SYNTHESIS, IN VITRO ANTIMICROBIAL ACTIVITY OF SCHIFF’S BASE, AZETIDINONES AND THIAZOLIDINONES

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ABSTRACT

Objective: The objective of the present study is to synthesize 3-Chloro-4-[3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-yl]-1-(substituted) azetidin-2-one [4a-n] and 2-[3-(2,4-Dichloro-5-fluoro phenyl)-1H-pyraol-4-yl]-3-(substituted phenyl)-1,3-thiazolidin-4-one [5a-n]. The structure of all synthesized compounds were characterized by IR, 1H NMR, 13C NMR and mass spectral studies.

Methods: The titled compounds 3-Chloro-4-[3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-yl]-1-(substituted) azetidin-2-one [4a-n] and 2-[3-(2,4-Dichloro-5-fluoro phenyl)-1H-pyraol-4-yl]-3-(substituted phenyl)-1,3-thiazolidin-4-one [5a-n] were synthesized by the reaction of N-[3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-yl] methylene substituted anilin [3a-n] with chloro acetyl chloride and thioglycolic acid respectively. Compounds N-[3-(2,4-dichloro-5-fluoro phenyl)-1H-pyraol-4-yl] methylene) substituted aniline [3a-n] were synthesized by the reaction of 3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-carbaldehyde [2] with primary aromatic amine in alcohol. All compounds were evaluated for their antimicrobial activity.

Results: Compounds 3a,3b,3d,3j,3l,4a,4b,4d,4e,4j,4m,5e,5g,5h,5n exhibited excellent to good antibacterial activity as compared to reference drugs.

Conclusion: In summary, N-[3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-yl] methylene) substituted anilin [3a-n], 3-Chloro-4-[3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-yl]-1-(substituted) azetidin-2-one [4a-n] and 2-[3-(2,4-Dichloro-5-fluoro phenyl)-1H-pyraol-4-yl]-3-(substituted phenyl)-1,3-thiazolidin-4-one [5a-n] derivatives have been synthesized and characterized. In vitro antimicrobial testing of the compounds was carried out by microdilution Method. Amongst the synthesised compounds, many of them have proven their antimicrobial potency which varies from good to excellent.

Keywords: Schiff’s base, 2-Azetidinone, 4-Thiazolidinone, Antimicrobial activity

INTRODUCTION

Heteroaromatic compounds have attracted considerable attention in the design of biologically active molecules and advanced organic materials. Heterocycles containing nitrogen atoms in the core structure shows a number of pharmacologically and biologically active compounds. Hence, a practical method for the preparation of such compounds is of great interest in synthetic organic chemistry. Structurally, a Schiff’s base (also known as imine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group has been replaced by an imine or azomethine group. Schiff’s bases of pyrazole aldehydes and aromatic amines exhibit a wide range of biological activities such as antifungal [1], antibacterial [2] and antitubercular [3] etc. The biological significance of this class of compounds impelled us to continue working on the synthesis of new Schiff’s bases of pyrazole derivatives.

β-Lactam containing antibacterial agents has become an integral part of the chemotherapeutic arsenal available to today’s medical practitioners. Although the number of existing agents are quite extensive, but the search for better and more effective drug is still going on. Azetidinones are the very important class of compounds possessing a wide range of biological activities such as antibacterial [4], anti-inflammatory [5], antihyperlipidemic [6], anticancer [7], antimicrobial [8], antitumor [9], antitubercular [10] etc. Furthermore, thiazolidinone derivatives found to possess a wide spectrum of biological activities [11-17].

MATERIALS AND METHODS

Melting points were determined by open capillaries and are uncorrected. The progress of the reaction was checked on aluminium coated TLC plates (E. Merck) using various solvent systems as mobile phase and visualised under iodine vapour. IR-spectra (cm⁻¹) were recorded on a Shimadzu FT-IR spectrophotometer using KBr pellet method. 1H NMR and 13C NMR spectra were recorded on a Bruker DRX-300 NMR instrument, using CDCl₃ as solvent and TMS as an internal reference (chemical shifts in δ, ppm). Mass spectra were obtained on a Agilent 6520 (Q-TOF) Mass spectrometer.

Synthesis of (1E)-1-(2,4-Dichloro-5-fluorophenyl) ethane hydrazone [1]

A mixture of 2,4-dichloro-5-fluoro acetophenone (0.01 mol) and hydrazine hydrate (0.012 mol) was refluxed in round bottom flask containing absolute alcohol (30 ml) for 2 h in the presence of few drops of acetic acid. The content of the flask was cooled to give a solid product which was filtered, washed with water, dried and recrystallized from ethanol as a yellow crystalline solid.

Synthesis of 3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-carbaldehyde [2]

To a cold solution of (1E)-1-(2,4-Dichloro-5-fluorophenyl)ethanone hydrazone (0.015 mol) in DMF (25 ml) was added POC13 (0.0395 mol) and resulting mixture was stirred at 55-60 °C for 5-6 h [18]. Then the mixture was cooled to room temperature and poured into ice cold water. A saturated solution of bicarbonate was added to neutralise the solution. The precipitate so formed was filtered, washed with water, dried and recrystallized from ethanol as a yellowish white crystalline solid.

General procedure for the synthesis of N-[3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-yl] methylene) substituted anilin [3a-n]

A mixture of 3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-carbaldehyde (0.01 mol), various primary aromatic amine (0.01 mol) and few drops of glacial acetic acid was refluxed in methanol for six hours. Then the refluxed content was cooled to room temperature and poured into ice cold water. A precipitate formed, was filtered and washed with water, dried and recrystallized from ethanol as a white crystalline solid.

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and the product thus obtained was filtered, washed with water and recrystallized from acetone.

[3d] IR (KBr cm\(^{-1}\)): \(3389.81\) (-NH), \(1567.08\) (C=N), \(807.10\) (C-Cl), \(1023.0\) (-OCH\(_3\)). 1\(3\)C NMR: \(161.38\) (C1), \(120.09\) (C2), \(129.63\) (C3), \(129.08\) (C4), \(139.48\) (C9), \(60.5\) (C10), \(62.0\) (C11), \(162.08\) (C12), \(140.75\) (C13), \(139.58\) (C14), \(125.85\) (C15), \(122.99\) (C16). Mass (m/z): 368.5 (M), \(374.5\) (M+6), \(257\), \(230\), \(205\), \(164\), \(138\).

The resulting solution was then poured into crushed ice mixture was stirred for 2 h. The reaction mixture was then refluxed below 10 °C and then tri ethyl amine (0.02 mol) was added drop wise with constant stirring maintaining the temperature.

Methylene}substituted anilin (0.01 mol) was dissolved in 1,4-dioxan (50 ml). To this solution chloro acetyl chloride (0.012 mol) was added. A mixture of N-[3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-yl]-1-(substituted) azetidin-2-one [4a-n] was obtained.

General procedure for the synthesis of 3-Chloro-4-[3-(2,4-dichloro-5-fluorophenyl)-1H-pyrazol-4-yl]-1-(substituted phenyl)azetidin-2-one [4a-n]

Compound N-[3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-yl]methylene}substituted anilin (0.01 mol) was dissolved in 1,4-dioxan (50 ml). To this solution chloro acetyl chloride (0.012 mol) was added. The mixture was stirred for 2 h. The reaction mixture was then refluxed for 9-10 h. The resulting solution was then poured into crushed ice and the product thus obtained was filtered, washed with water and recrystallized from ethanol acetate.

[4a] IR (KBr cm\(^{-1}\)): 1730 (C=O), 1203 (CH=N), 760 (C-Cl), 1062 (C-F). \(\delta\): 4.01 (CH2-S), 7.3 (Ar-H). \(\delta\): 6.927 (-NH pyrazol), 5.961 (-CH pyrazol), 5.871 (CH-N), 3.975 (-CH2-S), 7.323-7.704 (Ar-H). \(\delta\): 6.927 (-NH pyrazol), 5.961 (-CH pyrazol), 5.871 (CH-N), 3.975 (-CH2-S), 7.323-7.704 (Ar-H). \(\delta\): 6.927 (-NH pyrazol), 5.961 (-CH pyrazol), 5.871 (CH-N), 3.975 (-CH2-S), 7.323-7.704 (Ar-H).

General procedure for the synthesis of 2-[3-(2,4-Dichloro-5-fluoro phenyl)-1H-pyrazol-4-yl]-3-(substituted phenyl)-1,3-thiazolidin-4-one [5a-n]

A mixture of N-[3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-yl]methylene}substituted anilin (0.01 mol), thio glycolic acid (0.01 mol), and anhydrous zinc chloride (0.01 mol) in DMF was refluxed for 11-12 h. The resulting solution was then poured into crushed ice and the product thus obtained was filtered, washed with cold water and recrystallized from methanol.

[5a] IR (KBr cm\(^{-1}\)): 1720.20 (-NH), 1260.70 (CH=N), 760.26 (C-Cl), 1066.12 (-C=O). \(\delta\): 1712 (C=O), 1205 (CH-N), 758 (C-Cl), 1070 (C-F), 2919 (-C=H). \(\delta\): 161.59 (C1), 130.69 (C3), 129.5 (C4), 129.08 (C5), 117.18 (C6), 144.65 (C7), 108.74 (C8), 135.82 (C9), 66.16 (C10), 141.75 (C11), 126.4 (C12), 131.82 (C13), 129.82 (C14), 131.91 (C15), 119.76 (C16), 126.4 (C17), 126.4 (C18).

Mass (m/z): 4245 (M), 4305 (M+4), 3335, 307, 259, 196, 164.

Temperature and solid separated was filtered, washed with cold water and recrystallized from methanol.

[5b] IR (KBr cm\(^{-1}\)): 6927 (-NH pyrazol), 5959 (-CH pyrazol), 5871 (CH=N), 401 (CH=S), 7324-7704 (Ar-H). \(\delta\): 6.927 (-NH pyrazol), 5.961 (-CH pyrazol), 5.871 (CH-N), 3.975 (-CH2-S), 7.323-7.704 (Ar-H). \(\delta\): 6.927 (-NH pyrazol), 5.961 (-CH pyrazol), 5.871 (CH-N), 3.975 (-CH2-S), 7.323-7.704 (Ar-H).

IR (KBr cm\(^{-1}\)): 1733.35 (-CO), 1256.46 (CH=N), 766.17 (-C=O), 1063.31 (-F). \(\delta\): 1712 (C=O), 1205 (CH-N), 758 (C-Cl), 1070 (C-F), 2919 (-C=H). \(\delta\): 161.59 (C1), 130.69 (C3), 129.5 (C4), 129.08 (C5), 117.18 (C6), 144.65 (C7), 108.74 (C8), 135.82 (C9), 66.16 (C10), 141.75 (C11), 126.4 (C12), 131.82 (C13), 129.82 (C14), 131.91 (C15), 119.76 (C16), 126.4 (C17), 126.4 (C18).

Mass (m/z): 453 (M), 457 (M+4), 421, 331, 289, 230, 212, 164, 122.
Table 1: Physical characterization data of compound (3a-n), (4a-n) and (5a-n)

| S. No. | R          | Mol. formula  | Mol. Wt. gm/mol | M. P. °C | Yield % |
|--------|------------|---------------|-----------------|---------|---------|
| 3a     | H          | C₆H₄NO₂Cl₂F  | 334             |         | 120     |
| 3b     | 2-Cl       | C₆H₄NO₂Cl₂F  | 368.5           |         | 140     |
| 3c     | 3-Cl       | C₆H₄NO₂Cl₂F  | 368.5           |         | 120     |
| 3d     | 4-Cl       | C₆H₄NO₂Cl₂F  | 368.5           |         | 156     |
| 3e     | 2-NO₂      | C₆H₄NO₃Cl₂F  | 379             |         |         |
| 3f     | 3-NO₂      | C₆H₄NO₃Cl₂F  | 379             |         | 156     |
| 3g     | 4-NO₂      | C₆H₄NO₃Cl₂F  | 379             |         | 148     |
| 3h     | 2-CH₂      | C₆H₄NO₂Cl₂F  | 348             |         | 180     |
| 3i     | 3-CH₃      | C₆H₄NO₂Cl₂F  | 348             |         | 182     |
| 3j     | 4-CH₃      | C₆H₄NO₂Cl₂F  | 348             |         | 180     |
| 3k     | 2-OCH₃     | C₆H₄NO₂Cl₂F  | 364             |         | 210     |
| 3l     | 3-OCH₃     | C₆H₄NO₂Cl₂F  | 364             |         | 190     |
| 3m     | 4-OCH₃     | C₆H₄NO₂Cl₂F  | 364             |         | 204     |
| 3n     | C₆H₄H₂     | C₆H₄NO₂Cl₂F  | 384             |         | 180     |
| 3o     | H          | C₆H₄NO₂Cl₂F  | 410.5           |         | 130     |
| 3p     | 2-Cl       | C₆H₄NO₂Cl₂F  | 445             |         | 170     |
| 3q     | 3-Cl       | C₆H₄NO₂Cl₂F  | 445             |         | 186     |
| 3r     | 4-Cl       | C₆H₄NO₂Cl₂F  | 445             |         | 200     |
| 3s     | 2-NO₂      | C₆H₄NO₃Cl₂F  | 455.5           |         | 160     |
| 3t     | 3-NO₂      | C₆H₄NO₃Cl₂F  | 455.5           |         | 120     |
| 3u     | 4-NO₂      | C₆H₄NO₃Cl₂F  | 455.5           |         | 166     |
| 3v     | 2-CH₂      | C₆H₄NO₂Cl₂F  | 424.5           |         | 196     |
| 3w     | 3-CH₃      | C₆H₄NO₂Cl₂F  | 424.5           |         | 132     |
| 3x     | 4-CH₃      | C₆H₄NO₂Cl₂F  | 424.5           |         | 100     |
| 3y     | 2-OCH₃     | C₆H₄NO₂Cl₂F  | 440.5           |         | 220     |
| 3z     | 3-OCH₃     | C₆H₄NO₂Cl₂F  | 440.5           |         | 202     |
| 3aa    | 4-OCH₃     | C₆H₄NO₂Cl₂F  | 440.5           |         | 176     |
| 3ab    | C₆H₄H₂     | C₆H₄NO₂Cl₂F  | 460.5           |         | 190     |
| 3ac    | H          | C₆H₄NO₂Cl₂F  | 408             |         | 127     |
| 3ad    | 2-Cl       | C₆H₄NO₂Cl₂F  | 442.5           |         | 152     |
| 3ae    | 3-Cl       | C₆H₄NO₂Cl₂F  | 442.5           |         | 173     |
| 3af    | 4-Cl       | C₆H₄NO₂Cl₂F  | 442.5           |         | 200     |
| 3ag    | 2-NO₂      | C₆H₄NO₃Cl₂F  | 453             |         | 160     |
| 3ah    | 3-NO₂      | C₆H₄NO₃Cl₂F  | 453             |         | 120     |
| 3ai    | 4-NO₂      | C₆H₄NO₃Cl₂F  | 453             |         | 186     |
| 3aj    | 2-CH₂      | C₆H₄NO₂Cl₂F  | 422             |         | 120     |
| 3ak    | 3-CH₃      | C₆H₄NO₂Cl₂F  | 422             |         | 142     |
| 3al    | 4-CH₃      | C₆H₄NO₂Cl₂F  | 422             |         | 168     |
| 3am    | 2-OCH₃     | C₆H₄NO₂Cl₂F  | 438             |         | 260     |
| 3an    | 3-OCH₃     | C₆H₄NO₂Cl₂F  | 438             |         | 210     |
| 3ao    | 4-OCH₃     | C₆H₄NO₂Cl₂F  | 438             |         | 224     |
| 3ap    | C₆H₄H₂     | C₆H₄NO₂Cl₂F  | 458             |         | 230     |

Antimicrobial activity

Following common standard strains were used for screening of antibacterial and antifungal activities: E. Coli (MTCC 442), P. Aeruginosa (MTCC 441), S. Aureus (MTCC 96), S. Pyogenus (MTCC 443), C. Albicans (MTCC 227), A. Nigera (MTCC 282), A. Clavatus (MTCC 1323). The strains were procured from Institute of Microbial Technology, Chandigarh. DMSO was used as a diluents/vehicle to get desired concentration of drugs to test upon standard bacterial strains. Each synthesised drug was diluted for obtaining 2000 microgram/ml concentration, as a stock solution. In primary screening 1000 microgram/ml, 500 microgram/ml, and 250 microgram/ml concentrations of the synthesised drugs were taken. The actively synthesised drugs found in this primary screening were further tested in the second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 200 microgram/ml 100 microgram/ml, 50 microgram/ml, 25 microgram/ml, 12.5 microgram/ml and 6.25 microgram/ml concentrations. The highest dilution showing at least 99% inhibition zone is taken as MIC. The result of this is much affected by the size of the inoculums. Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin, Nystatin and Griseofulvin were used as a standard. The Comparative activities of the newly synthesised compounds and the control antibiotics on bacterial and fungal strains respectively were summarised in table 2 and table 3.

Excellent to good activity was observed in compounds 4d (against E. Coli, P. Aeruginosa, S. Aureus, S. Pyogenus), compounds 3g, 4e, 5g, 5n (against E. Coli, S. Aureus, S. Pyogenus), compounds 3a, 3b, 3j, 3l, 4j, 4l, 4m, 5e, 5n (against E. Coli, S. Aureus) as well as compounds 3a, 3c, 3f, 3g, 3h, 3j, 3l, 3k, 3l, 4e, 4f, 4g, 4h, 4k, 4l, 4m, 5b, 5e, 5f, 5g, 5i, 5j, 5l, 5m (against C. Albicans). The remaining compounds were found effective at a much higher concentration as compared to the standard drugs.

Table 2: Antibacterial activity of compounds 3a-n, 4a-n and 5a-n

| Code | E. Coli  | P. Aeruginosa | S. Aureus | S. Pyogenus |
|------|----------|--------------|-----------|------------|
| No.  | MTCC 442 | MTCC 441     | MTCC 96   | MTCC 443   |
| 3a   | 100      | 200          | 250       | 125        |
| 3b   | 62.5     | 100          | 125       | 200        |
| 3c   | 200      | 125          | 250       | 62.5       |
| 3d   | 250      | 200          | 200       | 200        |

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Table 3: Antifungal activity of compounds 3a-n, 4a-n and 5a-n

| Code | C. albicans | A. niger | A. clavatus |
|------|-------------|----------|-------------|
|      | MTCC 227    | MTCC 282 | MTCC 1323   |
| 3a   | 500         | 250      | 250         |
| 3b   | 1000        | 1000     | >1000       |
| 3c   | 250         | 1000     | 1000        |
| 3d   | >1000       | 1000     | 1000        |
| 3e   | >1000       | 1000     | 1000        |
| 3f   | 500         | 500      | 500         |
| 3g   | 500         | 500      | 500         |
| 3h   | 250         | 500      | 500         |
| 3i   | >1000       | 1000     | >1000       |
| 3j   | 1000        | >1000    | >1000       |
| 3k   | 500         | 1000     | 1000        |
| 3l   | 500         | >1000    | >1000       |
| 3m   | 1000        | 500      | 500         |
| 3n   | >1000       | 500      | 500         |
| 3o   | >1000       | 500      | 500         |
| 3p   | >1000       | 500      | 500         |
| 3q   | >1000       | 500      | 500         |
| 3r   | >1000       | 500      | 500         |
| 3s   | >1000       | 500      | 500         |
| 3t   | >1000       | 500      | 500         |
| 3u   | >1000       | 500      | 500         |
| 3v   | >1000       | 500      | 500         |
| 3w   | >1000       | 500      | 500         |
| 3x   | >1000       | 500      | 500         |
| 3y   | >1000       | 500      | 500         |
| 3z   | >1000       | 500      | 500         |
| 4a   | >1000       | 500      | >1000       |
| 4b   | >1000       | 500      | >1000       |
| 4c   | 500         | 1000     | 1000        |
| 4d   | 1000        | 1000     | 500         |
| 4e   | 500         | >1000    | >1000       |
| 4f   | 500         | 200      | 500         |
| 4g   | 250         | 1000     | 1000        |
| 4h   | 500         | 1000     | 1000        |
| 4i   | 1000        | 500      | 500         |
| 4j   | 1000        | 1000     | 1000        |
| 4k   | 250         | 1000     | >1000       |
| 4l   | 500         | 500      | 1000        |
RESULTS AND DISCUSSION

The compounds were synthesised as per scheme

| 4m  | 500 | 250 | 500 |
|-----|-----|-----|-----|
| 4n  | 1000| >1000| >1000|
| 5a  | 1000| 500 | 500 |
| 5b  | 500 | 500 | 500 |
| 5c  | 1000| 1000| 1000|
| 5d  | >1000| >1000| >1000|
| 5e  | 500 | 500 | 500 |
| 5f  | 250 | 500 | 500 |
| 5g  | 500 | >1000| >1000|
| 5h  | 1000| 500 | >1000|
| 5i  | 250 | >1000| >1000|
| 5j  | 250 | >1000| >1000|
| 5k  | 1000| >1000| >1000|
| 5l  | 500 | 500 | 500 |
| 5m  | 200 | 500 | 500 |
| 5n  | >1000| 500 | 500 |
| Nystatin | 100 | 100 | 100 |
| Greseofulvin | 100 | 100 | 100 |

CONCLUSION

In summary, N-[[3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-yl]-1H-pyrazol-4-yl] methylene substituted anilin [3a-n] were synthesized from 3-[2,4-dichloro-5-fluoro phenyl]-1H-pyrazol-4-carbaldehyde 2 and aromatic amine, which upon cyclization with chloro acetyl chloride and thiglycolic acid yields 3-Chloro-[3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-yl]-1(1substituted) azetidin-2-one [4a-n] and 2-[3-(2,4-dichloro-5-fluoro phenyl)-1H-pyrazol-4-yl]-3(3substituted phenyl)-1,3-thiazolidin-4-one [5a-n] respectively. The proposed structures of all the synthesized compounds were well supported by IR, 1H NMR, 13C NMR and mass spectral data. The formation of compounds 3a-n was confirmed by the appearance of singlet signal at δ 9.747-9.750 for CH=N ring system. The 1H NMR spectrum also displayed signals at 8 5.103-5.105 for CH=N of azetidine ring and at δ 4.01-3.975 for CH2 of thiazolidinone ring system respectively. Aromatic protons were observed in the usual region as multiplet between δ 7.328-7.535, δ 7.305-7.323 for aromatic protons of compounds 4a-n and at δ 7.535 for aromatic protons of compounds 5a-n.

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CONFLICT OF INTERESTS

Declared none

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