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SYNTHESIS OF 7-(MORPHOLINOMETHYL)-9-(TRIFLUOROMETHYL)-4-((4-(TRIFLUOROMETHYL)PHENYL)AMINO)-1-THIA-4,7,8-TRIAZASPIRO[4.4]NON-8-ENE-3,6-DIONE

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ABSTRACT:
Mannich base synthesis of 7-(morpholinomethyl)-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4.4]non-8-ene-3,6-dioneby thecondensation of 1-(morpholinomethyl)-3-(trifluoromethyl)-4-(2-(4-(trifluoromethyl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one with mercaptoaceticacid.The structure of these newly synthesized compounds were characterised by ^{1}H NMR,^{13}CNMR ,Mass ,IR, and elemental analysis.

KEYWORDS;-Pyrazole, morpholine,antimicro biologicalactivity.

INTRODUCTION

Heterocyclic compounds represents an important class of biological molecules.The hetero cyclic molecules which posses,pyrazole and azetidine moieties exhibit wide range of biological activities.Pyrazole are one of the most important alkaloids molecules found extensively in biological systems, which play vital role in many of the biochemical process. Pyrazole ring constitutes an important basic skeleton and development of the drug.The classical pyrazole shows highantibacterial,analgesic,antipyretic,antifungal,antiflamatory,anthelmintic,cardiovascular,anticonvalsantand selective COX-2 inhibitaryactivities,anticonvalsant,and selective COX-2 inhibitary activities .

Dermatophytes are infections of keratinized tissue, that is, the epidermis, hair and nails, caused by a group of specialized fungi. The dermatophytes do not invade subcutaneous or deep tissue. *Dermytophyte- Trichophytonschoenleinii*was the first microorganism that was proven to cause an infections disease of humans Pyrazolederivatives found to posses Highwhichincludes,antibacterial,analgesic,antipyretic,antifungal,antiflamatory,anthelmintic, cardiovascular,anticonvalsant activities [I-V].Among the five member heterocyclic compounds, have become an importantsynthon for the development new therapeutic agents. Compounds with pyrazole coresubstantiate for broad spectrum of biological activities including antimicrobial[VI].antifungal[VII]., antiinflammatory[VIII]., anticonvulsant[IX].,antioxidant, analgesic[X]. Andmutagenic acctivity[XI].. Compounds

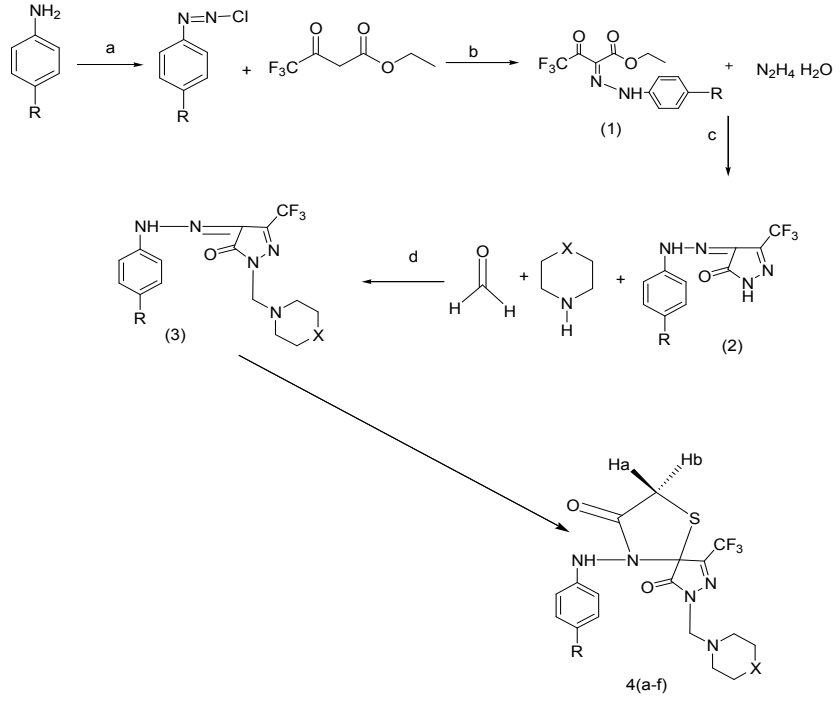
containing quinoline moiety are most widely used asantimalarials[XII]., antibacterials[XIII]., antifungals[XIV]., anticancer agents[XV]. and potentialHIV-1 integrase inhibitors[XVI-XVII].

MATERIALS AND METHODS

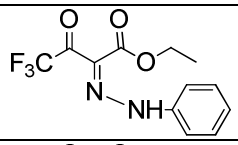
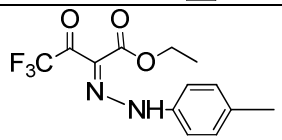
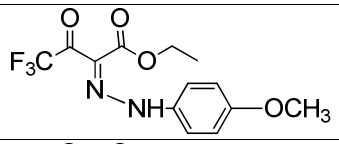
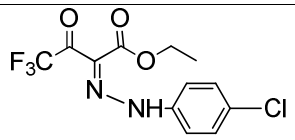
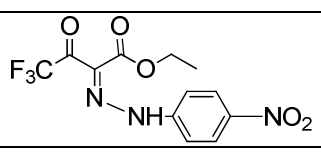
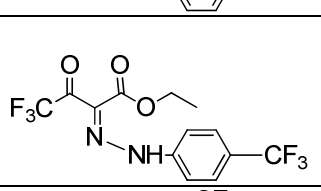
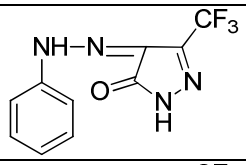
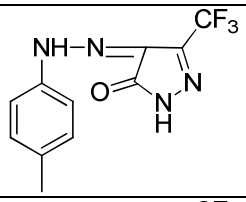
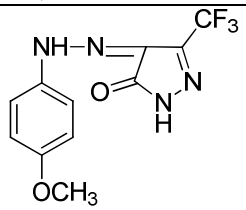
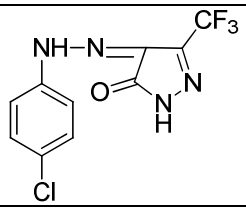
Melting points were determined on open capillaries using a cintex melting point apparatus .T.L.C. analysis were performed on precoatedsilicagel (E-Merck Kieselgel 60 F_{254}) plates and visualisation was done by exposing to iodine vapour.Solvent were purified by standard procedures before use.Column chromatography was conducted by using Silica gel with different solvent systems as elutes.IR Spectra were recorded KBr on perkin –elmer spectrum BX series FTIR spectrometer.H^1-NMR spectrum were recorded on varianzemini 300MHz and 200MHz spectrometers using TMS as internal standard(chemical shifts in & ppm) C^{13}NMR spectra were recorded on a brucker 75MHz spectrometer . Mass spectra were scanned on a varian MATCH -7 and jeol JMSD-300 mass spectrometer at 70 ev. Elemental analysis were carried out on carloerba 106 and perkin –analyser .All the chemicals used in the present investigation were perchased from Aldrich chemicals

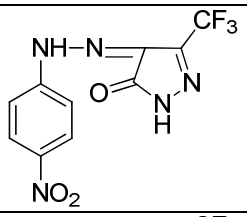
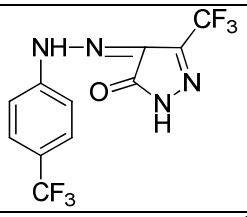
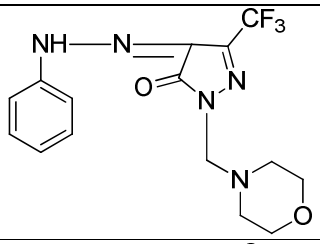
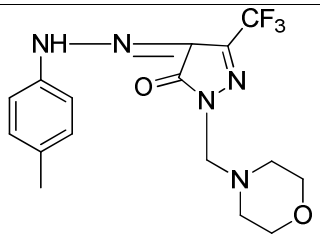
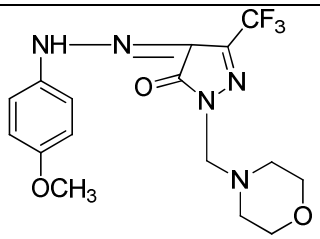
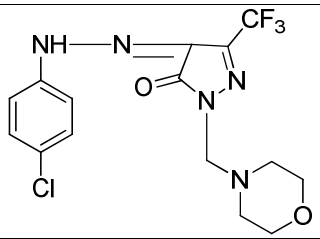
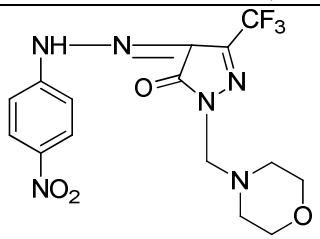
RESULTS AND DISCUSSION

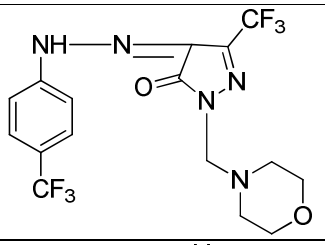
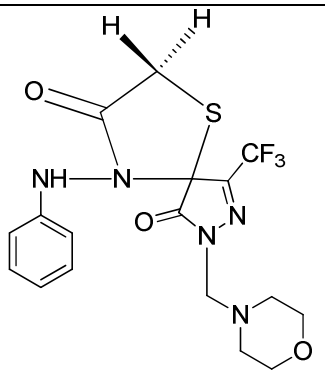
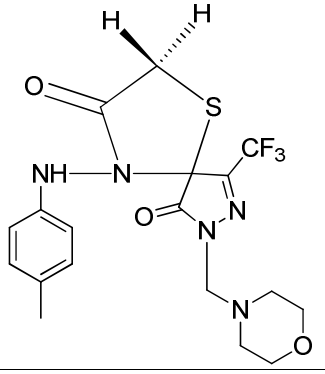
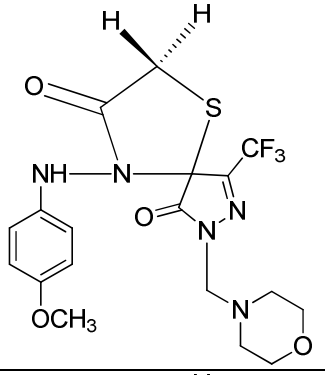
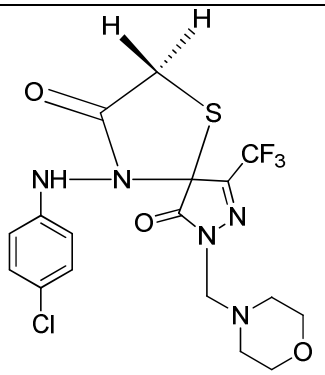
The target compounds were synthesized via the route as shown in Scheme above. The synthon required for thesynthesis of the target molecules indole-3-carbaldehyde was prepared by a reported method.Filtered andrecrystallized from ethanol.These reactions are summarised in the scheme-1.Yields were moderate to affair(55-70%). The purity of the compounds wasmonitered by TLC.

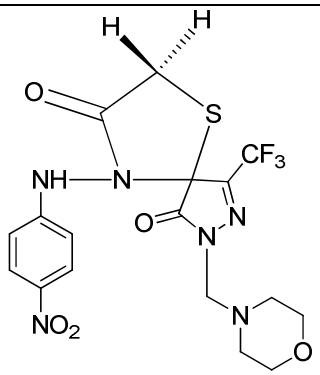
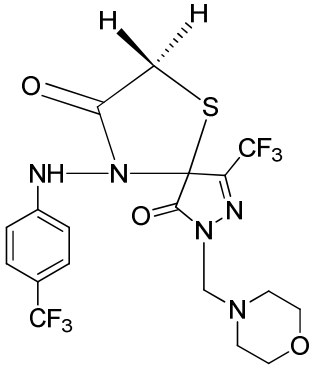


Compd	4a	4b	4c	4d	4e	4f
R	-H	-CH_3	-OCH_3	-Cl	-NO_2	-CF_3
X	-O-	-O-	-O-	-O-	-O-	-O-

Com	Structure	Name	MW/MF
1a		(Z)-ethyl 4,4,4-trifluoro-3-oxo-2-(2-phenylhydrazono)butanoate	$C_{12}H_{11}F_3N_2O_3$/ 288.22
1b		(Z)-ethyl 4,4,4-trifluoro-3-oxo-2-(2-(p-tolyl)hydrazono)butanoate	$C_{13}H_{13}F_3N_2O_3$/302.25
1c		(Z)-ethyl 4,4,4-trifluoro-2-(2-(4-methoxyphenyl)hydrazono)-3-oxobutanoate	$C_{13}H_{13}F_3N_2O_4$/318.25
1d		(Z)-ethyl 2-(2-(4-chlorophenyl)hydrazono)-4,4,4-trifluoro-3-oxobutanoate	$C_{12}H_{10}ClF_3N_2O_3$/322.67
1e		(Z)-ethyl 4,4,4-trifluoro-2-(2-(4-nitrophenyl)hydrazono)-3-oxobutanoate	$C_{12}H_{10}F_3N_3O_5$/333.22
1f		(Z)-ethyl 4,4,4-trifluoro-3-oxo-2-(2-(4-(trifluoromethyl)phenyl)hydrazono)butanoate	$C_{13}H_{10}F_6N_2O_3$/356.22
2a		4-(2-phenylhydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one	$C_{10}H_7F_3N_4O$/256.18
2b		4-(2-(p-tolyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one	$C_{11}H_9F_3N_4O$/270.21
2c		4-(2-(4-methoxyphenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one	$C_{11}H_9F_3N_4O_2$/286.21
2d		4-(2-(4-chlorophenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one	$C_{10}H_6ClF_3N_4O$/290.63

2e		4-(2-(4-nitrophenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one	$C_{10}H_6F_3N_5O_3$/301.18
2f		3-(trifluoromethyl)-4-(2-(4-(trifluoromethyl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one	$C_{11}H_6F_6N_4O$/ 324.18
3a		1-(morpholinomethyl)-4-(2-phenylhydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one	$C_{15}H_{16}F_3N_5O_2$/355.32
3b		1-(morpholinomethyl)-4-(2-(p-tolyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one	$C_{16}H_{18}F_3N_5O_2$/369.34
3c		4-(2-(4-methoxyphenyl)hydrazono)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one	$C_{16}H_{18}F_3N_5O_3$/385.34
3d		4-(2-(4-chlorophenyl)hydrazono)-1-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one	$C_{15}H_{15}ClF_3N_5O_2$/389.76
3e		1-(morpholinomethyl)-4-(2-(4-nitrophenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one	$C_{15}H_{15}F_3N_6O_4$/400.31

3f		1-(morpholinomethyl)-3-(trifluoromethyl)-4-(2-(4-(trifluoromethyl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one	$C_{16}H_{15}F_6N_5O_2$/423.31
4a		7-(morpholinomethyl)-4-(phenylamino)-9-(trifluoromethyl)-1-thia-4,7,8-triazaspiro[4.4]non-8-ene-3,6-dione	$C_{17}H_{18}F_3N_5O_3S$/429.42
4b		7-(morpholinomethyl)-4-(p-tolylamino)-9-(trifluoromethyl)-1-thia-4,7,8-triazaspiro[4.4]non-8-ene-3,6-dione	$C_{18}H_{20}F_3N_5O_3S$/443.44
4c		4-((4-methoxyphenyl)amino)-7-(morpholinomethyl)-9-(trifluoromethyl)-1-thia-4,7,8-triazaspiro[4.4]non-8-ene-3,6-dione	$C_{18}H_{20}F_3N_5O_4S$/459.44
4d		4-((4-chlorophenyl)amino)-7-(morpholinomethyl)-9-(trifluoromethyl)-1-thia-4,7,8-triazaspiro[4.4]non-8-ene-3,6-dione	$C_{17}H_{17}ClF_3N_5O_3S$/463.86

4e		7-(morpholinomethyl)-4-((4-nitrophenyl)amino)-9-(trifluoromethyl)-1-thia-4,7,8-triazaspiro[4.4]non-8-ene-3,6-dione	$C_{17}H_{17}F_3N_6O_5S$/474.41
4f		7-(morpholinomethyl)-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4.4]non-8-ene-3,6-dione	$C_{18}H_{17}F_6N_5O_3S$/497.41

Synthesis of3-(trifluoromethyl)-4-(2-(4-(trifluoromethyl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one
(2).

A solution of (1) (0.01mol) and hydrazine hydrate (0.018mol) in ethanol(20ml) was refluxed for 5hrs. The reaction mixture was cooled and poured in to ice cold water with stirring. Theseparated solid was filtered, washed with water and recrystalised from ethanol to afford 3-(trifluoromethyl)-4-(2-(4-(trifluoromethyl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one(2).

^{1} H NMR spectra(300MHZ,$(CD)_2$SO,TMS):δ:-3.77 (s,2H N-CH_2-C =O), 4.29 (s,2H of –NH_2), 9.68(s,1H,-NH),7. 35-7.40 (m,pyrazole and ,4H of phenyl ring).IR data of (2)1615 (C=N),3220(NH),1690 (-C=O),2125(NΞN),3496,342(-NH_2two bands)

Synthesis of 1-(morpholinomethyl)-4-(2-phenylhydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (3).

A mixture of 3-(trifluoromethyl)-4-(2-(4-(trifluoromethyl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one(0.01mol),in DMF(10ml) and various mannich (0.01)in ethanol (10ml),was stirred at room temperature for 1-2 hours. The solid separated was filtered, dried and recrystalized from ethanol –DMF mixture. The yield, meltingpoint and other characterization data of compounds prepared by this procedure are given in the table.

^{1} H NMR spectra(300MHZ,$(CD)_2$ SO,TMS):δ:- 3.79 (s,2H N-CH_2-C =O), 9.54 (s,1H,-NH),9.38-10.29 (2H due to NH-NH group appeared as two broad signals), 7.32 -7.37 (m,,4H of phenyl ring), 7.0-7.1(s,1H,thiazole ring),10.65(s,1H,-CO-NH). IR data of(3) . 1630 (C=N),3220(NH),1675 (-C=O),2135(NΞN),3496,342(-NH_2 two),1180(C=S) TABLE.- Antibacterial activity by disc diffusion method.

7-(morpholinomethyl)-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4.4]non-8-ene-3,6-dione 4(a-f)

Equimolar quantities of 1-(morpholinomethyl)-3-(trifluoromethyl)-4-(2-(4-(trifluoromethyl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one was converted into thiazolidinone on treatment with mercaptoaceticacid Yield 75%,m.p.:155-150^{0}C. This

general procedure was extended to 3-chloro-6-(morpholinomethyl)-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6,7-triazaspiro[3.4]oct-7-ene-2,5-dione 4(a-f) the structure of 4(a-f) were established by IR and H^1 NMR data

^{1} H NMR spectra(300MHZ,$(CD)_2$ SO,TMS):δ 4(a) show signals 1.30 (t,3H,CH_3 of C_2H_5), 4.75 (s,2H N-CH_2-C =O), 4.15 (q,2H,-O-CH_2 Of OC_2H_5), 5.16(d,1H,-CH of thiazolidine attached to phenyl ring), 5.44(d,1H,-CH of thiazolidine attached to -Cl), 6.94-7.59 (m,10H,Ar-H). IR(KBr) spedtra ; The compound 1(a) shows signals at, 1578(C=N),1177(-C-O-C-),1765(-C=O),826(CCl) are due to strectching vibrations of –C=O , C=N,C-O-C , CCl respectively .

Anti-Bacterial Actillity

The anti bacterial activity of synthesised compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram-positivebacteriascreened were staphylocococcusaureasnccs 2079 and bacillus cereus nccs 2106. The gram negative bacteria screened were Escherichia chia coli nccs 2065 and pseudomonas acruginosa NCCS 2200.

The synthesized compounds were used at the concentration of250 uglml and500uglml using dmso as asolvent**Chloromphenicol(5)**disc was used as a standard .(himedia laboratories ltd, Mumbai)

The test results presented in the table -1, suggest that exhibit high activity against the tested bacteria, the rest of the compounds were found to be moderate active against the tested microorganisms.

Antifungal activity

The antifungal activity of synthesized compounds were studied by disc diffusion against the organisms of aspergillusniger NCCS1196 and cadidaalbicas NCCS34471

Compounds were treated at the counteractions of 500uglm and 1000uglml using DMSO as solicit. The standard used was clot rigmarole 50uglml against both organisms. the test results were presented in the table-2.

TABLE.- Antibacterial activity by disc diffusion method of pyrazole having thiazolidine 4(a.f)

Compound	Zone of inhibition (mm)			
	Staphylococcus aures	Bacillus cereus	Escherichia coli	Pseudomonas aeruginosa
4a	15	15	12	17
4b	14	12	18	10
4c	12	12	10	09
4d	16	17	12	11
4e	18	19	18	12
4f	14	15	13	16
Chloromphenicol(5)	28	29	25	17

Table-;2 Antifungal activity by disc diffusion method for of pyrazole having thiazolidine4(a-f).

Compound	Zone of inhibition (mm)	
	Aspergillums Niger	Candida alb cans
4a	14	16
4b	15	13
4c	17	15
4d	18	17
4e	23	21
4f	15	13
Ketocanazole(50)	21	19

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