for their antibacterial activity against the staphylococcus aureus and streptococcus epidermidis, proteus mirabilis, and Klebsiella pneumonia for the concentrations (100 mg/ mL) and the results are provided in Table 1.

From table 1, the activites were better against S. epidermidis and K. pneumoia, while S. Aureus and P. mirabilis shows some resistance against some prepared compounds.

TABLE 1: Antibacterial activity against the staphylococcus aureus and streptococcus epidermidis, proteus mirabilis, and Klebsiella pneumonia (100 mg/ mL)

	S. Aureus	S. Epidermidis	P. Mirabilis	K. Pneumonia
Comp.	mm	mm	mm	mm
3a	15	17	12	17
3b	R	12	R	15
3c	R	13	R	15
3d	R	R	R	12
3e	R	R	R	11
3f	12	15	R	12
AX	R	R	R	R
DMSO	0	0	0	0

Methods

All produced compounds were verified using ^{1}H and some ^{13}C NMR spectroscopy, recorded on a Bruker AV 400 MHz spectro-meter. The synthesized compounds were dissolved in DMSO-d_6 in the laboratories of the Department of Chemistry, University of Tehran, Iran. The FT-IR spectra were recorded as pressed thin films on KBr disks, using a SHIMADZU, 8400S spectrophptometer in the region of 4000-400 cm^{-1}. The melting points were measured on a Stuart SMP3 apparatus by open capillary tube method and are uncorrected, in the labs of the Department of Chemistry, College of Education for Pure Scienec, University of Diyala, Iraq. The reactions were monitered using thin layer chromatography (TLC) and silica gel.

Synthesis of [5-((1H-indol-3-yl) methyl)-1, 3, 4-thiadiazol-2-amine] 1

A mixture of indole-3-acetic acid (0.5 g, 2.85 mmol), thiosemicarbazide (0.26 g, 2.85 mmol) and $POCl_3$ (5 mL) was heated at 150 ^oC. After 3 hour, the mixture was cooled to room temperature and water (25 mL) was added slowly. The reaction mixture was heated under reflux for 2 hour. The mixture was cooled to room temperature and basified to pH 8 by the dropwise addition of 50 % KOH solution and under stirring. The product was filtered and recrystallized form mixture of DMF and ethanol (3:7).

The product was obtained as a dark olive powder (0.64 g, 97 %). Molecular formula ($C_{11}H_{10}N_4S$), M.wt = 230 g / mol. m.p= 231-233 $\mathring{C}$. Rf 0.37

[Petrol-EtOAc (3:7)]. FT-IR (KBr disk, cm^{-1}) ν_{max}: 3371, 3294 (NH_2), 3186 (N-H), 3078 (C-H Ar), 2978, 2893 (C-H aliphatic), 1620 (C=N thiadiazole), 1573, 1489 (C=C Ar), 748 (C-S).

General Procedure for Synthesis of Compounds (2a-f)

To compound 1 (0.2 g, 0.87 mmol) in ethanol (6.6 mL), 5 drops of concentrated sulfuric acid were added, and stirred for 20 min. Benzaldehyde derivatives (a-f) (0.85 mmol) were dissolved in 5 mL ethanol and added dropwise to the mixture. The reaction mixture was refluxed for 6 hours, and monitored using TLC silica gel, ice water is poured into the mixture and was left overnight at room temperature until a solid appeared. The products were filtered, washed with cold water 25 mL, and crystalized from diethylether.

1-(((5-((1H-indol-3-yl) methyl)-1, 3, 4-thiadiazol-2-yl) imino) methyl) naphthalen-2-ol 2a

The Product was obtained as a black solid (0.32 g, 96%). Molecular formula ($C_{22}H_{16}N_4OS$), M.wt = 384 g/mol. m.p = 163-165˚C. Rf 0.35 [Petrol-EtOAc (3:7)]. FT-IR (KBr disk, cm^{-1}) ν_{max}: 3402 (OH), 3224 (N-H), 3070 (C-H Ar), 2985, 2893 (C-H aliphatic), 1635 (C=N imine), 1620 (C=N thiadiazole), 1512, 1465 (C=C Ar), 748 (C-S).

5-((1H-indol-3-yl)methyl)-1,3,4-thiadiazol-2-yl)-1-(4-bromophenyl) methanimine 2b

The product was obtained as a black solid (0.26 g, 76%). Molecular formula ($C_{18}H_{13}BrN_4S$), M.wt = 397 g/mol. m.p = 301-303 ˚C. R_f 0.36 [Petrol-EtOAc (4:6)]. FT.IR (KBr disk, cm^{-1}) νmax: 3317 (N-H), 3062 (C-H Ar), 2954, 2854 (C-H aliphatic), 1689 (C=N imine), 1620 (C=N thiadiazole), 1589, 1489 (C=C Ar), 748 (C-S).

5-((1H-indol-3-yl)methyl)-1,3,4-thiadiazol-2-yl)-1-(4-methoxyphenyl) methanimine 2c

The Product was obtained as a dark solid (0.22 g, 73%). Molecular formula ($C_{19}H_{16}N_4SO$), M.wt = 348 g/mol. m.p = 338-340 ˚C. R_f 0.35 [Petrol-EtOAc (4:6)]. FT-IR (KBr disk, cm^{-1}) ν_{max}: 3309 (N-H), 3062 (C-H Ar), 2978,2900 (C-H aliphatic), 1674 (C=N imine), 1604 (C=N thiadiazole), 1512, 1458 (C=C Ar), 1018 (C-O), 748 (C-S).

4-(((5-((1H-indol-3-yl)methyl)-1,3,4-thiadiazol-2-yl)imino)methyl)-2-methoxyphenol 2d

The Product was obtained as a black solid (0.24 g, 76%), Molecular formula ($C_{19}H_{16}N_4O2S$), M.wt = 364 g/mol. m.p = 327-329 ˚C. R_f 0.37 [Petrol-EtOAc (5:5)] FT-IR (KBr disk, cm^{-1}) ν_{max}: 3417 (O-H), 3332 (N-H), 3055 (C-H Ar), 2978,2908 (C-H aliphatic), 1658 (C=N imine), 1620 (C=N thiadiazole), 1512, 1458 (C=C Ar), 1026 (C-O), 748 (C-S).

4-(((5-((1H-indol-3-yl)methyl)-1,3,4-thiadiazol-2-yl)imino)methyl)-N,N-dimethylaniline 2e

The Product was obtained as a black solid (0.25 g, 80%).Molecular formula ($C_{20}H_{19}N_5S$), M.wt = 361 g / mol. m.p= 307-309˚C. R_f 0.34 [Petrol-EtOAc (6:4)]. FT-IR (KBr disk, cm^{-1}) ν_{max}: 3332 (N-H), 3070 (C-H Ar), 2924, 2831 (C-H aliphatic), 1651 (C=N imine), 1597 (C=N thiadiazole), 1535, 1489 (C=C Ar), 748 (C-S).

5-((1H-indol-3-yl)methyl)-1,3,4-thiadiazol-2-yl)imino)methyl)-2,6-dimethoxyphenol 2f

The Product was obtained as a black solid (0.18 g, 53%). Molecular formula ($C_{20}H_{18}N_4O_3S$), M.wt = 395 g/mol. m.p = 143-145 oC. R_f 0.36 [Petrol-EtOAc (4:6)]. FT-IR (KBr disk, cm^{-1}) ν_{max}: 3572 (O-H), 3201 (N-H), 3055 (C-H Ar), 2954, 2831 (C-H aliphatic), 1674 (C=N imine), 1612 (C=N thiadiazole), 1512, 1458 (C=C Ar), 1211 (C-O), 748 (C-S).

General Procedure for Synthesis of Compounds 3a-f

To a well–stirred solution of compounds 2a-f (0.2 g, 0.50 mmol) with trimethylamine (0.50 mmol) in dioxane 5 mL, the chloroacetylchloride (0.60 mmol) in 5 mL dioxane was added dropwise at 0-5 ˚C. The solution was heated under reflux for 4 h. Then, the solvent was evaporated under vacuum. Ice water was added to the products,

filtered, washed with cold water, and crystallized from diethyl ether.

1-(5-((1H-indol-3-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-(2-hydroxynaphthalen-1-yl) azetidin-2-one 3a

The product was obtained as a black solid (0.18, 75%).Molecular formula ($C_{24}H_{17}C_lN_4O_2S$). M.wt = 460 g/mol. m.p = 105-107 ̊C. R_f 0.38 [Petrol-EtOAc (6:4)]. FT-IR (KBr disk, cm^{-1}) ν_{max}: 3402 (O-H), 3224 (N-H), 3070 (C-H Ar), 2931, 2854 (C-H aliphatic), 1735 (C=O), 1627 (C=N thiadiazole), 1597, 1465 (C=C Ar), 794 (C-Cl), 748 (C-S). ^{1}H-NMR (400 MHz, DMSO-d6, δ ppm), 11.87 (s, 1H, N-H), 10.65 (s, 1H, O-H), 8.79-7.10 (d, 10H, Ar-H), 4.33(s, 1H, HC-NH), 4.20 (d, 1H, HC-Cl), 4.07 (d, 1H, HC-N), 4.12 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6), 168 (C=O), 164 (C=N), 138 (C-OH), 132 ($C_{aldehyde}$-C_{lactam}), 112 ($C_{thiadiazole}$-N_{lactam}), 129.74-119.22 (10 $CH)_{aromatic}$, 63 (C-Cl) $_{lactam}$, 41 (C-N) $_{lactam}$.

1-(5-((1H-indol-3-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-(4-(dimethylamino)phenyl)azetidin-2-one 3b

The product was obtained as a black solid (0.2 g, 84%). Molecular formula ($C_{20}H_{14}BrClN_4OS$), M.wt = 473 g/mol. m.p = 342-344 ̊C. R_f 0.40 [Petrol-EtOAc (3:7)]. FT-IR (KBr disk, cm^{-1}) ν_{max}: 3394 (N-H), 3078 (C-H Ar), 2954-2877 (C-H aliphatic), 1712 (C=O), 1620 (C=N thiadiazole), 1489, 1458 (C=C Ar), 748 (C-S). 1HNMR (400 MHz, DMSO-d6, δ ppm), 9.99 (s, H, NH), 8.34-7.22 (m, 8H, Ar-H), 6.70 (s, 1H, HN-C-H)$_{indole}$, 4.40 (d, 1H, HC-Cl), 4.28 (s, 2H, CH2), 4.18 (d, 1H, HC-N).

1-(5-((1H-indol-3-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-(4-methoxyphenyl)azetidin-2-one 3c

The product was obtained as a black solid (0.17 g, 70%). Molecular formula ($C_{21}H_{17}ClN_4O_2S$), M.wt = 424 g/mol. m.p = 335-337 ̊C. R_f 0.35 [Petrol-EtOAc (4:6)]. FT-IR (KBr disk, cm^{-1}) νmax: 3402 (N-H), 3039 (C-H Ar), 2924, 2831 (C-H aliphatic), 1766 (C=O), 1620 (C=N thiadiazole), 1512, 1450 (C=C Ar), 1033 (C-O), 848 (C-Cl), 748 (C-S).

1-(5-((1H-indol-3-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-(4-hydroxy-3-methoxyphenyl)azetidin-2-one 3d

The product was obtained as a black solid (0.2 g, 82%). Molecular formula ($C_{21}H_{17}ClN_4O_3S$), M.wt = 440 g/mol. m.p = 333-335 ̊C. R_f 0.36 [Petrol-EtOAc (6:4)]. FT-IR (KBr disk, cm^{-1}) ν_{max}: 3356 (OH), 3240 (N-H), 3078 (C-H Ar), 2931, 2854 (C-H aliphatic), 1712 (C=O), 1620 (C=N thiadiazole), 1458 (C=C Ar), 1033 (C-O), 925 (C-Cl), 748 (C-S).

1-(5-((1H-indol-3-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-(4-(dimethylamino)phenyl) azetidin-2-one 3e

The product was obtained as a black solid (0.2 g, 83%). Molecular formula ($C_{22}H_{20}ClN_5OS$), M.wt = 437 g/mol. m.p = 323-325 ̊C. R_f 0.34 [Petrol-EtOAc (4:6)]. FT-IR (KBr disk, cm^{-1}) ν_{max}: 3387 (N-H), 3255 (C=C-H Ar), 2931 (C-C-H aliphatic), 1743 (C=O), 1620 (C=N thiadiazole), 1589, 1458 (C=C Ar), 1072 (C-O), 902 (C-Cl), 748 (C-S).). 1HNMR (400 MHz, DMSO-d6, δ ppm), 10.50 (s, 1H, N-H), 8.34-7.23 (m, 7H, Ar-H), 6,78 (s, 1H, NH-CH), 4.50(d,1H, HC-Cl), ,4.27 (s, 2H,CH2), 4.13 (d, 1H, HN-C-H), 3.03 (s, 6H, 2CH3).

1-(5-((1H-indol-3-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-(4-hydroxy-3,5-dimethoxyphenyl)azetidin-2-one 3f

The product was obtained as a black solid (0.16 g, 68%). Molecular formula ($C_{22}H_{19}ClN_4O_4S$), M.wt = 470 g/mol. m.p = 337-339 ̊C. R_f 0.38 [Petrol-EtOAc (4:6)]. FT-IR (KBr disk, cm^{-1}) ν_{max}: 3394(O-H), 3263 (N-H), 3070 (C-H Ar), 2931,2823 (C-H aliphatic), 1720 (C=O), 1620 (C=N thiadiazole), 1543, 1450 (C=C Ar), 1033 (C-O), 748 (C-S). 1HNMR (400 MHz, DMSO-d6, δ ppm), 8.33 (s, 1H, N-H), 8.14 (s, 1H, O-H), 7.41-7.25 (m, 6H, Ar-H), 6.70 (s, 1H, CHindole), 4.46 (s, 2H, CH2), 4.35(d, 1H, NC-H), 4.41 (d, 1H, HC-Cl), 4.28 (s,6H, 2OCH3).

CONCLUSION

1,3,4-thiadiazole ring and four membered ring 2-azetidinone were successfully synthesized which derived from indole carboxylic acid. The biological test of the prepared compound against selected bacteria gave moderate to good activities.

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