Synthesis of Some N-(4-(Aryl)-2-Thioxo-1,3-Thiazol-3(2H)-yl)Pyridine-4-Carboxamide as Antimicrobial and Anti-inflammatory Agents

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Abstract

A series of potential bioactive compounds, N-(4-aryl-2-thioxo-1,3-thiazol-3(2H)-yl)pyridine-4-carboxamide has been synthesized and screened for antibacterial, antifungal, anti-inflammatory activity by minimum inhibitory concentration and protein denaturation method respectively. The compounds Iic and IIj were found to be broad spectrum antimicrobial agents at minimum inhibitory concentration value against E. coli, K. pneumonia, S. aureus, B. subtilis, A. nigra, and S. cerevisiae respectively. In anti-inflammatory activity, compounds Iic, IIf, Iih, and IIj at 100 mg/ml and compound III at 200 mg/ml were found significant active agent.

Keywords: Antimicrobial; Anti-inflammatory; MIC; Thiazol

Introduction

There has been a constant battle between humans and the multitude of microorganisms that cause infections and diseases; the treatment of bacterial infections remains a challenging job because of the increasing number of multidrug-resistant microbial pathogens. Despite the many chemotherapeutics available, the emergence of old and new antibiotic-resistant bacterial strains, mutations in microbial genomes, the incorrect use of antibiotics has been thoroughly demonstrated to greatly increase the development of resistant genotypes has generated a substantial need for new classes of anti-bacterial agents [1-2]. Various antibacterial agents greatly increase the development of resistant genotypes has generated a substantial need for new classes of anti-bacterial agents [1-2], hypoglycemic [4], anti-inflammatory and analgesic agents [5], anti-diabetic [6], antihyperglycemic [7]. Above mentioned facts prompted us to synthesis a series of N-(4-(aryl)-2-thioxo-1,3-thiazol-3(2H)-yl)pyridine-4-carboxamide compounds having antimicrobial and anti-inflammatory activity. The structures of the compounds were confirmed by FT-IR, 1H-NMR, GC-mass spectroscopy and elemental analysis data studies; their antibacterial, antifungal, and anti-inflammatory activities were performed by MIC (Minimum Inhibitory Concentration) method.

Experimental

Material and methods

All reagents and solvents used in the present study were of analytical grade and procured from Loba Chemie (India). The progress of the reactions were monitored by TLC using Merck silica gel precoated plate, with appropriate mobile phase, visualization by iodine vapour and UV chamber and product are purified by recrystallization technique. All the melting points recorded on a Veego apparatus (Mumbai, India) and the IR spectra were recorded on FT-IR spectrophotometer, Varian, Model: 600. The NMR spectra were recorded on Bruker′s 200 MHz spectrometer and spectral data are recorded in ppm downfield to TMS (tetramethylsilane), GC Mass were recorded on GCMS-QP-5050 Shimadzu (Japan), and Perkin Elmer 2400 Series II CHN Elemental Analyzer. The standard drugs norfloxacin, ketocazole, and ibuprofen were obtained as gift sample from Wockhardt Ltd., Aurangabad, India.

Synthesis of potassium-pyridine-dithiocarbazate (I)

In a 250 ml round bottom flask, isoniazide (0.075 mol, 10.28 g) was dissolved in a solution of potassium hydroxide (0.075 mol, 4.2 g) in 100 ml of absolute ethanol and carbon disulphide (0.075 mol). The reaction mixture was agitated overnight and diluted with 200 ml of dry ether. The solid obtained was filtered and washed with dry ether, yield 15.05 g ( 80% ) [8].

General procedure for synthesis of N-(4-(aryl)-2-thioxo-1,3-thiazol-3(2H)-yl)pyridine-4-carboxamide (II)

In a 250 ml round bottom flask, potassium-pyridine-dithiocarbazate I (0.01 mol, 2.51 g) was dissolved in a solution of α-bromo ketone (0.01 mol) in 100 ml of absolute ethanol and was refluxed for 8 h. The resultant solution was concentrate, and precipitate obtained after cooling was collected, washed with cold water, dried and recrystallized from ethanol to give good yield [9,10]. All the compounds were obtained in good yield, TLC mobile phase - benzene:pet ether (6:4). Scheme 1 and Table 1.

N-(4-biphenyl-4-yl-2-thioxo-1,3-thiazol-3(2H)-yl)pyridine-4-carboxamide IIa: FT-IR ν max (KBr, cm⁻¹): 1368 (C=S), 1402(C=C), 1651 (O-C), 1661(C=N), 2235(C=N), 3150(N-H), 1H-NMR (DMSO, 400 MHz) δ: 5.20 (s, 1H, NH), 7.41-7.59 (m, 9H, aromatic), 8.11 (s, 1H, sec. amide), 8.89-7.81 (m, 4H, pyridine), MS: [M⁺] at m/z 389.

N-[4-(2-hydroxyphenyl)-2-thioxo-1,3-thiazol-3(2H)-yl]pyridine-4-carboxamide IIb: FT-IR ν max (KBr, cm⁻¹): 1000 (C-O), 1370 (C=S), 1453 (C=C), 1636 (O=C), 1665 (C=N), 2250 (C-N), 3120 (N-H), 3645 (OH). 1H-NMR (DMSO, 400 MHz) δ: 5.15 (s, 1H, ethylene), 8.0 (s, 1H, sec. amide), 8.00 (s, 1H, pyridine), 6.80-7.50 (m, 4H, aromatic), 4.90 (s, 1H, OH). MS: [M⁺] at m/z 329.

N-[4-(4-chlorophenyl)-2-thioxo-1,3-thiazol-3(2H)-yl]pyridine-4-carboxamide IIc: FT-IR ν max (KBr, cm⁻¹): 750 (C-Cl), 1360 (C-S), 1600 (C-C), 1610 (O=C), 1709 (C=N), 2275 (C-N), 3160 (N-H). 1H-NMR (DMSO, 400 MHz) δ: 5.20 (s, 1H, ethylene), 7.38-7.50 (m, 5H, aromatic), 7.90 (s, 1H, sec. amide), 8.70-7.95 (m, 4H, pyridine), MS: [M⁺] at m/z 347.

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N-[4-(4-bromophenyl)-2-thioxo-1,3-thiazol-3(2H)-yl]pyridine-4-carboxamide IIc: FT-IR ν max (KBr, cm⁻¹): 995 (C-Br), 1393 (C=S), 1453 (C=S), 1540 (C=C), 1636 (O=C), 1734 (C=N), 1755 (C=O), 1793 (C=O). 1H-NMR (DMSO, 400 MHz) δ: 5.21 (s, 1H, ethylene), 7.72-7.54 (m, 4H, aromatic), 8.16 (s, 1H, sec. amide), 8.82-7.61 (m, 4H, pyridine). MS: [M]+ at m/z 327.

N-[4-(4-methylphenyl)-2-thioxo-1,3-thiazol-3(2H)-yl]pyridine-4-carboxamide II: FT-IR v max (KBr, cm⁻¹): 1444(C=S), 1490 (C=CH), 1448(C=S), 1635(O=C), 1675(C=N), 2240(C-N), 3210(N-H).

1H-NMR (DMSO, 400 MHz) δ: 2.38 (s, 3H, CH₃), 5.57 (s, 1H, ethylene), 7.18-7.26 (m, 4H, aromatic), 8.20 (s, 1H, sec. amide), 8.95-7.61 (m, 4H, pyridine). MS: [M]+ at m/z 328.

N-[4-(4-methoxyphenyl)-2-thioxo-1,3-thiazol-3(2H)-yl]pyridine-4-carboxamide II: FT-IR v max (KBr, cm⁻¹): 1444(C=S), 1587(C=C), 2252(C=N), 1490(C=O), 1636(O=C) 1675(C=N), 2220(C-N), 3208 (N-H), 3.85 (s, 3H, OCH₃). MS: [M]+ at m/z 328.

H-NMR (DMSO, 400 MHz) δ: 3.85 (s, 3H, OCH₃), 5.65 (s, 1H, ethylene) 7.27-7.36 (m, 4H, aromatic), 7.96 (s, 1H, sec. amide), 8.99-7.76 (m, 4H, pyridine). MS: [M]+ at m/z 328.

Isoniazide

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Table 1: Physicochemical characterization of N-[4-(aryl)-2-thioxo-1,3-thiazol-3(2H)-yl]pyridine-4-carboxamide (II).

| Comp       | R          | Mole. formula | M.W  | M.P. (°C) | Yield (%) |
|------------|------------|---------------|------|-----------|-----------|
| IIA        | Br–Ph      | C₈H₅N₂O₂S₃   | 389  | 240-242   | 60        |
| IIb        | o-HO-Ph    | C₇H₆N₂O₂S₃   | 329  | 125-126   | 57        |
| IIc        | p-Cl-Ph    | C₇H₆N₂O₂S₃   | 347  | 240-241   | 60        |
| IID        | p-Br-Ph    | C₇H₅BrN₂O₂S₃ | 392  | 139-140   | 59        |
| IEEE       | Chromene   | C₃H₄N₂O₃S   | 381  | 130-131   | 67        |
| IIF        | p-OCH₃-Ph  | C₇H₅N₂O₂S₃   | 343  | 95-101    | 55        |
| IIG        | p-NH₃-Ph   | C₇H₅N₂O₂S₃   | 328  | 160-161   | 72        |
| IIH        | m-NH₂-Ph   | C₇H₆N₂O₂S₂   | 328  | 160-161   | 72        |
| IIJ        | p-OH-Ph    | C₇H₆N₂O₂S₃   | 329  | 90-91     | 50        |
| IIK        | Ph         | C₇H₅N₂O₂S₃   | 315  | 137-138   | 78        |
| IIL        | p-NO₂-Ph   | C₇H₅N₂O₂S₂   | 358  | 120-121   | 72        |
| IIM        | m-NO₂-Ph   | C₇H₆N₂O₂S₃   | 358  | 132-133   | 45        |

Scheme 1: Scheme of synthesis for N-[4-(aryl)-2-thioxo-1,3-thiazol-3(2H)-yl]pyridine-4-carboxamide (II).
The relationship between chemical structure and antimicrobial, anti-inflammatory activity is summarized as follows.

The aryl ring should contain one substituent. Some substituents that seem to enhance antimicrobial, anti-inflammatory activity are chloro, methyl, methoxy, hydroxyl, amino and nitro groups. Compounds containing the p-Cl or -OH substituent are orders of broad spectrum than the original (first generation) compounds. It is believed that the high activity of these compounds is a function of the electron withdrawing group substitution on aryl ring at position no. 4 on thiazol ring. Among these compounds, it is thought that the spatial relationship between the electron donating groups contain compounds are less or inactive.

**Results and Discussion**

The synthesis of N-(4-(aryl)-2-thioxo-1,3-thiazol-3(2H)-yl)pyridine-4-carboxamide derivatives are depicted in Scheme 1. The IR spectra, reveals that functional groups present in the molecule appeared at their characteristic frequency characteristic frequency C=O, str. between 1661-1755 cm$^{-1}$, str. between 1344-1348 cm$^{-1}$, str. between 1360-1456 cm$^{-1}$, C=N, str. between 2357-2370 cm$^{-1}$, C-NO$_2$, str. between 1597-1666 cm$^{-1}$, C-Cl, str. between 1402-1456 cm$^{-1}$, C-CH$_3$, str. between 2920-2930 cm$^{-1}$, C-H, str. between 2955-2985 cm$^{-1}$, C-NH, str. between 1661-1755 cm$^{-1}$, C-H, str. between 1402-1607 cm$^{-1}$, O-H, str. between 3545-3647 cm$^{-1}$, C-Cl, str. between 750 cm$^{-1}$, C-Br, str. between 880-950 cm$^{-1}$, C-N, str. between 1490-1940 cm$^{-1}$, C=N, str. between 3548-3556 cm$^{-1}$, C-NO$_2$, str. between 1342-1344 cm$^{-1}$, C=O, str. between 1597-1677 cm$^{-1}$, C-O-C, str. at 1711 cm$^{-1}$, C-CH$_3$, str. at 1490 cm$^{-1}$ etc. The chemical shift (δ) for sec. amide hydrogen was observed in the range of 9.70-9.85 ppm, δ value for methyl hydrogen was observed at 2.38 ppm, δ value for methoxy hydrogen was observed at 3.85 ppm, δ value for ethylene hydrogen was observed in the range of 5.15-5.69 ppm, δ value for hydroxyl hydrogen was observed in the range of 4.90-5.68 ppm, δ value for amino hydrogen was observed in the range of 5.41-5.42 ppm, δ value for aromatic hydrogen was observed in the range of 6.25-8.24 ppm, δ value for pyridine hydrogen was observed in the range of 7.61-8.99 ppm. The m/e value was observed, e.g., in case of Ia-Ilm at 313-392 (M$^+$). So, from the physical and spectral data, we can conclude that the desired compounds synthesized successfully.

**Antimicrobial activity**

From in *vivo* antibacterial activity. In case of *E. coli, K. pneumonia*, *S. aureus* and *B. subtilis* compounds IIC, IId, IIg and Ilm (p-Cl-PH, p-OCH$_3$-PH, p-CH$_3$, p-OH, m-NO$_2$-PH ) were found to have significant anti-inflammatory activity which is 1 folds less than the standard drug nirfloxacin, while in *vitro* antifungal activity. In case of *A. niger* and *S. cerevisiae* compounds IIC, III, IIIf and IId (p-Cl-PH, p-CH$_3$, p-OH, m-NO$_2$-PH) found to have significant activity which is 1 folds less than the standard drug ketoconazole. In anti-inflammatory activity, compounds IIC, III, IIIf, and IIg at 100 mg/mL (p-Cl-PH, p-OH, p-NH$_2$-PH, and p-OH) were found to have significant activity which is 1 folds less than the standard drug ibuprofen and at 200 mg/mL compound III (p-NO$_2$-PH) found significant active which is 1/10th less than standard drug ibuprofen (Tables 2 and 3). Thus from the obtained antibacterial, antifungal and anti-inflammatory activity data we could conclude that the electron withdrawing groups substituted at specific position on phenyl ring i.e., (p-Cl-PH, p-OCH$_3$-PH, p-OH, m-NO$_2$-PH, p-CH$_3$-PH, p-NH$_2$-PH and p-NO$_2$-PH) are contributing positively for antibacterial and anti-inflammatory activity.

**Conclusion**

A series of N-(4-(aryl)-2-thioxo-1,3-thiazol-3(2H)-yl)pyridine-4-carboxamide had been synthesized in quantitative yields with the use of conventional method and evaluated for their *in vitro* antimicrobial and anti-inflammatory activity result are shown in Tables 2 and 3.

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Table 2: Minimum inhibitory concentration values (µg/ml) of derivatives (IIa-IIm) against microbes.

| Comp | E. Coli | K. pneumoniae | S. aureus | B. subtilis | A. niger | S. cerevisiae |
|------|---------|---------------|-----------|-------------|---------|--------------|
|      |         |               |           |             |         |              |
| Ila  | 45      | 68            | 49        | 33          | 59      | 57           |
| IIb  | 48      | 45            | 38        | 36          | 32      | 36           |
| Iic  | 27      | 39            | 31        | 27          | 36      | 25           |
| IId  | 52      | 62            | 74        | 37          | 37      | 61           |
| Ile  | 67      | 69            | 49        | 45          | 52      | 77           |
| IIf  | 58      | 68            | 77        | 43          | 31      | 27           |
| IIf  | 24      | 38            | 30        | 25          | 56      | 57           |
| III  | 76      | 88            | 82        | 67          | 72      | 72           |
| Ilj  | 60      | 70            | 55        | 62          | 61      | 46           |
| Ilk  | 22      | 36            | 28        | 23          | 29      | 23           |
| Ill  | 63      | 69            | 58        | 41          | 90      | 58           |
| IIm  | 51      | 88            | 79        | 52          | 47      | 68           |
| IIg  | 27      | 51            | 47        | 34          | 60      | 48           |
| IIh  | 48      | 51            | 47        | 34          | 60      | 48           |
| IIi  | 60      | 70            | 55        | 62          | 61      | 46           |
| IJf  | 63      | 69            | 58        | 41          | 90      | 58           |
| IIg  | 27      | 51            | 47        | 34          | 60      | 48           |
| IIl  | 48      | 51            | 47        | 34          | 60      | 48           |
| Norfloxacin |      | --            | --        | --          | --      | --           |
| Ketoconazole |   | --            | --        | --          | --      | --           |

Table 3: Anti-inflammatory activity by % inhibition of protein denaturation for derivatives (IIa-IIm).

| Comp | Anti-inflammatory effect (%) | Inhibition (%) |
|------|-------------------------------|----------------|
|      | 100 µg/ml                     | 200 µg/ml      | 100 µg/ml     | 200 µg/ml     |
| Ila  | 0.042 ± 0.00108               | 0.0467 ± 0.00039 | 55.78          | 48.73          |
| IIb  | 0.031 ± 0.00083               | 0.0423 ± 0.00080 | 66.63          | 55.47          |
| Iic  | 0.021 ± 0.00082               | 0.0321 ± 0.00193 | 77.15          | 66.21          |
| IId  | 0.033 ± 0.00086               | 0.0473 ± 0.00102 | 64.73          | 50.21          |
| Ile  | 0.028 ± 0.00100               | 0.0362 ± 0.00095 | 69.89          | 59.78          |
| IIf  | 0.025 ± 0.00097               | 0.0332 ± 0.00116 | 72.94          | 65.05          |
| IIg  | 0.048 ± 0.00047               | 0.0528 ± 0.00140 | 49.26          | 44.42          |
| IIh  | 0.017 ± 0.00396               | 0.0495 ± 0.00285 | 80             | 48.21          |
| III  | 0.049 ± 0.00030               | 0.0558 ± 0.00186 | 48.42          | 41.26          |
| Ilj  | 0.023 ± 0.00045               | 0.0318 ± 0.00017 | 75.78          | 66.52          |
| IIk  | 0.036 ± 0.00023               | 0.0481 ± 0.00039 | 62.1           | 49.36          |
| III  | 0.037 ± 0.00029               | 0.0216 ± 0.00084 | 60.42          | 70.26          |
| IIm  | 0.029 ± 0.00037               | 0.0317 ± 0.00062 | 69.26          | 66.63          |
| Ibuprofen | 0.018 ± 0.00039 | 0.0225 ± 0.00010 | 80.42          | 76.31          |
| Control | 0.095 ± 0.00023 | 0.0950 ± 0.00023 | ---            | ---            |

The results are expressed as mean ± SDM (n=6). Significance was calculated by using one-way ANOVA with Dunnet’s t-test.

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