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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF NOVEL COMPOUNDS OF 3-AMINO-1-(2, 5-DIFLUOROBENZOYL)-4-(2-(4-NITROPHENYL) HYDRAZONO)-1H-PYRAZOL-5(4H)-ONE MOIETIES

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ABSTRACT

New novel derivatives of 3-amino-1-(2,5-difluorobenzoyl)-4-(2-(4-nitrophenyl) hydrazono)-1H-pyrazol -5(4H)-one were prepared by condensation of of ethyl 2-isocyano-2-(2-(4-nitrophenyl) hydrazono)acetate (3). The synthon (3) was obtained by the condensation of 1,4- di fluoro benzoyl hydrazide(2) with Ethyl 2-(2-(4-(tri fluoromethyl) phenyl) hydrazono)-2-iso cyano acetate(1). The synthon(1) was obtained by the condensation of 1-chloro-2-(4-(trifluoro methyl) phenyl)diazene(A) with ethyl-2-iso cyano acetate (B). The newly synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra & Elemental analysis. The newly synthesized compounds were screened for their Biological activity.

KEYWORDS: Pyrazolone-5-one, Antibacterial and Antifungal activity.

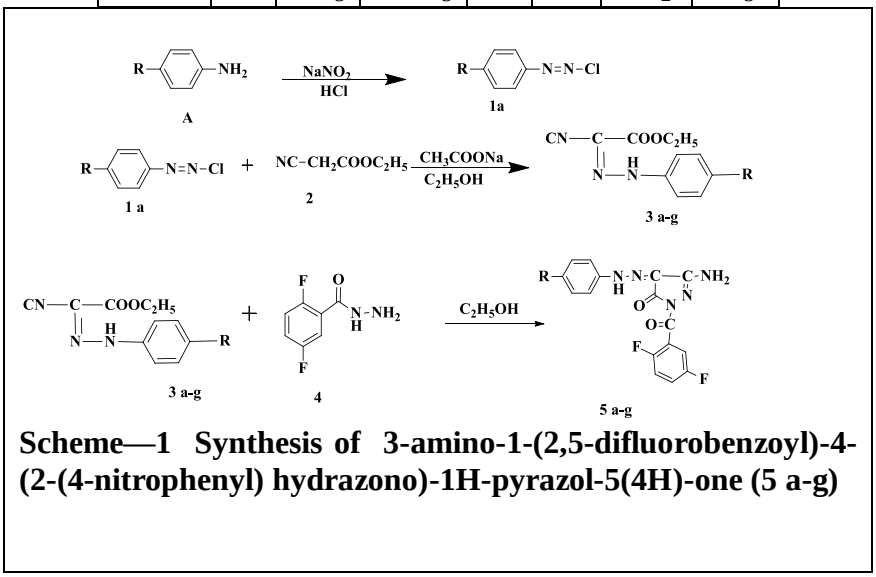
INTRODUCTION

Hetero cyclic compounds represent an important class of biological active molecules specifically those containing the pyrazolone nucleus besides triazaspiro ring have been shown to possess high biological activities[1-12] such as anti-tuberculosis, anti-neoplastic, anti-fertility and anti-hydro thyroid activity. The derivatives of pyrazolone-5-ones are important class of nitrogen hetero cycles, they found to possess tranquillizing, muscle relaxant, Psycho

analeptic, anti convulsing, anti hypertensive, antidepressant, antipyretic and analgesic reactivates.

In recent years, the synthesis of pyrrazoline derivatives remains a main focus of medicinal research. Pyrazolines are heterocyclic compounds which posses wide range of biological activities such as anti inflammatory[13] antituberculosis,[14-15] kinase inhibitor,[16] oxidase inhibitor,[17] anti cancer,[18] antiproliferative activity,[19] MAOl inhibitors,[20,21] anti hepatotoxic activity,[22] antibacterial,[23,24] anti analegisic,[25,26] anti coagulant,[27] anti tumor[28] and anti diabetic activities.[29] Pyrazoline is five-membered heterocyclic having two adjacentnitrogen atoms within the ring. It has only one endocyclic double bond and is basic in nature[30] and plays a crucial role in the development of theory in hetero cyclic chemistry and is also extensively used as useful synthons in organic synthesis.[31] Among its various derivatives, 3, 5-diaryl-pyrazolines[32] seem to be the most frequently studied pyrazoline type compounds. Encouraged by these interesting biological activities associated with pyrazoline derivatives, in this paper we report here in the synthesis and antimicrobial activity of some new pyrrazoline derivatives screened against *Escheria. Coli, Pseudomonas. aeruginosa, Staphylococcus. aureus* and *Streptococus. pyogenes,* bacterial strains using ampicillin as standard.

Comp	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**
R	H	CH_3	OCH_3	Cl	Br	NO_2	CF_3



Scheme—1 Synthesis of 3-amino-1-(2,5-difluorobenzoyl)-4-(2-(4-nitrophenyl) hydrazono)-1H-pyrazol-5(4H)-one (5 a-g)

MATERIALS AND METHODS

All the chemicals used in the present investigation were purchased from Sigma-Aldrich Chemicals Company, Inc.USA. And used without further purification. TLC was performed on aluminum sheet of silica gel 60F254, E-Merk, Germany using iodine as visualizing agent. Melting point was determined in open capillary tubes on Mel-Tempapparatus and is uncorrected. Column chromatography was performed on silica gel with different solvent systemsas eluents to afford the pure compound. The IR Spectra were recorded as KBr pellets on Perkin-Elmer 1000 units, instruments. All 1H and 13C-NMR spectra were recorded on a Varian XL-300 spectrometer operating at 400MHzfor 1H -NMR and 75 MHz for ^{13}C-NMR were recorded on a Varian XL-spectrometer operating at161.89MHz. The compounds were dissolved in DMSO-d6 and Chemical shifts were referenced to TMS (1H and^{13}C-NMR) .Mass spectral data was recorded on FAB-MS instrument at 70ev with direct inlet system. Elemental analysis was recorded on a Carlo Erba 1108 elemental Analyzer, Central Drug Research Institute, Lucknow, India.

Experimental section

Synthesis of ethyl 2-isocyano-2-(2-(4-nitrophenyl) hydrazono) acetate (3 a-g)

The required primary amine is diazotized with sodium nitrite and HCl mixture at 0-5^0 C and it is coupled with cyano acetic ester to afford ethyl 2-isocyano-2-(2-(4-nitrophenyl)hydrazono) acetate(3a-g). The compound (3) was prepared by the procedure described by H.M.Walborsky, M.E. Baum.[33]

Synthesis of 3-amino-1-(2,5-difluorobenzoyl)-4-(2-(4-nitrophenyl)hydrazono)-1H-pyrazol-5(4H)-one (5 a-g)

A mixture of ethyl 2-isocyano-2-(2-(4-nitrophenyl)hydrazono)acetate (3 a)and 1,4-difluoro benzoyl hydrazide(B) and dimethyl formamide(1 ml) was subjected to microwave irradiation at 150 W intermittently at 30 seconds intervals for 2 min.After complete conversion as indicated by TLC,the reaction mixture was cooled and treated with cold water. The precipitate 3-amino-1-(2,5-difluorobenzoyl)-4-(2-(4-nitrophenyl)hydrazono)-1H-pyrazol-5(4H)-one (5 a-g) was filtered and recristalized from ethyl alcohol, The yield is 85% with Mp 184^0 C. The structure of (3) was established by IR,^{1}H-NMR and Elemental analysis.

Physical, analytical and spectral data for the compounds

3-amino-1-(2, 5-difluorophenylcarbonoyl)-4-(2-(4-Substituted) phenyl) hydrazono)-1H-pyrazole-5(4H) - one ***(5a)***

Yield 85%. M.P: 183-184^{0}C. IR (KBr):3385,3405(two bands stretching vibration of NH2), 3225(stretching vibration of -NH),1620(stretching vibration of >C=N),1675(stretching vibration of cyclic carbonyl five membered hetero cyclic ring),1656(exo cyclic >C=O group), 1H-NMR (400 MHZ DMSO-d6): 2.15(s,2H,-NH2 group),6.81-8.37(m,7H,C6H4 and C6H3), 10.15(s,1H,Ar –NH-N= group). 13CNMR(75MHz, DMSO-d6): 154.3,113.5,125.6,126.9,163.5,55.4,78.1,176.1,171.2,170.2,126.7,154.9,118.7,120.5,158.6,113.9,163.7,126.0,130.2,114.4,162.9,124.1,55.8. Corresponding to C_1,C_2,C_3, C_4,C_5,C_6,C_7,C_8,C_9, C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17}, C_{18},C_{19},C_{20},C_{21}, C_{22}, C_{23},C_{24}.C_{25},C_{26}, C_{27} Anal. Calcd. For $C_{17}H_{10}F_5N_5O_2$ C 49.64% , H 2.45% and N 17.03%. Found: C 49.53%, H 2.23% and N 16.80%.

3-amino-1-(2, 5-difluorophenylcarbonoyl)-4-(2-(4-Substituted) phenyl) hydrazono)-1H-pyrazole-5(4H) - one ***(5b)***

Yield 85%.

M.P.: 184^{0}C.

IR (KBr)

3385, 3405(two bands stretching vibration of NH2), 3225(stretching vibration of-NH), 1620(stretching vibration of >C=N), 1675(stretching vibration of cyclic carbonyl five membered hetero cyclic ring), 1656(exo cyclic >C=O group).

^{1}H-NMR (400 MHZ DMSO-d_6)

2.15(s, 2H,-NH2 group), 6.81-8.37(m, 7H, C6H4 and C6H3), 10.15(s, 1H, Ar –NH-N= group).

^{13}CNMR(75MHz,DMSO-d_6)

154.3,113.5,125.6,126.9,163.5,55.4,78.1,176.1,171.2,170.2,126.7,154.9,118.7,120.5,158.6,113.9,163.7,126.0,130.2,114.4,162.9,124.1,55.8. Corresponding to C_1,C_2,C_3, C_4,C_5,C_6,C_7,C_8,C_9, C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17}, C_{18},C_{19},C_{20},C_{21}, C_{22}, C_{23},C_{24}.C_{25},C_{26}, C_{27}Anal.Calcd.For $C_{17}H_{10}F_5N_5O_2$ C 49.64% , H 2.45% and N 17.03%. Found: C 49.53%, H 2.23% and N 16.80%.

3-amino-1-(2, 5-difluorophenylcarbonoyl)-4-(2-(4-Substituted) phenyl) hydrazono)-1H-pyrazole-5(4H) - one ***(5c)***

Yield 75%.

M.P.: 162-164^{0}C.

IR (KBr)

3385, 3405(two bands stretching vibration of NH2), 3225(stretching vibration of -NH),1620(stretching vibration of >C=N),1675(stretching vibration of cyclic carbonyl five membered hetero cyclic ring),1656(exo cyclic >C=O group), 1H-NMR (400 MHZ DMSO-d6): 2.15(s,2H,-NH2 group),6.81-8.37(m,7H,C6H4 and C6H3), 10.15(s,1H,Ar –NH-N= group).

^{13}CNMR(75MHz,DMSO-d_6)

154.3,113.5,125.6,126.9,163.5,55.4,78.1,176.1,171.2,170.2,126.7,154.9,118.7,120.5,158.6,113.9,163.7,126.0,130.2,114.4,162.9,124.1,55.8. Corresponding to C_1,C_2,C_3,C_4,C_5,C_6, C_7,C_8,C_9, C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17}, C_{18},C_{19},C_{20},C_{21}, C_{22}, C_{23},C_{24}.C_{25},C_{26}, C_{27} Anal.Calcd.For $C_{17}H_{10}F_5N_5O_2$ C 49.64% , H 2.45% and N 17.03%. Found: C 49.53%, H 2.23% and N 16.80%.

3-amino-1-(2, 5-difluorophenylcarbonoyl)-4-(2-(4-Substituted) phenyl) hydrazono)-1H-pyrazole-5(4H) - one ***(5d)***

Yield 75%

M.P.: 142-144^{0}C.

IR (KBr)

3385, 3405(two bands stretching vibration of NH2), 3225(stretching vibration of -NH), 1620(stretching vibration of >C=N), 1675(stretching vibration of cyclic carbonyl five membered hetero cyclic ring), 1656(exo cyclic >C=O group).

^{1}H-NMR (400 MHZ DMSO-d_6)

2.15(S, 2H, -NH2 group), 6.81-8.37(m, 7H, C_6H_4 and C_6H_3), 10.15(S, 1H, Ar –NH-N= group).

^{13}CNMR(75MHz,DMSO-d_6)

154.3,113.5,125.6,126.9,163.5,55.4,78.1,176.1,171.2,170.2,126.7,154.9,118.7,120.5,158.6,113.9,163.7,126.0,130.2,114.4,162.9,124.1,55.8. Corresponding to C_1,C_2,C_3, C_4,C_5,C_6,C_7,C_8,C_9, C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17}, C_{18},C_{19},C_{20},C_{21}, C_{22}, C_{23},C_{24}.C_{25},C_{26}, C_{27} Anal.Calcd.For $C_{17}H_{10}F_5N_5O_2$ C 49.64% , H 2.45% and N 17.03%. Found: C 49.53%, H 2.23% and N 16.80%.

3-amino-1-(2,5-difluorophenylcarbonoyl)-4-(2-(4-Substituted) phenyl) hydrazono)-1H-pyrazole-5(4H) - one ***(5e)***

Yield 64%.

m p: 128-130^{0}C.

IR (KBr)

3385, 3405(two bands stretching vibration of NH2), 3225(stretching vibration of -NH),1620(stretching vibration of >C=N),1675(stretching vibration of cyclic carbonyl five membered hetero cyclic ring),1656(exo cyclic >C=O group).

^{1}H-NMR (400 MHZ DMSO-d6)

2.15(s, 2H, -NH2 group), 6.81-8.37(m, 7H, C_6H_4 and C_6H_3), 10.15(s, 1H, Ar –NH-N= group).

^{13}CNMR(75MHz,DMSO-d_6)

154.3,113.5,125.6,126.9,163.5,55.4,78.1,176.1,171.2,170.2,126.7,154.9,118.7,120.5,158.6,113.9,163.7,126.0,130.2,114.4,162.9,124.1,55.8. Corresponding to C_1,C_2,C_3, C_4,C_5,C_6,C_7,C_8,C_9, C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17}, C_{18},C_{19},C_{20},C_{21}, C_{22}, C_{23},C_{24}.C_{25},C_{26}, C_{27}.Calcd.For $C_{17}H_{10}F_5N_5O_2$ C 49.64% , H 2.45% and N 17.03%. Found: C 49.53%, H 2.23% and N 16.80%.

3-amino-1-(2, 5-difluorophenylcarbonoyl)-4-(2-(4-Substituted) phenyl) hydrazono)-1H-pyrazole-5(4H) - one ***(5f)***

Yield 68%.

M.P: 123-125^{0}C.

IR (KBr)

3385, 3405(two bands stretching vibration of NH2), 3225(stretching vibration of -NH), 1620(stretching vibration of >C=N), 1675(stretching vibration of cyclic carbonyl five membered hetero cyclic ring), 1656(exo cyclic >C=O group).

^{1}H-NMR (400 MHZ DMSO-d_6)

2.15(S, 2H, -NH_2 group), 6.81-8.37(m, 7H, C_6H_4 and C_6H_3), 10.15(s, 1H, Ar –NH-N= group).

^{13}CNMR(75MHz,DMSO-d_6)

154.3,113.5,125.6,126.9,163.5,55.4,78.1,176.1,171.2,170.2,126.7,154.9,118.7,120.5,158.6,113.9,163.7,126.0,130.2,114.4,162.9,124.1,55.8. Corresponding to C_1,C_2,C_3, C_4,C_5,C_6,C_7,C_8,C_9, C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17}, C_{18},C_{19},C_{20},C_{21}, C_{22}, C_{23},C_{24}.C_{25},C_{26}, C_{27}Anal.Calcd.For

$C_{17}H_{10}F_5N_5O_2$ C 49.64% , H 2.45% and N 17.03%. Found: C 49.53%, H 2.23% and N 16.80%.

3-amino-1-(2, 5-difluorophenylcarbonoyl)-4-(2-(4-Substituted) phenyl) hydrazono)-1H-pyrazole-5(4H) - one ***(5g)***

Yield 85%.

M.P.: 132-134^{0}C.

IR (KBr)

3385, 3405(two bands stretching vibration of NH2), 3225(stretching vibration of -NH),1620(stretching vibration of >C=N),1675(stretching vibration of cyclic carbonyl five membered hetero cyclic ring),1656(exo cyclic >C=O group), 1H-NMR (400 MHZ DMSO-d_6): 2.15(s,2H,-NH_2 group),6.81-8.37(m,7H,C_6H_4 and C_6H_3), 10.15(s,1H,Ar –NH-N= group).

^{13}CNMR(75MHz, DMSO-d_6)

154.3,113.5,125.6,126.9,163.5,55,.4,78.1,176.1,171.2,170.2,126.7,154.9,118.7,120.5,158.6,113.9,163.7,126.0,130.2,114.4,162.9,124.1,55.8. Corresponding to C_1,C_2,C_3,C_4,C_5,C_6, C_7,C_8,C_9,C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15}, C_{16},C_{17}, C_{18},C_{19},C_{20},C_{21}, C_{22}, C_{23},C_{24}.C_{25},C_{26}, C_{27}Anal.Calcd.For C17H10F5N5O2 C 49.64% , H 2.45% and N 17.03%. Found: C 49.53%, H 2.23% and N 16.80%.

Mass Spectra

The mass spectral fragmentation process of (5a) was presented below. The molecular ion peak was observed at m/z=577.08(33%) and the base peak was noticed at m/z 575.08(100%) peaks appeared at different m/z values .

Mass spectral data of primary fragmented ions for *3-amino-1-(2, 5-difluorophenylcarbonoyl)-4-(2-(4-Substituted) phenyl) hydrazono)-1H-pyrazole-5(4H) - one* **(5a)**

Molecular ion	Lost radical	Primary fragmented ion	m/z values	Relative abundance (R.A) (%)
$C_{24}H_{13}F_5N_8O_2$ M/Z=649.06 (100%)	$C_{18}H_{10}F_3N_8O_2$	$C_6H_3F_2$	428.09	13.2
	$C_6H_3F_2$	$C_{18}H_{10}F_3N_8O_2$	114.02	11.4
	$C_{17}H_{10}F_3N_8O$	$C_7H_3F_2O$	400.10	29.2
	$C_7H_3F_2O$	$C_{17}H_{10}F_3N_8O$	142.02	19.3
	$C_{18}H_7F_5N_7O$	C_6H_6N	449.06	34.1
	C_6H_6N	$C_{18}H_7F_5N_7O$	92.05	11.5
	$C_{17}H_9F_2N_8O_2$	$C_7H_4F_3$	396.09	16.7
	$C_7H_4F_3$	$C_{17}H_9F_2N_8O_2$	146.03	27.6

The molecular ion signal was obeying nitrogen rule, while the primary fragmented ions derived from molecular ion signal may or may not obey nitrogen rule.

The fragmented ions containing one chlorine atom showed two m/z values with difference of two units and the corresponding relative abundances were in the ratio of 3:1.

Biological activity

The antimicrobial activity of these newly synthesized compounds was performed according to disc diffusion method, as recommended by the National Committee for Clinical Laboratory. The synthesized compounds Were used at the concentration of 250µg/ml DMF as a solvent.

Antibacterial activity

The antibacterial activity of *3-amino-1-(2, 5-difluorophenylcarbonoyl)-4-(2-(4-Substituted) phenyl) hydrazono)-1H-pyrazole-5(4H) - one* (5a-g) were screened against the Staphylococcus aureus (gram positive) and Escherichiacoli (gram negative) organisms. Most of the compounds exhibited moderate antibacterial activity against both bacteria. The presence of chloro, bromo and nitro in the structure has shown increased effect on their antibacterial activity

Antifungal activity

Antifungal activity of *3-amino-1-(2, 5-difluorophenylcarbonoyl)-4-(2-(4-Substituted) phenyl) hydrazono)-1H-pyrazole-5(4H) - one* (5a-f) were screened against Aspergillus niger, Candida albicans. The presence of chloro, bromo and nitro in the structure has shown increased effect on their antibacterial activity .

Entry	**Bacteria**						**fungi**			
	Staphylococcus aureus NCCS2079		**Bacillus cereus NCCS 2106**		**Escherichia coli NCCS2065**		**Aspergillus niger NCCS 1196**		**Candida albicans NCCS 2106**	
	25	50	25	50	25	50	25	50	25	50
5a	-	07	-	06	-	05	-	08	-	09
5b	-	06	-	08	-	07	-	07	-	10
5c	-	08	-	08	-	09	-	08	-	10
5d	08	12	08	13	07	11	06	11	05	10
5e	07	10	08	12	06	10	05	10	04	09
5f	11	14	11	15	10	13	09	14	10	13
5g	08	12	08	13	07	11	06	11	05	10
Chloromphenicol (5)	-	25	-	26	-	22	-	-	-	-
Ketocanazole (50)	-	-	-	-	-	-	-	16	-	18

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