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Der Chemica Sinica, 2013, 4(4):68-72

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis, characterization and antimicrobial activity studies of (E)-1-cyclopropyl-6-fluoro-7-(4-(4-(2-isonicotinoyl-hydrazinyl)-6-(2-(4-substituted-benzylidene)-hydrazinyl-1,3,5,-triazin-2-yl)-piperazin-1-yl)-4-oxo-1,4-dihydroquinoline carboxylic acid

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ABSTRACT

In the present study we have synthesized (E)-1-cyclopropyl-6-fluoro-7-(4-(4-(2-isonicotinoylhydrazinyl)-6-(2-(4-substituted-benzylidene) hydrazinyl-1, 3, 5,-triazin-2-yl) piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid using conventional methods and studied theirH[1] NMR and IR spectrum. We also studied antifungal and anti bacterial activities of the synthesized compound.

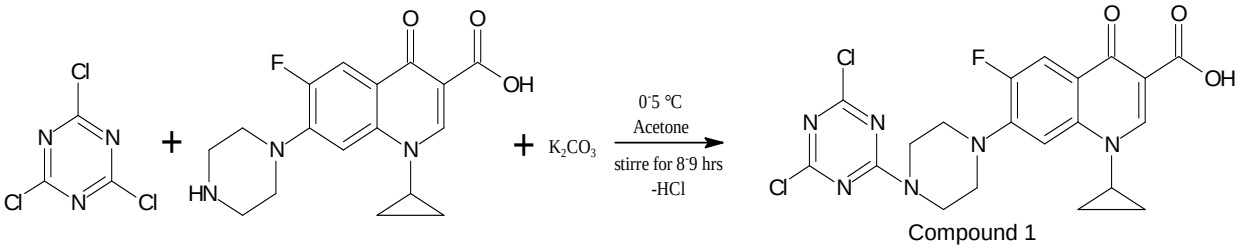
Keywords: 1, 3, 5-S-triazine, Ciprofloxacin, Isoniazid, IR/NMR Spectroscopy, Antibacterial, Antifungal activity.

INTRODUCTION

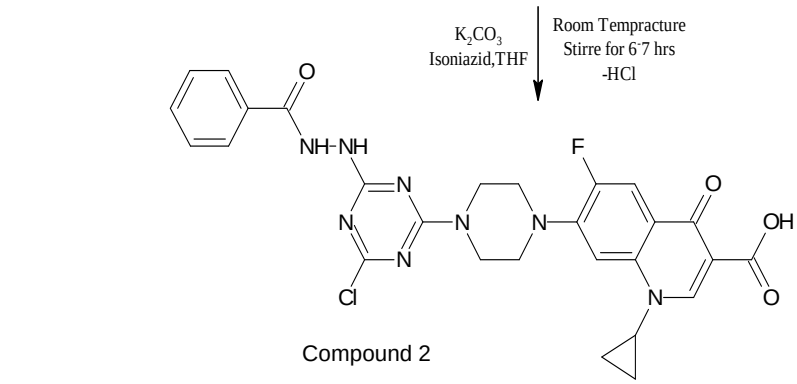
Schiff base are condensation products of primary amine and aromatic aldehydes. They are known to exhibit potent antibacterial [1-4], antifungal [5-6], anticonvulsant, anti inflammatory activities [7]. In addition some Schiff base show pharmacologically useful activities like anticancer [8-9], antihypertensive and hypnotic [10] activites. Heterocyclic compounds like Ciprofloxacin is one of the most widely used antibiotic against intestinal Gram-negative bacteria, enterococci and Bacteroidfragilis in clinical activity (Krueger et al., 1997; Sullivan et al., 2004). It is a second-generation fluoroquinolone class drug, synthetic broadspectrum antibiotics and that inhibit DNA gyrase and topoisomerase activity [11]. The action of ciprofloxacin on gastrointestinal infection is secreted through the mucosa to intestinal lumen that may affect indirectly the existence of lactobacilli amounted and influence the ecological balance of intestinal bacteria. Therefore, it is important to understand the resistant extent of ciprofloxacin inlactobacilli in human medicine.

In view of these facts, synthesis of certain Schiff bases containing ciprofloxacin moiety has been undertaken in the hope of getting better bioactive agents. For the synthesis of such compounds, 1, 3, 5 S-triazine and potassium carbonet was treated with ciprofloxacin HCl to get 1-Cyclopropyl-7-[4-(4, 6-dichloro-[1, 3, 5] triazin-2-yl)-piperazin-1-yl]-6-fluoro-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid compound-[I]. This upon treatment with potassium carbonet and isoniazid to gave 7-(4-{4-chloro-[N'-(pyridine-4-carbonyl)-hydrazino]-[1, 3, 5] triazin-2-yl}-piprazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1, 4-dihydro-quinoline-3 carboxylic acid Compound-[II] on treatment with Hydrazine hydrate to yield 1-cyclopropyl-6-fluoro-7-(4-(4-hydrazinyl-6-(2-isonicotinoylhydrazinyl)-1,3,5-triazine-2-yl)pip razin-1-yl)-4-oxo-1,4dihydroquinolinec-3-carboxylic acid compound[III].The intermediate compound[III] upon treatment with substituted benzaldehyde yield (E)-1-cyclopropyl-6-fluoro-7-(4-(4-(2-isonicotinoylhydrazinyl)-6-(2-(4-substituted-benzylidene)hydrazinyl-1,3,5,-triazin-2-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid compound-[V].The constitution of all compounds synthesized was established by elemental analysis, IR and H1 NMR spectral study. Compounds were also evaluated for anti bacterial and anti fungal activites.

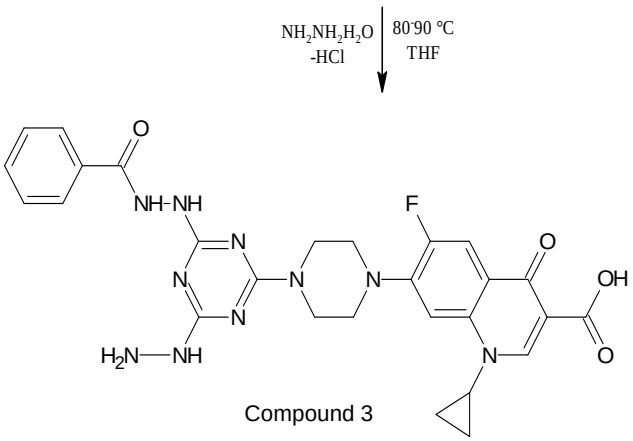
REACTION SCHEME



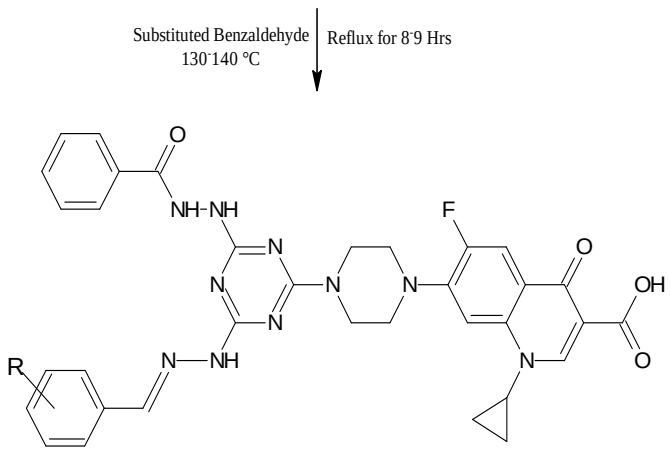
Compound 1



Compound 2



Compound 3



Compound 4

Where R =4-CH_3,3-CH_3-4-OH, 4-Cl, 2-NO_2, 2:4-Cl_2, 2-OCH_3, 4-NO_2, 4-H, 4-$N(CH_3)_2$,2OH

MATERIALS AND METHODS

All the chemicals used were of pure grade (Merck and B.D.H). The melting points of all compounds were determined by open capillary method and were uncorrected.

Preparation of 1-Cyclopropyl-7-[4-(4, 6-dichloro-[1, 3, 5] triazin-2-yl)-piperazin-1-yl]-6-fluoro-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid

In 250ml F.B.F, the Cyanuric chloride (1.84gm, 0.01mole) in acetone and K_2CO_3 (1.12gm, 0.01mole) were taken. Ciprofloxacin (3.31gm, 0.01mole) in acetone was added drop wise with stirring and temperature was maintaining between0- 5^0C by using external cooling. After the completion of the addition, the clear reaction mixture was stirred at room temperature for 2-4 hrs. The off white precipitate was isolated on filter paper and washed with 1:1 Acetone: Water. The precipitate was dried and recrystallized using ethanol.

Preparation of 7-(4-{4-chloro-[N'-(pyridine-4-carbonyl)-hydrazino]-[1, 3, 5] triazin-2-yl}-piprazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid

In 250ml F.B.F, the 1-Cyclopropyl-7-[4-(4,6-dichloro-[1, 3, 5]triazin-2-yl)-piperazin-1-yl]-6-fluoro-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid (0.01mole) in acetone and K_2CO_3 (1.12gm, 0.01mole) were taken. Isoniazid (1.37gm, 0.01mole) in acetone was added drop wise with stirring and temperature was maintaining between 30-35^0C. After the completion of the addition, the clear reaction mixture was stirred for 2-4 hrs. The white precipitate was isolated on filter paper and washed with 1:1 Acetone: Water. The precipitate was dried and recrystallized using ethanol.

Preparation of 1-cyclopropyl-6-fluoro-7-(4-(4-hydrazinyl-6-(2-isonicotinoylhydrazinyl)-1,3,5-triazine-2-yl)piprazin-1-yl)-4-oxo-1,4dihydroquinolinec-3-carboxylic acid

7-(4-{4-chloro-[N'-(pyridine-4-carbonyl)-hydrazino]-[1, 3, 5]triazin-2-yl}-piprazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid (0.01 mole) in THF (25 ml) were taken in a 250 ml R.B.F. Hydrazine (0.052ml, 0.01 mole) was added and the reaction mixture was refluxed at 80^0-90^0C for 6-8 hr. Excess solvent was removed by distillation under reduced pressure and the residue was poured into ice-cold water. The resulting solid was filtered, washed, dried and recrystallised by using methanol.

Preparation of (E)-1-cyclopropyl-6-fluoro- 7-(4-(4-(2-isonicotinoylhydrazinyl)-6-(2-(4-substituted-benzylidene) hydrazinyl-1, 3, 5,-triazin-2-yl) piperazin-1-yl)-4-oxo-1, 4-dihydroquinoline -3-carboxylic acid

In a 250 ml R.B.F 1-cyclopropyl-6-fluoro-7-(4-(4-hydrazinyl-6-(2-isonicotino ylhydrazinyl)-1, 3, 5-triazine-2-yl) piprazin-1-yl)-4-oxo-1, 4 dihydroquinolinec-3-carboxylic acid (0.01 mole) and substituted aldehyde (0.01 mole) were taken in THF (30 ml) as a solvent. The reaction mixture was refluxed for 8-9 hr in presence of acid catalyst (H_2SO_4) (2 ml to 4 ml). The resulting solution was cooled and poured into crushed ice. The product obtained was filtered, washed, dried and recrystallized by ethanol.

RESULTS AND DISCUSSION

All the tested compounds have shown antibacterial activity to some extent. Among the tested compounds **4c**, **4g** and **4j** showed very good activity against the tested organisms. Compounds **4a**, **4d**, **4f**, **4h** and **4i** are moderate antibacterial activity. The compounds **4a**, **4c**, **4i** and **4j** showed good antifungal activity. All the compounds synthesized possess electron releasing groups, on both the aromatic rings. Therefore from the results it is evident that compounds having electron releasing groups like methyl, hydroxy and methoxy may be responsible for antibacterial and antifungal activities.

Table- 1: Characterization Table of (E)-1-cyclopropyl-6-fluoro- 7-(4-(4-(2-isonicotinoyl hydrazinyl)-6-(2-(4-substituted-benzylidene) hydrazinyl-1, 3, 5,-triazin-2-yl) piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

No	R	Molecular formula (M. wt.)	Yield (%) (per./ hrs.)	M.P. ^{0}C
4a	4-CH_3	$C_{33}H_{32}FN_{11}O_4$ (677.70)	71 (10)	167-08
4b	3-OCH_3,4-OH	$C_{34}H_{32}FN_{11}O_5$ (693.70)	83 (10)	175-77
4c	2-NO_2	$C_{33}H_{29}FClN_{11}O_4$ (698.12)	80 (11.5)	205-06
4d	4-Cl	$C_{33}H_{29}FN_{12}O_6$ (708.67)	73 (10.5)	161-62
4e	2,4-$(Cl)_2$	$C_{33}H_{28}FCL_2N_{11}O_4$ (732.56)	64 (11)	170-71
4f	2-OCH_3	$C_{34}H_{32}FN_{11}O_5$ (693.70)	77 (10)	212-13
4g	4-NO_2	$C_{33}H_{29}FN_{12}O_6$ (708.70)	75 (11)	202-03
4h	4-H	$C_{33}H_{30}FN_{11}O_4$ (663.67)	87 (12)	147-49
4i	4-$N(CH_3)_2$	$C_{35}H_{35}FN_{12}O_4$ (706.74)	61 (111.5)	196-97
4j	2-OH	$C_{33}H_{30}FN_{11}O_5$ (679.67)	70 (10.5)	153-54

^{1}H NMR Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy is one of the latest physical methods of investigating organic compounds. The scale of the spectrum is usually marked in parts per million (ppm) of the applied field or in frequency units (Hz). ^{1}H-NMR spectra were recorded on Bruker WM 400FT MHz NMR instrument using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal reference. The data of compound (4a) is summarized in table -2.

Table-2

PROTONS	VALUE
–CH2 protons cyclopropen	0.80
–CH proton of cyclopropen	2.29
-CH2 Proton of Piperazine	2.85 &3.05
-CH3 Group	2.37
-NH (a)	8.50
-NH(b)	6.24
-NH(c)	10.13
Aromatic Protons	5.99 TO 8.15

Infrared spectra

The systematic interpretation of the infra - red spectrum is based upon the empirical data obtained by assigning infra-red absorption values to the structural units a characteristic of different structural units. Infra - red spectra were recorded in KBr on a Shimadzu FTIR spectrophotometer. The data of the structure is summarized in table-3 as below.

Table-3:

ADSORPTION	4a	4f
N-H (st)	3358.56	3326.7
O-H (st)	3188.14	2965.1
-CO (st)	1638.30	1629.9
-CH_3	2960.32	---------
-Cl	----------	723.55
Ar (C=C)	1603.58	1606.2
Ar (C-N) (st)	1508.12	1542.8
In plane ST	1505.23	1479.9
-CH_2	1462.80	1454.7
Ar (C-N) link	1390.48	1394.3
(C-N) (st)	1366.37	1359.4
In plane Ar-H	1160.98	1092.5
In plane -CH_2-	974.88	965.8
Ar-H (b) Vib.	859.16	833.2
Out plane ST	775.27	791.8
Out plane -CH_2-	709.70	739.6
Out plane Ar-H	682.70	699.4

Antimicrobial activity

Table-4 Antimicrobial activity of compound

Code No	*S. aureus*	*P.aeruginosa*	*E. coli*	*S. pyogenus*
4a	250	250	100	200
4b	500	125	100	500
4c	100	100	50	100
4d	250	250	200	250
4e	500	200	200	500
4f	200	125	62.5	200
4g	250	100	100	100
4h	100	200	200	250
4i	125	250	250	200
4j	250	100	50	100
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50

The examination of antimicrobial activity of organic compound and its all substitution reveals that the compound is moderately more or less active against various organisms. The synthesized compounds were screened for their antibacterial activity using *S.aureus, E. coli, P.aeruginosa and S. pyogenus* (Table-4). Control experiment was carried out under similar condition by using ampicillin and chlorempheniсol as standard. The inhibition zone measure in mm showed that compound **4a** and **4c** were more active than other compounds tested against the above microbes. Anti-bacterial activity of Compounds was investigated via the broth dilution method [12-14].

Anti-fungal activity

The investigation of antifungal activity of Compound4a-4j was carried out with the stiff plate agar diffusion method [15]. against *C.albicans,A.niger and A.clavatus.* The amount of microbial cells was 109c.f.u. /ml. Incubation period was 24 h at 35 °C for bacteria. Antibiotics nystatin and greseofulvin were used as standards. The bacterial cultures, standards, and obtained substances in 5 mg/ml concentration were streaked across grooves and then allowed to diffuse in the agar nutrient plate (Table-5).

Table-5 Antifungal activity of compound

Code No	*C.albicans*	*A.niger*	*A.clavatus*
4a	250	100	100
4b	1000	250	500
4c	500	100	100
4d	500	250	100
4e	1000	500	1000
4f	1000	205	500
4g	500	1000	500
4h	1000	500	1000
4i	100	100	100
4j	500	100	100
Nystatin	100	100	100
Greseofulvin	500	100	100

CONCLUSION

The work has approached towards the synthetic and biological approach of these wonder molecules. Anti-bacterial property of the synthesized compounds has exhibited very good inhibition; the compounds **4c**, **4g** and **4j** have exhibited outstanding activity towards *S.aureus, E. coli, P.aeruginosa and S. pyogenus.* Compound **4a**, **4b** and **4f** shows good activity against E.Coli.compoound **4a**, **4d**, **4f**, **4h** and **4i** shows good activity against S.aureus. But the systematic substitution at various position and other derived compounds have shown remarkable antifungal properties. The compounds **4a**, **4c**, **4i** and **4j** have exhibited god activity towards *A.niger, A.clavatus* and C. *albicans.* Compound **4d** shows good activity against *A.clavatus* and C. *albicans* the remaining compounds have shown poor antifungal activity indicating less biological importance for a synthetic chemist.

Acknowledgement

The authors are thankful to Department of Chemistry, Arts, Science & Commerce College, Kholwad, Surat for providing laboratory facilities.

REFERENCES

[1] C.r.prakash,s.raja and p.dineshkumar,*rashyan.j.chem*., **2009**, 2, 960-968.
[2] Santosh kumar,niranjan m s,dayanandan kadadevar.,*jcpr*, **2010**, 01, 39-42.
[3] Desai.K.G & Desai.K.R, *Indian J Chem*, **2005,** 44(B), 2097.
[4] Desai.K.R. & Naik.B.D., *Asian J Chem*, **2004,** 16(3-4), 174.
[5] Aliasghar jarrahpour, eric de clercq,jane Michel brune,*Molecules*, **2007,** 12, 1720-1730.
[6] Kumar.V & Dhakarey.R, *J Ind Council of Chemists*, **2003**, 20(1), 46.
[7] SpasovAI. Phensoitiva, Tet.HEd.Lett, 571, ChemicalAbst, **1971,** 77(s).
[8] Nair.R, Shah.A, Baluja.S and Chanda.S, *J. Serb. Chem. Soc*., **2006,** 71 (7), 733–744.
[9] Ebrahimzadeh.M.A, Honary.S, & Khani.K, *Chemistry: An Indian Journal*, **2004,** 1(9), 624.
[10] Seshaiah Krishna Sridhar, s. n.pandeya and james p stables,*Europian Journal of Pharmaceutical Science*, **2002,** 16(3), 129-132.
[11] Xiao-su pan,jane ambler, L.mark fisher,*antimicrobial agent and chemotherapy*, **1996,** 40, 2321-2326.
[12] Carson.C.F, Hammer.K.A, Riley.T.V, *Europe pub med centre Microbios*, **1995**, 82(332), 181-185.
[13] M Radetsky, R C Wheeler, M H Roe and J K Todd *journel of clinical Microbiology*, , **1986**, 24(4), 600-606.
[14] Clyde Thornsberry Donald R.and Stalons *Antimicrob. Agents Chemotherapy*.January, **1975**, 7(1), 15-21.
[15] David N. Leach, Shane G. Griffin and Julie L. Markham, *Journal of Essential Oil Research*, **2000**, 12 (2), 249-255.