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Design, synthesis of some new pyrazolo [3, 4-c] pyrazol thiazolone and evaluation of their antimicrobial activity

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ABSTRACT

An efficient and convenient procedure has been developed for the synthesis of some new substituted pyrazolo [3,4-c] pyrazol Thiazolone derivatives were synthesized and evaluated for their in vitro antimicrobial activity. All the synthesized compounds were subjected to in vitro antimicrobial screening. Some of the compounds showed excellent activity against panel of microorganism.

Keywords: 4-(substitutedbenzylidene)-3-methyl-1-phenyl-1H–pyrazol-5-ones, thiosemicarbazide, pyrazolo[3,4-c] pyrazol thiazolone, antimicrobial activity.

INTRODUCTION

Among the wide variety of heterocycles that have explored for the developing pharmaceutical important molecules. In the family of heterocyclic compounds, nitrogen containing heterocycles with a sulphur atom are an important class of compounds in medicinal chemistry. Pyrazole containing compounds have practical application in the medicinal and agrochemical field [1, 2]. The pyrazole ring has shown to be the basic moiety for a number of dyes and drugs [3, 4]. Several pyrazoles with antimicrobial, antiviral and anticancer properties have been reported [5] .Certain allyl pyrazoles have shown significant antiallergic, anti-inflammatory, and antiarthritic properties [6,7]. Many pyrazole- fused heterocyclic compounds have been to exhibit biological activity widely used in pesticides and medicine [8, 9]. Pyrazoline derivatives have also been reported in the literature to exhibit various pharmacological activities such as anti-inflammatory

[10], antihypertensive [11] and antimicrobial. On the other hand thiazoles and their derivatives have attracted continuing interest over the years because of their biological activities [12, 13] recently found application in the drug development for the treatment of allergies [14] hypertensive [15] bacterial [16] to identify new class that may be value in designing new potent antimicrobial agents. Our continuation work on heterocycles [17-21] that having potent biological activities, these assets prompted us to prepare some new pyrazolo [3,4-c] pyrazol thiazolone derivatives with potent biological activity by using polyethylene glycol-400 as green and recyclable solvent.

MATERIALS AND METHODS

Chemistry:

Melting points were uncorrected and determined in an open capillary tube. IR spectra were recorded on FTIR Shimadzu spectrometer. ^{1}H NMR spectra were recorded in DMSO-d_6 on Avance 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

General procedure for the synthesis of 4-(4-Substituted benzylidine)-3-methyl-1-phenyl-1H-Pyrazol-5(4H)-one [22]

General procedure for the synthesis of substituted 4-methyl- 3,6-diphenylpyrazolo [3, 4-c] pyrazol-2(6H)-carbothioamide(2a-f)

A mixture of substituted 4-Benzylidine-3-methyl-1-phenyl-1H-Pyrazol-5(4H)-one (1mmol) and thiosemicarbazide (2mmol) was stirred in polyethylene glycol (PEG-400) 20 ml at 40^{0}c for 1 hours. After completion the reaction (monitored by TLC), contents were poured into cold water. The separated solid was filtered and recrystallized from proper solvent to give pure compound.

General procedure for the synthesis of substituted 3-(4-methyl)-3,6-diphenyl pyrazolo[3,4-c]pyrazol-2(6H)-yl)thiazol-4-(5H)-one

A Mixture of substituted 4-methyl-3,6-diphenylpyrazolo [3, 4-c] pyrazol-2(6H)-Carbothioamide (0.34gm,0.01) and monochloro acetic acid (0.74gm.0.01) dissolved in15 ml of acetic acid. Solid sodium acetate (0.82gm, 0.01 mole) was added and then the reaction mixture was refluxed for 2-3 hrs. After completion of the reaction (Cheked by TLC), contents were poured into cold water. The separated solid was filtered and recrystallalized from ethanol to give pure compound.

Spectroscopic data of selected compounds

2-(3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-4-methyl-6-phenylpyrazolo [3,4-c] pyrazolo-2-(6H)-yl) thiazol-4(5H)-one

IR (KBr): 1650(>C=O),1598 (>C=N),1512(>C=C<)cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.09-3.20 (dd, 1H, Ha), δ 4.02-4.20 (dd, 1H, Hb), δ 1.30 (s, 3H, -CH_3), 0.92 (s, 3H, -CH_3), δ 3.98 (s, 2H, -CH_2), δ 6.90-8.00 (m, 10H, Ar-H), δ ppm; EIMS (*m/z*): 490[M^+]; Anal. Calcd for $C_{24}H_{20}ON_7ClS$: C, 58.83; H, 4.11; N, 20.01%. Found: C, 58.76; H, 4.12; N, 19.79%.

2-(3-(2-butyl-4-chloro-1H-imidazol-5-yl)-4-methyl-6-phenylpyrazolo[3,4-c]pyrazol-2(6H)-yl)thiazol-4(5H)-one

IR (KBr): 1654(>C=O), 1599(>C=N),1510(>C=C<)cm-1; 1H NMR (DMSO-d6, 300 MHz): δ 3.10-3.30 (dd, 1H, Ha), δ 4.0-4.20 (dd, 1H, Hb), 1.31 (m, 2H, -CH_2-), 1.64 (m, 2H, -CH_2), 2.68

(t, 2H, -CH_2), 8.16 (s, 1H,NH), 0.94 (s, 3H, -CH_3), δ 3.70 (s, 2H, -CH2), δ 6.95-7.90 (m, 5H, Ar-H), δ ppm; EIMS (*m/z*): 453[M^+]; Anal. Calcd for $C_{24}H_{18}ON_7Cl$: C, 55.56; H, 4.44; N, 21.60%. Found: C, 55.55; H, 4.35; N, 21.30%.

2-(3-(3-(4-chlorophenyl)-1-phenyl-1-H-pyrazol-4-yl)-4-methyl-6-phenylpyrazolo[3,4-c]pyrazol-2(6H)-yl)thiazol-4(5H)-one

IR (KBr): 1650(>C=O), 1580(>C=N), 1514(>C=C<)cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz):δ 3.04-3.20 (dd,1H,Ha), δ 4.08-4.28 (dd,1H, Hb), δ 0.94 (s, 3H, -CH_3), δ 3.65 (s, 2H, -CH_2), δ 6.75-7.85 (m, 14H, Ar-H), δ 8.01 (s, 1H, 5H of pyrazole), δ ppm; EIMS (*m/z*): 550[M^+]; Anal. Calcd for $C_{29}H_{20}OSN_7Cl$: C, 63.33; H, 3.66; N, 17.83%. Found: C, 63.25; H, 3.44; N, 17.24%.

2-(3-(3-(4-fluorophenyl)-1-phenyl-1-H-pyrazol-4-yl)-4-methyl-6-phenylpyrazolo[3,4-c]pyrazol-2(6H)-yl)thiazol-4(5H)-one

IR (KBr): 1650(>C=O), 1584(>C=N), 1518(>C=C<)cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.0-3.20 (dd,1H,Ha), δ 4.1-4.30 (dd,1H, Hb),δ 0.98(s, 3H, -CH_3), δ 3.76 (s, 2H, -CH_2), δ 6.75-7.90(m, 14H, Ar-H), δ 8.01 (s, 1H, 5H of pyrazole), δ ppm; EIMS (*m/z*): 534[M^+]; Anal. Calcd for $C_{29}H_{20}OFN_7Cl$: C, 65.28; H, 3.78; N, 18.38%. Found: C, 65.20; H, 3.79; N, 18.44%.

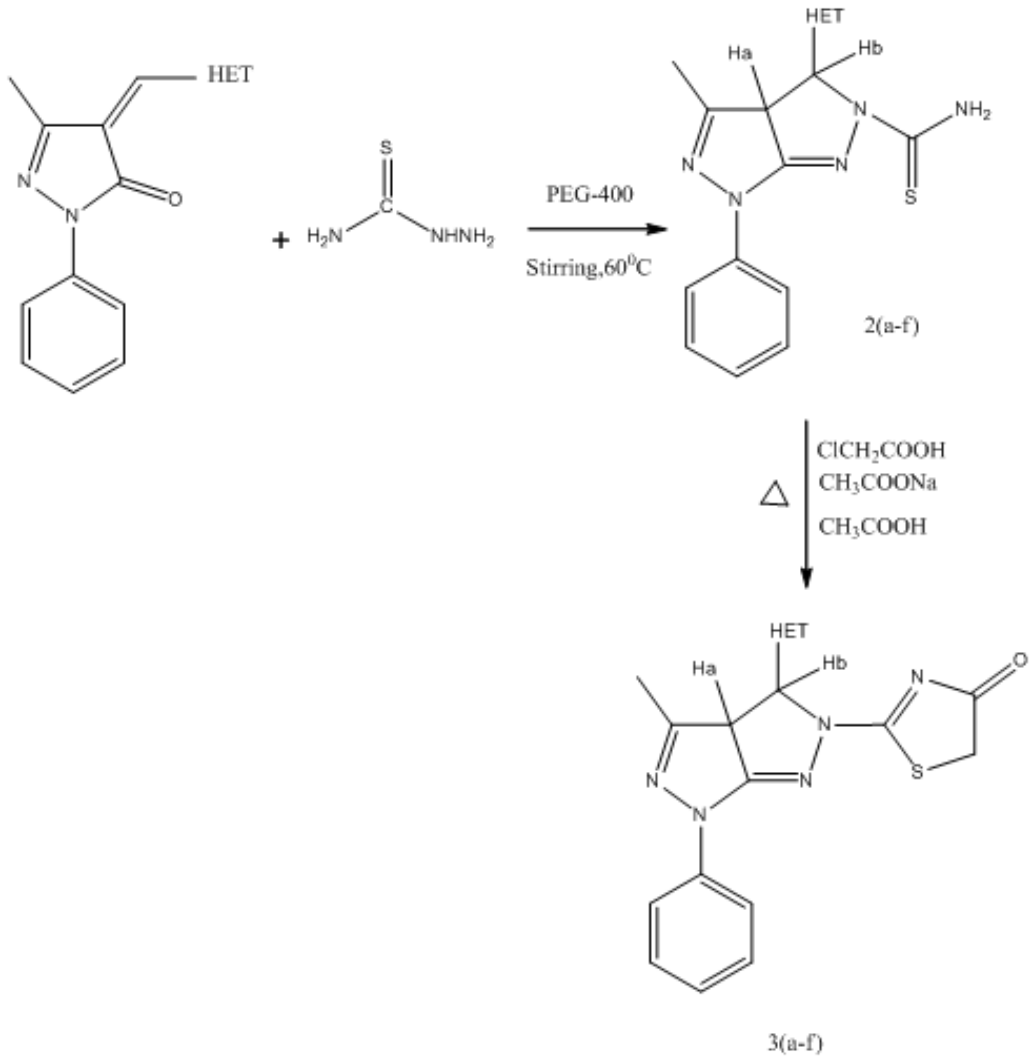
Biology

The antimicrobial activities of the synthesized compounds **II(a-f)** were determined by agar well diffusion method [23]. The compounds were evaluated for antibacterial activity against *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus* and *Bacillus subtilis*. The antifungal activity was evaluated against *Aspergillus niger*, *Aspergillus flavus*, and *Penicillium chrysogenum* were procured from Institute of Microbial technology (IMTech), Chandigarh, India. The antibiotic penicillin (25µg/mL) and nystatin (25µg/mL) was used as reference drug for antibacterial and antifungal activity, respectively. Dimethyl sulphoxide (1%, DMSO) was used a control with out compound.

RESULTS AND DISCUSSION

In a view of the recent emphasis toward the development of new, selective and environmental friendly using PEG-400 or a solvent for the synthesis of fine chemicals and biologically important compound, herein we report an efficient method for the synthesis of pyrazolo[3,4-c] pyrazol thiazolone derivatives using PEG-400. To avoid the use of volatile organic solvents can minimize the generation of waste, which is a requirement of one of the principles of green chemistry [24, 25]. Recently, PEG is found to be an interesting solvent system. The important difference between using PEG and other neoteric solvents is that all of the toxicological properties, the short and long-term hazards, and the biodegradability.

Polyethylene glycol (PEG) as environmentally benign protocol prompted to have many applications, in substitution, oxidation and reduction reaction [26]. Hence, in this present study, a series of pyrazolo[3,4-c] pyrazol thiazolone were synthesized from the 4-(substitutedbenzylidene)-3-methyl-1-phenyl-1H–pyrazol-5-ones in polyethylene glycol (PEG-400) as green solvent under mild reaction condition is described. The reaction sequence for the preparation of title compounds is represented in Scheme.



Scheme-1

Structures of the synthesized compounds were established on the basis of spectral analysis (IR, ^{1}HNMR and MASS). The results of antimicrobial data are summarized in Table. In comparison with standard antibacterial penicillin, compounds IIb, IIc, IId and were found to be growth of fungi against *A. niger*. Compounds IIa, IId, IIe were observed no fungal growth against *A. flavus*. Compounds IIa, IIc, IIe, found to be reduced growth activity aginst *P. chrysogenum*. On the other hand IIb, IId, IIe found to be active against *E. coli*. Compounds were IIc, IId, IIf also found to be active against *S. aureus*. Compounds IIa, IIb, IId, showed good activity comparatively active against *B. subtillis*. As compared with standard antibacterial compounds IIa, IIc, and IIf were observed as active against *S. typhi*.

Table-1: Physical and analytical data of synthesized derivatives III (a-f)

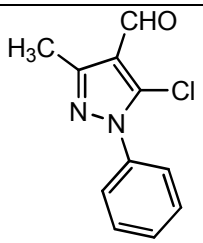
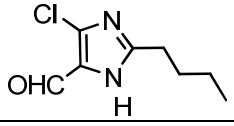
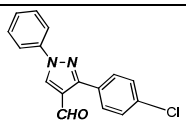
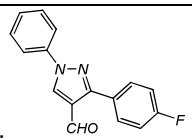
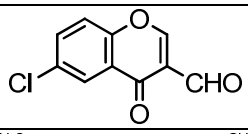
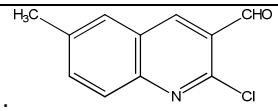
Entry	HET	Yield (%)	M. P (^{O}C)
1		**85**	**140**
2		**88**	**160**
3		**90**	**155**
4		**82**	**170**
5		**84**	**165**
6		**80**	**180**

Table-2: The antimicrobial data of the synthesized derivatives II(a-f)

Product	Bacteria (Zone of inhibition in mm)				Fungi (Growth)		
	Ec	St	Sa	Bs	An	Af	Pc
IIa	11	12	--	14	RD	-ve	RD
IIb	14	11	10	15	+ve	+ve	-ve
IIc	12	10	12	10	+ve	+ve	RD
IId	13	10	13	12	+ve	+ve	+ve
IIe	15	12	10	09	RD	-ve	RD
IIf	13	12	13	07	RD	-ve	-ve
Penicillin	16	15	18	14	NA	NA	NA
Nystatin	NA	NA	NA	NA	-ve	-ve	-ve

Ec-Escherichia coli; St-Salmonella typhi; Sa-Staphylococcus aureus; Bs-Bacillis subtilis; An-Aspergillus niger; An-Aspergillus flavus; Pc-Penicillium chrysogenum; -ve-No growth; +ve-Growth of fungi; RD-Reduced growth; NA-Not Appilcable

CONCLUSION

In summary, we have designed and synthesized some 3-(3-(4-Hydroxy phenyl)-4-methyl-6-phenyl-3,3a-dihydropyrazolo[3,4-c]pyrazol-2(6H)-yl)thiazol-2-(3H)-one. The preliminary *in*

vitro antimicrobial screening of this series revealed that, compounds, showed moderate to good activities as compared with standard antibacterial and antifungal drugs.

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