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Synthesis, Antibacterial and Antifungal Activities of Some Newer Schiff Bases derived from pyrimidine-5-Carbonitrile

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Abstract: A new series of Schiff base derived from pyrimidine were synthesised. Schiff bases were obtained by the condensation of 1-ethyl-4-(4-fluorophenyl)-2-hydrazinyl-1,6-dihydro-6-oxopyrimidine-5-carbonitrile with aromatic aldehyde. The chemical structure of newly synthesized compound was confirmed by ^{1}H NMR, FTIR and Mass spectroscopy.

Keywords: Aromatic aldehyde, Benzylidinehydrazinyl, Thiopyrimidine, Biological activities

1. INTRODUCTION

Due to various biological functions of pyrimidine and other heterocycles with pyrimidine play significant roles in many biological processes and have chemical and pharmacological importance. Pyrimidines have a leading position in medicinal chemistry in relevance with Schiff Base because of their important therapeutic properties in clinical application.[1]

Schiff bases were discovered by a German chemist, Nobel Prize winner, Hugo Schiff in 1864. Schiff base (also known as imines) possess important place in organic chemistry. Most of them have antibacterial, antifungal and antitumor activities as biologically important molecules.[2]

Schiff bases are formed by condensation of primary amine with compound containing an active carbonyl group & removal of water molecule. This compound is related to the azomethine group having the general formula RHC=N-R_1, where R and R1 are alkyl, aryl, cycloalkyl, or heterocyclic groups. [3]

They are the most stable and versatile intermediates for the preparation of numerous important medicinal compounds.[4] Literature survey reveals that Schiff bases derived from various heterocyclic possess Anti-microbial,[5-7] Anti-bacterial,[8,9] Anti-tubercular,[10, 11] Anti-tumour,[12,13] Anti-fungal activities. [14-16]

Schiff bases are also important synthons in the preparation of azetidinones, thiazolidinones oxadiazolines, imidazolinones which are pharmacologically active compounds.[17]

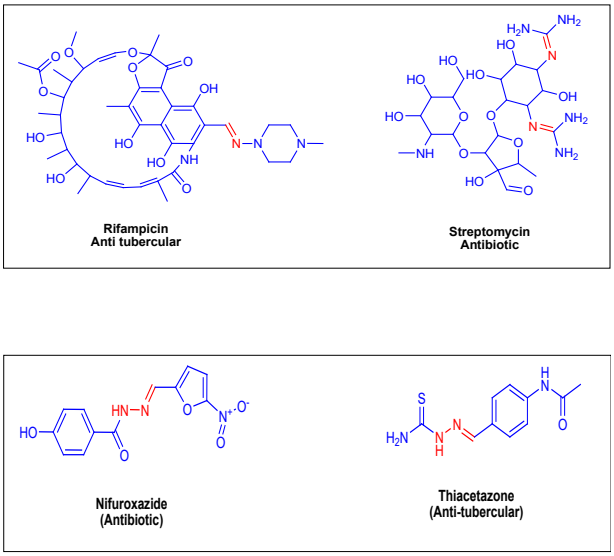


Fig. 1. Structures of some marketed drugs contain imine group

2. EXPERIMENTAL

2.1 Material and method

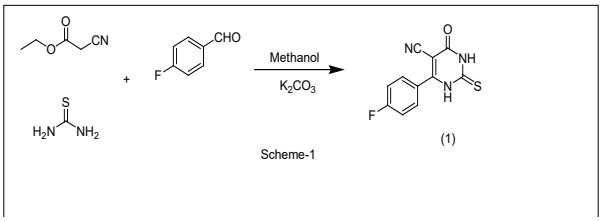
AR grade chemicals and solutions were used. Progress of reaction and completion was checked by thin layer chromatography on silica gel precoated aluminium sheets and the spots were detected by to exposure to UV lamp or an iodine chamber. The IR spectra were recorded on Shimadzu-FTIR-8400 spectrometer using KBr pallet. Mass spectra were determined on UC03-MASS spectrometer. ^{1}H NMR spectra were recorded on Bruker 400 MHz spectrometer with DMSO as a solvent.

TMS (trimethyl silane) as internal standard. The chemical shifts are expressed in part per million (δ ppm). All melting points were determined in open capillary and are uncorrected.

Step 1. Synthesis of 6-(4-fluorophenyl)-1,2,3,4- tetrahydro-4-oxo-2-thioxopyrimidine-5-carbonitrile(3)

A mixture of thiourea (0.01 mol), ethyl cyanoacetate (0.01 mol) 4-flurobenzaldehyde (0.01 mol) and potassium carbonate (0.01 mol) in methanol (100 ml) was refluxed for 6 hours. Reaction mixture was poured into minimum quantity of crushed ice and neutralized with acetic acid the product obtained was isolated and crystalized from appropriate solvent.

Yield 65 % m.p. 285 °C MS (EI) m/z (M^+) 247; FTIR (KBr) (cm^{-1}): 1257 (C-F), 1635(-CO), 2206(-CN), 2349(-CH_3 Asym.), 2855 (-CH_3 Sym.); ^{1}H NMR (δ ppm) (400 MHz, DMSO) δ ^{1}H NMR: δ 11.6 (s, 2H, NH), δ 7.53-7.8 (m,4H, Ar-H). Anal. For $C_{11}H_6FN_3OS$ calcd. C, 53.44; H, 2.45; F, 7.68; N, 17.00; O, 6.47; S, 12.9 Found; C, 53.0 H, 2.3 F,7.5 N,16.5 S,12.8.

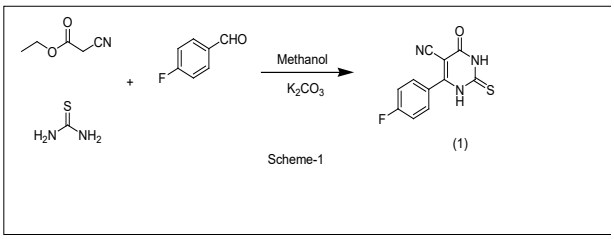


Scheme-1

Step 2. Synthesis of 1-ethyl-2-(ethylthio)-4-(4- fluorophenyl)-1,6-dihydro-6-oxopyrimidine-5-carbonitrile (2)

A mixture of (1) (0.5 g, 0.0016 mol), potassium carbonate (0.45 g, 0.0032 mol) and appropriate alkyl iodide such as ethyl iodide in dimethyl formamide (20 ml) was stirred 5 hours at room temperature and then diluted with water (10 ml). The formed precipitate was filtered. The obtained precipitate was filtered, dried and crystallized from absolute alcohol.

Yield 40 % m.p. 105 °C MS (EI) m/z (M^+) 303; FTIR (KBr) (cm^{-1}): 1234 (C-F str.), 1674 (C=O), 2222 (CN), 2985(C–H aliphatic); ^{1}H-NMR δ(ppm) (400 MHz, DMSO): δ 1.4 (t,3H, S-CH_2-CH_3), 1.4 (t,3H, N-CH_2- CH_3), 3.2 (q,2H, S-CH_2-CH_3), 4.6 (q,2H, N-CH_2- CH_3), 7.4-8.0 (m,4H, Ar-H). Anal. For $C_{15}H_{14}FN_3OS$ calcd.C, 59.39; H, 4.65; F, 6.26; N, 13.85; O, 5.27; S, 10.57; Found C, 59.20 H, 4.7 F, 6.1 N,13.6 O, 5.1 S,10.8



Scheme-1

Step 3. Synthesis of 1-ethyl-4-(4-fluorophenyl)-2-hydrazinyl-1,6-dihydro-6-oxopyrimidine-5-carbonitrile (3)

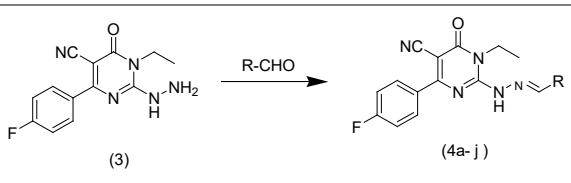
A mixture of 1-ethyl-2-(ethylthio)-4-(4-fluorophenyl)-1,6-dihydro-6-oxopyrimidine-5- carbonitrile (3.03 gm,0.01 mol) and hydrazine hydrate (3ml) in absolute alcohol (30 ml) was refluxed for 6 hours. The reaction mixture was poured into ice cold water and solid product obtained after neutralization with acetic acid was kept in water overnight. The product was isolated and crystallized from ethanol.

Yield- 52% m.p. 230 °C MS (EI) m/z (M^+) 274; FTIR (KBr) (cm^{-1}): 1234 (C-F str.), 1674 (C=O), 2222 (CN), 2985(C-H aliphatic); ^{1}H-NMR δ(ppm) (400 MHz, DMSO): δ 1.13 (t,3H, S-CH_2-CH_3), 3.9 (q,2H, S-CH_2-CH_3),7.3-8.0, (m,4H, Ar-H), 9.19 (s, 2H, NH_2) Anal. For $C_{15}H_{14}FN_3OS$ calcd, 59.39; H, 4.65; F, 6.26; N, 13.85; O, 5.27; S, 10.57; found C, 59.20 H, 4.7 F, 6.1 N,13.6 O, 5.1 S,10.8.

Step. 4 General procedure for the synthesis of Schiff base (4a-j)

A mixture of 1-ethyl-4-(4-fluorophenyl)-2-hydrazinyl-1,6-dihydro-6-oxopyrimidine-5-carbonitrile (2.73 gm, 0.01 mol), appropriate aromatic aldehyde (0.01 mol) in absolute alcohol (20 ml) and 2-3 drop of glacial acetic acid was added to RBF. And the reaction mixture was refluxed for 3 hours (progress of reaction checked by TLC). After the completion of reaction content was poured in ice water, neutralized and obtained solid was collected and washed with water. Product was crystalized with absolute alcohol.

Other Schiff's bases were also synthesized by following this method.



Scheme 3

3. RESULT AND DISCUSSION

The series of compound 4a-j was synthesized by condensation of different aromatic aldehydes with 1-ethyl-4-(4-fluorophenyl)-2-hydrazinyl-1,6-dihydro-6-oxopyrimidine-5-carbonitrile(3) with good yield and also well characterized by

^{1}H NMR, Mass and FT-IR spectroscopy. Reaction scheme for present work is given in scheme 1, 2 and 3. Biological evaluation of synthesized compound is presented in table.1.

Biological activity

All the synthesized compound was screened for their in vitro activity against some bacterial strains such as *Enterobacter aerogenes & Pseudomonas aeruginosa* (Gram Negative) *Staphylococcus aureus & Bacillus megaterium* (Gram positive) and fungi like *Aspergillus flavus & Aspergillus niger* at different concentrations.

Streptomycin, ampicillin (Antibacterial against gram-negative and gram-positive bacteria) and nystatin was used as a standard drug for antifungal activity. The anti-microbial activity was determined by using the cup-plate agar diffusion method.

Table-1- antibacterial and antifungal activities of compound 4a-j

	Bacillus megaterium	*Staphylococcus aureus*	*Enterobacter aerogenes*	*Pseudomonas aeruginosa*	*Aspergillus flavus*	*Aspergillus niger*
Streptomycin			50	50		
Ampicillin	100	100				
Nystatin					100	100
4a	125	125	250	250	250	250
4b	1000	1000	1000	1000	1000	1000
4c	250	250	250	250	1000	1000
4d	125	125	250	250	125	125
4e	1000	1000	250	250	500	500
4f	250	250	1000	1000	1000	1000
4g	500	500	250	250	1000	1000
4h	250	250	1000	1000	500	500
4i	500	500	250	250	1000	1000
4j	500	500	500	500	1000	1000

Compound 4a, 4c, 4d, 4f and 4h is highly effective broad-spectrum drug which can inhibit the growth of both gram-positive and gram-negative bacteria. Compound 4f and 4h is showing antagonistic activity against mainly gram-positive bacteria. Compound4a and 4d shows antifungal activity. It can be concluded that compound4a and 4d is most effective against gram positive bacteria. Therefore, 4a and 4d is considered as potent drug against all gram positive, negative bacteria and fungi.

4. Spectral discussion

(4a)2-benzylidenehydrazinyl)-1-ethyl-4-(4-fluorophenyl)-1,6-dihydro-6-oxopyrimidine-5-carbonitrile

Yield- 72 % m.p. 245 °C MS (EI) m/z (M^+) 362.1; FTIR (KBr) (cm^{-1}): 3248 (NH), 2222 (CN), 1581 (C=O), 1612 (C=N)^{1}H NMR (δ ppm) (400 MHz, DMSO) δ1.1 (t, 3H, N-CH_2-CH_3); δ 3.5 (q, 2H, N-CH_2-CH_3); δ 7.11-8.21 (m, 9H, Ar-H); δ 9.5 (s, 1H, N=CH); δ 11.3(s, 1H,

NH) ppm. Anal. for $C_{20}H_{16}FN_5O$; calcd, C, 66.47; H, 4.46; F, 5.26; N, 19.38; O, 4.43; found:C, 66.41; H, 4.22;F, 5.25; N,19.30; O,4.40.

(4b)2-(4-chlorobenzylidene) hydrazinyl)-1-ethyl-4-(4-fluorophenyl)-1,6-dihydro-6-oxopyrimidine-5-carbonitrile

Yield- 69 % m.p. 215 °C MS (EI) m/z (M^+) 396; FTIR (KBr) (cm^{-1}): 3240 (NH), 2220 (CN), 1571 (C=O), 1620 (C=N) ^{1}H NMR (δ ppm) (400 MHz, DMSO) δ 1.17 (t, 3H, N-CH_2-CH_3); δ 3.41 (q, 2H, N-CH_2-CH_3); δ 7.3-8.1 (m, 9H, Ar-H); δ 9.3 (s, 1H, N=CH); δ 11.1(s, 1H, NH) ppm. Anal. for $C_{20}H_{15}ClFN_5O$calcd,C, 60.69; H, 3.82; Cl, 8.96; F, 4.80; N, 17.69; O, 4.04 found; C, 60.50; H, 3.72; Cl, 8.16; F, 4.80; N, 17.61; O, 4.0.

(4c)2-(4-methoxybenzylidene) hydrazinyl)-1-ethyl-4-(4-fluorophenyl)-1,6-dihydro-6-oxopyrimidine-5-carbonitrile

Yield- 65 % m.p. 261 °C MS (EI) m/z (M^+) 392; FTIR (KBr) (cm^{-1}): 3250 (NH), 2215 (CN), 1561 (C=O), 1610 (C=N) ^{1}H NMR (δ ppm) (400 MHz, DMSO) δ 1.4 (t, 3H, N-CH_2-CH_3); δ 3.2 (q, 2H, N-CH_2-CH_3); δ 7.01-8.2 (m, 9H, Ar-H); δ 9.81 (s, 1H, N=CH); δ 11.3(s, 1H, NH) ppm. Anal. for $C_{21}H_{18}FN_5O_2$ calcd, C, 64.44; H, 4.64; F, 4.85; N, 17.89; O, 8.18. found:C, 64.34; H, 4.61; F, 4.79; N, 17.83; O, 8.11.

(4d)2-(4-N, Dimethyl benzylidene) hydrazinyl)-1-ethyl-4-(4-fluorophenyl)-1,6-dihydro-6-oxopyrimidine-5-carbonitrile

Yield- 68 % m.p. 255 °C MS (EI) m/z (M^+) 405; FTIR (KBr) (cm^{-1}): 3248 (NH), 2222 (CN), 1575 (C=O), 1622 (C=N) ^{1}H NMR (δ ppm) (400 MHz, DMSO) δ 1.35 (t, 3H, N-CH2-CH3); δ 3.3 (q, 2H, N-CH2-CH3); δ 7.14-8.2 (m, 9H, Ar-H); δ 9.40 (s, 1H, N=CH); δ 11.2(s, 1H, NH) ppm. Anal. For $C_{22}H_{21}FN_6O$ calcd, C, 65.33; H, 5.23; F, 4.70; N, 20.78; O, 3.96, found;C, 65.13; H, 5.15; F, 4.60; N, 20.68; O, 3.91; found;

(4e)2-(3,4-dimethoxybenzylidene) hydrazinyl)-1-ethyl-4-(4-fluorophenyl)-1,6-dihydro-6-oxopyrimidine-5-carbonitrile

Yield- 58 % m.p. 230 °C MS (EI) m/z (M^+) 422; FTIR (KBr) (cm^{-1}): 3260 (NH), 2218 (CN), 1554 (C=O), 1600 (C=N) ^{1}H NMR (δ ppm) (400 MHz, DMSO) δ 1.2 (t, 3H, N-CH2-CH3); δ 3.45 (q, 2H, N-CH2-CH3); δ 7.0 -8.1 (m, 9H, Ar-H); δ 9.1 (s, 1H, N=CH); δ 11.2 (s, 1H, NH) ppm. Anal. For $C_{22}H_{20}FN_5O_3$ calcd, C, 62.70; H, 4.78; F, 4.51; N, 16.62; O, 11.39, found; C, 62.66; H, 4.68; F, 4.45; N, 16.55; O, 11.29.

(4f)2-(4-methyl benzylidene) hydrazinyl)-1-ethyl-4-(4-fluorophenyl)-1,6-dihydro-6-oxopyrimidine-5-carbonitrile

Yield- 61 % m.p. 249 °C MS (EI) m/z (M^+) 376; FTIR (KBr) (cm^{-1}): 3230 (NH), 2200(CN), 1585 (C=O), 1618 (C=N) ^{1}H NMR (δ ppm) (400 MHz, DMSO) δ 1.19 (t, 3H, N-CH2-CH3); δ 3.9 (q, 2H, N-CH2-CH3); δ 7.1-8.21 (m, 9H, Ar-H); δ 9.41 (s, 1H, N=CH); δ 11.4 (s, 1H, NH) ppm. Anal. For $C_{21}H_{18}FN_5O$ calcd, C, 67.19; H, 4.83; F, 5.06; N, 18.66; O, 4.26, found;C, 67.10; H, 4.73; F, 5.01; N, 18.56; O, 4.22.

(4g)2-(4-bromobenzylidene) hydrazinyl)-1-ethyl-4-(4-fluorophenyl)-1,6-dihydro-6-

oxopyrimidine-5-carbonitrile

Yield- 66 % m.p. 266 °C MS (EI) m/z (M^+) 441; FTIR (KBr) (cm^{-1}): 3255 (NH), 2220 (CN), 1583 (C=O), 1620 (C=N) ^{1}H NMR (δ ppm) (400 MHz, DMSO) δ 1.39 (t, 3H, N-CH2-CH3); δ 4.0 (q, 2H, N-CH2-CH3); δ 7.1-8.12 (m, 9H, Ar-H); δ 9.3 (s, 1H, N=CH); δ 11.2(s, 1H, NH) ppm. Anal. For $C_{20}H_{15}BrFN_5O$ calcd, C, 54.56; H, 3.43; Br, 18.15; F, 4.32; N, 15.91; O, 3.63, found, C, 54.36; H, 3.41; Br, 18.09; F, 4.22; N, 15.81; O, 3.53.

(4h)2-(4-nitrobenzylidene) hydrazinyl)-1-ethyl-4-(4-fluorophenyl)-1,6-dihydro-6-oxopyrimidine-5-carbonitrile

Yield- 62% m.p. 215 °C MS (EI) m/z (M^+) 407; FTIR (KBr) (cm^{-1}): 3249 (NH), 2223 (CN), 1582 (C=O), 1613 (C=N) ^{1}H NMR (δ ppm) (400 MHz, DMSO) δ 1.2 (t, 3H, N-CH_2-CH_3); δ 3.9 (q, 2H, N-CH_2-CH_3); δ 7.0-8.2 (m, 9H, Ar-H); δ 9.1 (s, 1H, N=CH); δ 11.4 (s, 1H, NH) ppm. Anal. For $C_{20}H_{15}FN_6O_3$ calcd, C, 59.11; H, 3.72; F, 4.68; N, 20.68; O, 11.81, found:C, 59.01; H, 3.62; F, 4.38; N, 20.58; O, 11.75.

(4i)2-(4-hydroxy benzylidene) hydrazinyl)-1-ethyl-4-(4-fluorophenyl)-1,6-dihydro-6-oxopyrimidine-5-carbonitrile

Yield- 72 % m.p. 240 °C MS (EI) m/z (M^+) 378; FTIR (KBr) (cm^{-1}): 3255 (NH), 2202 (CN), 1580 (C=O), 1610 (C=N) ^{1}H NMR (δ ppm) (400 MHz, DMSO) δ 1.19 (t, 3H, N-CH2-CH3); δ 4.0 (q, 2H, N-CH2-CH3); δ 7.0-8.11 (m, 9H, Ar-H); δ 9.3 (s, 1H, N=CH); δ 11.2 (s, 1H, NH) ppm. Anal. for $C_{20}H_{16}FN_5O_2$ calcd, C, 63.65; H, 4.27; F, 5.03; N, 18.56; O, 8.48, found:C, 63.65; H, 4.17; F, 5.01; N, 18.49; O, 8.35.

(4j)2-(2-chlorobenzylidene) hydrazinyl)-1-ethyl-4-(4-fluorophenyl)-1,6-dihydro-6-oxopyrimidine-5-carbonitrile

Yield- 58 % m.p. 278 °C MS (EI) m/z (M^+) 396; FTIR (KBr) (cm^{-1}): 3260 (NH), 2225 (CN), 1584 (C=O), 1615 (C=N) ^{1}H NMR (δ ppm) (400 MHz, DMSO) δ 1.31 (t, 3H, N-CH_2-CH_3); δ 3.7 (q, 2H, N-CH_2-CH_3); δ 7.11-8.2 (m, 9H, Ar-H); δ 9.2 (s, 1H, N=CH); δ 11.1(s, 1H, NH) ppm. Anal. For $C_{20}H_{15}ClFN_5O$ calcd, C, 60.69; H, 3.82; Cl, 8.96; F, 4.80; N, 17.69; O, 4.04, found:C, 60.51; H, 3.79; Cl, 8.91; F, 4.75; N, 17.62; O, 4.01;

CONCLUSION

In this present work we have reported potent Schiff base derived from pyrimidine and the reaction yield overall good amount of product. Compound 1,3,4,5 and 7 shows good biological activity against gram-positive and gram-negative bacteria and compound 1 and 4 exhibit good antifungal activity.

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Conflict of interest

The authors declare that there is no conflict of interests regarding to the publication of this article.

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