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Thiazolo[3,2-a] pyrimidin-5-ones: Design, Synthesis and Antimicrobial Evaluation

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Abstract

Bacterial and fungal infections represent one of the most common health problem that cause functional disability and other complications. Upcoming needs for the clinical drugs candidates for the improvement signifies an exciting and challenging approach to improve the clinical effectiveness of current drugs in the development of new therapeutic approaches. In the existing report, we here report our results for extensive SAR study of novel thiazolo pyrimidin-5-ones derivatives, synthesis, antibacterial and antifungal activity. We are happy to display our most active compounds **5a, 5d, 5e, 5i** owned incredible antimicrobial and antifungal potency. Altogether, compound **5i** was found to be a lead candidate, displayed maximum potency in both antifungal and antibacterial segments. These findings recommend the prospective to explore this series as antimicrobial and anti-fungal agents.

Key words : Antibacterial, Antifungal, Thiazolo pyrimidin-5-ones, SAR.

Introduction

Heterocyclic compounds containing nitrogen or sulphur have been described for their biological activity against various micro-organisms. Indole unit is the key building block for a variety of compounds which have crucial roles in the functions of biologically important molecules. Introduction of different groups to the modified Indole structure can produce a series of compounds with multiple activities. Various 3-substituted Indoles had been used as starting materials for the synthesis of a number of alkaloids, agrochemicals, pharmaceuticals and perfumes. Also 3-substituted Indole derivatives possess various types of broad spectrum's biological activities such as antimicrobial, antitumor, hypoglycemic, anti-inflammatory, analgesic and antipyretic activities[1, 2]. Moreover the substitution at the 3-position of the Indole ring can take place by connecting an additional heterocyclic ring, such as thiazolo pyrimidinone. For the rapid development of bacterial drug resistance is a very important global problem. Because of that, there is a urgent need to develop new antimicrobial drugs with potent activity in order to overcome the bacterial drug resistance. Electron-rich nitrogen and sulfur having compounds play an important role in diverse biological

activities. Thiazolo [3,2-*a*] pyrimidinone nucleus have been consistently regarded as structural similarities of biogenic purine bases and can be considered as potential purine antagonists[3]. These heterocyclic systems are the key chemical building blocks for numerous compounds that also play important roles in the functioning of biologically active molecules. As one type of those heterocyclic rings, 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones are considered a promising class of bioactive heterocyclic compounds having a wide range of biological activities such as anti-inflammatory[4,5]. These compounds also have Anti- hypertensive[6], antifungal[7], antibiofilm[8], antibacterial[9], antiviral[10], antioxidant[11], antitumor[12,13], anti-HIV[14], calcium channel blocking[15], antitubercular[16] activities. Apart from this our research group also newly synthesize earlier some potent biologically active compounds like antimicrobial[17], anti tubercular agents[18]. These applications have motivated a continuous search for the synthesis of new compounds in this field and ready to the appearance of some drugs in the market.

Materials and Methods

The melting points of the synthesized compound were determined in open capillary tubes and uncorrected. The ^{1}H NMR and for the compound synthesized were recorded (DMSO-d_6) on a Varian (400 MHz) using TMS as an internal standard. Chemical values are given δ scales. The spectra of mass were recorded on ES-MS. The completion of reactions was monitored by thin layer chromatography (TLC) on silica gel coated aluminum sheets. The spots were visualized by UV light. Necessary chemicals were ordered from Sigma-Aldrich and Spectrochem (INDIA). Commercial grade solvents were used without further purification.

Experimental

Synthesis of 5-oxo-5H-[1, 3] thiazolo[3,2-a]pyrimidin-7-ylmethyl (triphenyl) phosphonium chloride (2):

To a stirred suspension of 7-(chloromethyl)-5H-thiazolo [3,2-a] pyrimidin-5-one**1** (0.029 mole) in acetonitrile was added triphenylphosphine (0.032mole) at room temperature. The resulting reaction mixture was slowly heated to reflux for 30 min. Then it was cooled and solvent was concentrated in vacuo. The residue was stirred with diisopropyl ethyl ether and filtered. The solid isolated was dried under vacuum to afford the desired compound **2** as an off-white solid (79%). M.p. 158-160^{0}C; ^{1}H NMR (400 MHz, DMSO- d_6) δ: 4.86 (d, J=15.0 Hz, 2H), 6.45 (br. s,1H), 7.32 (br. s, 1H), 7.60 -7.74 (m, 15H), 7.86 (br. s, 1H); MS (m/z): 463[M+H]$^+$.

Synthesis of (E)-7-(2-(1H-indol-3-yl)vinyl)-5H-thiazolo[3,2-a] pyrimidin-5-one (4): By dissolving 0.1 gm (0.0002mole) of thizolo triphenyl phosphonium chloride salt in 5 ml DMF at 0-5° C. Then add this solution NaH (0.0004mole) portionwise slowly. This reaction mixture was stirred for 30 min. at same temperature. Then Indole-3-Carbaldehyde (0.0002mole) in DMF added slowly in above reaction mixture dropwise and stirred about 4-6 hrs. at room temperature. Completion of reaction checked by TLC. Reaction mixture was poured into ice water then a yellowish product precipitate out. Filtered and recrystallised by ethanol.

Table 1. Substitution Statergy of derivatives

Sr.No.	Sample	R
1	5a	H
2	5b	Benzyl
3	5c	Cyclopentyl
4	5d	Methyl
5	5e	Ethyl
6	5f	Isopropyl
7	5g	Cyclohexyl
8	5h	Acetyl
9	5i	Propionyl
10	5j	Benzoyl

General Procedure for Synthesis of (E)-7-(2-(1- Acyl Indol-3-yl)vinyl)-5H thiazolo [3,2-a] pyrimidin-5-one(5a-j):

Indole thiazolo pyrimidinone (0.0034mole) was dissolved in N, N-dimethylformamide (5ml). The reaction mixture was cooled to 0-5ºC and added sodium hydride (60 % in mineral oil, 0.0068mole) portion wise. The reaction mixture was stirred for 30 min. at same temperature. To the above stirred solution added solution of acetic unhydried (0.0034mole) in N, N-dimethylformamide (5ml) dropwise. The resulting reaction mixture was stirred for overnight at 30-35ºC. After completion of reaction (checked by TLC) reaction mass poured into ice cold water, solid was precipitated out, which was then seperated by filtration, washed with water to get titled compound which was recrystallised by alcohol.

Similarly the other derivatives of the series were prepared. Their structures have been confirmed by IR, ^{1}HNMR and Mass spectra.

Synthesis of(E)-7-(2-(1H-indol-3-yl)vinyl)-5H-thiazolo [3,2-a] pyrimidin-5-one (5a): Pale green solid (78%) ; m.p. 142-144^{0}C**;** IR (KBr, cm^{-1}): 1678 (C=O), 2964 (Ar-H), 1560 (C=C), 3215 (NH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.48 (d, 1H, thiazolo H,), 7.60 (d, 1H, thiazolo H), 8.20 (s, 1H, indole H), 7.19 (d,1H, olefin H), 7.25 (d,1H, olefin H), 8.0 (s, 1H, thiazolo H), 7.4-7.5 (m, 4H, Ar-H), 12.10 (s,1H); MS (m/ z): 294 [M+H]$^+$.

(E)-7-(2-(1-benzyl-1H-indol-3-yl)vinyl)-5H-thiazolo[3,2-a]

pyrimidin-5-one(5b): Yellow solid (68%); m.p. 170-172^{0}C**;** IR (KBr, cm^{-1}): 1680 (C=O), 2918 and 3032 (Ar-H), 1571 and 1655 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.31 (s, 5H, benzyl Ar-H), 5.54 (s, 2H, benzyl CH_2), 7.31 (d, 1H, thiazolo H,), 7.31 (d, 1H, thiazolo H), 8.46 (s, 1H, indole H), 7.31(d,1H, olefin H), 7.31 (d, 1H, olefin H), 8.11 (s, 1H, thiazolo H), 7.57 (s, 4H, Ar-H); MS (m/ z): 384[M+H]$^+$.

(E)-7-(2-(1-cyclopentyl-1H-indol-3-yl)vinyl)-5H-thiazolo[3,2-a]pyrimidin-5-one(5c): Pale brown solid (62%); m.p. 112-114^{0}C**;** IR (KBr, cm^{-1}): 1683 (C=O), 3035 (Ar-H), 1635 (C=C); ^{1}H NMR (400 MHz, DMSO- d_6) δ: 1.79-2.00 (m, 7H, cyclopentyl H), 2.25 (m, 2H, cyclopentyl H), 7.23 (d, 1H, thiazolo H,), 7.29 (d, 1H, thiazolo H), 8.98 (s, 1H, indole H), 7.43 (d, 1H, olefin H), 7.31 (d, 1H, olefin H), 8.41 (s, 1H, thiazolo H), 7.62 (s, 4H, indole Ar-H); MS (m/ z): 362[M+H]$^+$.

(E)-7-(2-(1-methyl-1H-indol-3-yl)vinyl)-5H-thiazolo[3,2-a] pyrimidin-5-one(5d): Buff white solid (68%); m.p. 181-183^{0}C**;** IR (KBr, cm^{-1}): 1690 (C=O), 3056 (Ar-H), 1610 (C=C); ^{1}H NMR (400 MHz, DMSO- d_6) δ: 3.45 (s, 3H, methyl H), 7.02 (d, 1H, thiazolo H,), 7.39 (d, 1H, thiazolo H), 8.02 (s, 1H, indole H), 7.42 (d, 1H, olefin H), 7.48 (d, 1H, olefin H), 8.12 (s, 1H, thiazolo H), 7.19-7.61 (s, 4H, indole Ar-H); MS (m/ z): 308 [M+H]$^+$.

(E)-7-(2-(1-ethyl-1H-indol-3-yl)vinyl)-5H-thiazolo[3,2-a] pyrimidin-5-one(5e): Colourless solid (75%) ; m.p. 165-167^{0}C**;** IR (KBr, cm^{-1}): 1683 (C=O), 3042 (Ar-H), 1545 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.42 (t, 3H, methyl H), 4.40 (q, 2H, ethyl CH_2), 6.90 (d, 1H, thiazolo H), 7.10 (d, 1H, thiazolo H), 8.20 (s, 1H, indole H), 7.32 (d, 1H, olefin H), 7.40 (d, 1H, olefin H), 7.60 (s, 1H, thiazolo H), 7.19-7.70 (s, 4H, indole Ar-H); MS (m/ z): 322 [M+H]$^+$.

(E)-7-(2-(1-isopropyl-1H-indol-3-yl)vinyl)-5H-thiazolo[3,2-a] pyrimidin-5-one(5f): Brown solid(62%); m.p. 155-157^{0}C**;** IR (KBr, cm^{-1}): 1688 (C=O), 3056 (Ar-H), 1559 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ:1.74 (d, 6H, isopropyl CH_3), 5.45 (m, 1H, isopropyl CH), 5.95 (d, 1H, thiazolo H,), 7.10 (d, 1H, thiazolo H), 8.40 (s, 1H, indole H), 7.15 (d, 1H, olefin H), 7.21 (d, 1H, olefin H), 7.97 (s, 1H, thiazolo H), 7.29-7.55 (m, 4H, Ar-H);MS (m/ z): 336 [M+H]$^+$.

(E)-7-(2-(1-cyclohexyl-1H-indol-3-yl)vinyl)-5H-thiazolo[3,2-a]pyrimidin-5-one(5g): Brown solid (67%); m.p. 198-200^{0}C**;** IR (KBr, cm^{-1}): 1695 (C=O), 3054 (Ar-H), 1610 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.48-2.00 (m, 10H, cyclohexyl H), 3,40 (m, 1H, cyclohexyl H), 6.90 (d, 1H, thiazolo H,), 7.10 (d, 1H, thiazolo H), 8.42 (s, 1H, indole H), 7.0 (d, 1H, olefin H), 7.05 (d, 1H, olefin H), 8.40 (s, 1H, thiazolo H), 7.10-7.42 (s, 4H, indole Ar-H); MS (m/ z): 376 [M+H]$^+$.

(E)-7-(2-(1-acetyl-1H-indol-3-yl)vinyl)-5H-thiazolo[3,2-a] pyrimidin-5-one(5h): Pale yellow solid (74%) ; m.p. 118-120^{0}C**;** IR (KBr, cm^{-1}): 1680 (C=O), 3035 (Ar-H), 1623 (C=C); ^{1}H NMR (400 MHz, DMSO- d_6) δ: 2.81 (s, 3H, acetyl CH_3), 7.11 (d, 1H, thiazolo H,), 7.20 (d, 1H, thiazolo H), 8.60 (s, 1H, indole H), 6.90 (d, 1H, olefin H), 6.98 (d, 1H, olefin H), 8.01 (s, 1H, thiazolo H), 7.25-7.60 (m, 4H, indole Ar-H);MS (m/ z): 336 [M+H]$^+$.

(E)-7-(2-(1-propionyl-1H-indol-3-yl)vinyl)-5H-thiazolo [3,2-a] pyrimidin-5-one(5i): Pale yellow solid (78%) ; m.p. 110-112^{0}C**;** IR (KBr, cm^{-1}): 1690 (C=O), 3048 (Ar-H), 1623 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.25 (t, 3H, methyl), 3.21 (q, 2H,CH_2), 8.28 (d, 1H, thiazoloH,), 8.15 (d, 1H, thiazolo H), 8.92 (s, 1H, indole H), 7.56 (d, 1H, olefin H), 7.62 (d, 1H, olefin H), 8.28 (s, 1H, thiazolo H), 7.21-7.56 (s, 4H, indole Ar-H); MS (m/ z): 350 [M+H]$^+$.

(E)-7-(2-(1-benzoyl-1H-indol-3-yl)vinyl)-5H-thiazolo[3,2-a] pyrimidin-5-one(5j): Faint brown solid(81%) ; m.p. 202-204^{0}C**;** IR (KBr, cm^{-1}): 1696 (C=O), 2978 and 3034 (Ar-H), 1556 and 1623 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.95 (d, 1H, thiazolo H,), 7.15(d, 1H, thiazolo H), 8.10 (s, 1H, indole H), 7.05 (d, 1H, olefin H) ,7.12 (d, 1H, olefin H), 8.01 (s, 1H, thiazolo H), 7.25-7.93 (m, 9H, Ar-H); MS (m/ z): 398[M+H]$^+$.

Results and Discussion

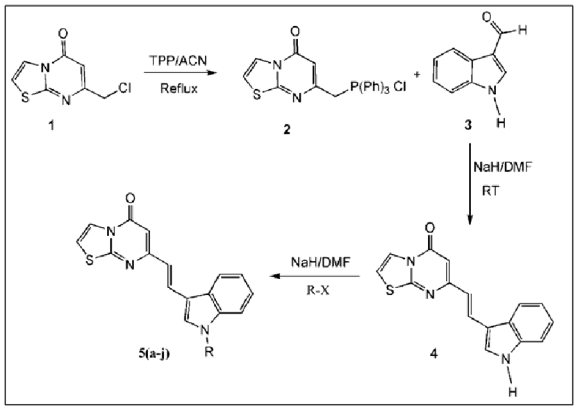

Figure 1: Synthetic Scheme

We started our synthetic course with witting reagent preparation. Initially commercially available 7-(chloromethyl)-5H-thiazolo (3,2-a) Pyrimidin-5-one was treated with triphenyl phosphine in acetonitrile at room temperature to yield 5-oxo-5H-[1, 3] thiazolo [3,2-a] pyrimidin-7-yl methyl triphenyl phosphonium chloride (**2**) (Wittig Reagent) in excellent yield. Further after activation of **2** with NaH in DMF, it was then treated with indole carbaldehyde (**3**) and the coupled product (E)-7-(2-(1H-

indol-3-yl) vinyl)-5H-thiazolo [3,2-a] pyrimidin-5-one (**4**) was isolated in comfortable yield. Finally, the targeted compounds (**5a-j**) were isolated after alkylation / acylation to **4**.

The progress of all reactions was monitored by thin layer chromatography. The synthesized derivatives (**5a-j**) were isolated in moderate to good yield. Final molecules **5(a-j)** structurally was ensured by spectroscopic analysis methods (Mass, IR, ^{1}H-NMR etc).

Antimicrobial activity:

Antifungal and antibacterial activities were performed using different fungal and bacterial culture. Ciprofloxacin was used as standard reference for antibacterial assay and flucanazole was used as standard reference in antifungal assay. While performing the SAR driven synthesis, different variations in the targeted molecules was bring by introducing different R group across the indole nitrogen. The results data is illustrated in Table 2.

Table 2. Antimicrobial Activity of Synthesized compounds (5a-j)

Sr. No.	Comp. No.	Inhibition Zone Diameter(mm)						
		I	II	III	IV	V	VI	VII
1	5a	10	16	10	13	12	11	13
2	5b	10	09	04	03	05	09	08
3	5c	09	10	06	03	09	10	06
4	5d	12	16	13	13	15	13	11
5	5e	13	15	12	12	17	18	12
6	5f	10	09	10	07	07	08	09
7	5g	10	04	10	09	08	02	07
8	5h	10	07	11	11	12	06	07
9	5i	13	17	12	13	16	14	13
10	5j	07	08	09	10	07	10	09
11	Ciprofloxacin	-	18	-	14	16	15	14
12	Fluconazole	13	-	12	-	-	-	-

Fungus Culture: I-*Aspergillus niger,* I-*Bacillus subtilis,* III-*Candida albicans,* IV-*Escherichia coli,* V- *Pseudomonas aeruginos,* VI- *Sallemonella abony,* VII-*Staphylococcus aureus.*

Initially Antifungal assay were performed using *Aspergillus niger* and *Candida albicans.* In this screenings, compound **5d, 5e, 5i** displayed superior performance than standard, for the rest compounds although the activity profiles was not better, but almost all the showed comparable performance to fluconazole.

In Antibacterial assay, compounds **5a, 5d, 5e** and **5i** was superior performer. For all these compounds, it was in our strategy to go for smaller R groups, accordingly, H, ethyl, methyl and propionyl group was brought across R, the antibacterial assay for all these derivatives in different culture was good which gives encouragement for us since our idea was worked out. Further to explore the activity profiles, R was replaced by a bigger group (benzoyl, benzyl, cyclopentyl etc). As a results derivative **5b, 5c, 5j** demonstrated very poor activity results. These findings were expected based on our thinking. Hence derivatives with smaller R groups were comfortable for the activity profile and that of bulkier group was making results inferior. Overall compound **5i** displayed best activity profiles in different antifungal and antibacterial cultures.

Conclusion

The current study reported the series of novel pyrimidin-5-one as antimicrobial and antifungal agents. The synthesized compounds after structural illustrations were subsequently subjected for their antimicrobial and antifungal studies. As results, all the synthesized compounds displayed almost comparable antifungal profile, moreover, compound **5e, 5g** and **5j** was found to be superior in *Aspergillus niger* and *Candida albicans* when compared with flucanazole as standard reference. Similarly, in antibacterial evaluation**, 5a, 5d, 5e** and **5i** was superior derivative exhibited good performance. In summary, compound **5i** was found to the best compound in the series, displayed both anti-fungal and antibacterial properties in different cultures.

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