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Efficient MCR synthesis and antimicrobial activity evaluation of methyl 3-methyl-1-phenyl-1*H*-pyrazol-5-ylcarbamodithioate derivatives

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Abstract*: Amongst dithiobarbamates of pyrazole or pyrazolones are very rarely studied. The synthesis of dithiobarbamates of pyrazoles i.e. substituted phenylcarbamoyl) methyl 3-methyl-1-phenyl-1H-pyrazol-5-yl carbamodithioate derivatives,* ***5*** *have been synthesized from 3-methyl-1-phenyl-1H- pyrazol-5-amine* ***1****, anilines* ***2****, carbon disulfide,* ***3*** *and chloroacetyl chloride,* ***4*** *via one pot the multicomponent condition at room temperature. Some of these compounds showed excellent to moderate antimicrobial activities against gram positive bacteria Staphylococcus aureus; gram negative bacteria Escherichia coli and fungi like Candida albicans, Aspergillus niger.*

Keywords*: MCR synthesis, pyrozole, dithiocarbamate, antimicrobial activity*

I. Introduction

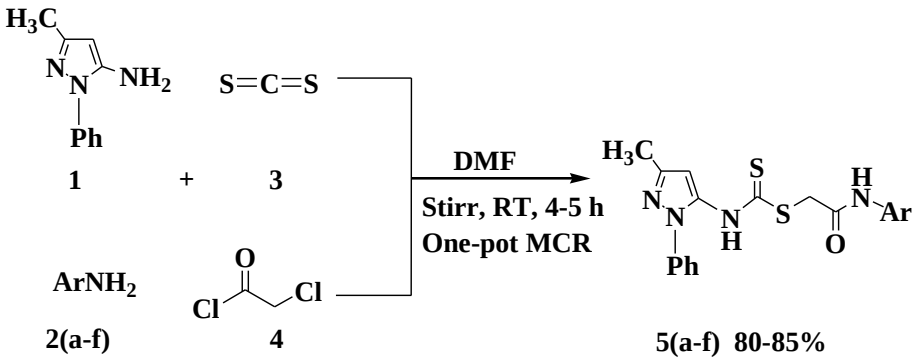
A dithiocarbamate (DTC) is functional group in organic chemistry analogous to carbamate where both of oxygen atoms are replaced by sulfur atoms. These are organosulfur ligands form complexes with metals [1]. A dithiocarbamate (DTC) was commercially used as fungicide first time during Second World War [2]. Dithiocarbamates have wide applications in the fields of accelerating vulcanization, acting as flotation agents, agriculture (pesticide), materials science, medicine, organic synthesis, photo-stabilizing polymers, and protecting radiators [3]-[5].Dithiocarbamates (DTCs) showed numerous biological applications as anticancer [6], antifungal [6], toxicity studies [7], antibacterial [8],[9], rodent repelling [10], growth depressing [11] and anti-HIV, antibacterial, double aged spermicidal agents, mono glyceride lipase inhibitors, antialcoholism [12]. Various synthetic protocols were employed for the synthesis of DTCs. *Veenu Bala* et. al. [13] prepared morpholin/piperidin-1-yl-carbamodithioates via conventional and green approach. The morpholin/piperidin-1-yl-carbamodithioates were evaluated for their *anti-Trichomonas* activity against MTZ susceptible and resistant strains along with their spermicidal and antifungal potential and also all the synthesized compounds were assessed for their safety through cytotoxic assay against human cervical cell line (HeLa) and compatibility with vaginal flora, *Lactobacillus*. The alkyl 4-(alkyl/arylcarbamothioyl)piperazine-1-carbodithioates were synthesized by *Veenu Bala* et. al. [14] from alkyl piperazine-1-carbodithioate and evaluated for multiple activities such as anti-Trichomonas, spermicidal and reverse transcriptase inhibition. *Sidhu et.al.*[15] synthesized Benzothiazol-2-ylcarbamodithioates from substituted benzothiazole, CS_2 and KSCN and evaluated for their antifungal activity against various phytopathogenic fungi and the experimental results of antifungal potential were also supported by molecular docking of compounds and log P values in the active site of CYP51. *El-Nassan* [16] synthesized tetrahydrocarbazoledithioate derivatives starting from 2-chloro-1-(1,2,3,4-tetrahydro-9Hcarbazol-9-yl)ethanone was prepared via acylation of1,2,3,4-tetrahydrocarbazole with chloroacetyl chloride in refluxing toluene and were tested in vitro on human breast adenocarcinoma cell line (MCF7) and the human colon tumor cell line (HCT116).*Sharda et.al.* [17] prepared 4-aminoantipyrine dithiocarbamates and were screened for their antimicrobial activities. They were utilized for molecular docking computational drug design technique to understand the mode of binding and binding affinities which showed very good hydrophobic interactions with target receptors. *Kumar et.al.*[18] synthesized azole and carbodithioate hybrids i.e. alkyl 1*H*-azole-1-carbodithioates and evaluated for spermicidal/microbicidal activities against human sperm, *Trichomonas vaginalis* and *Candida* species, performed molecular docking studies and found that these compounds could be used as vaginal anti-candida contraceptive agents. Electrogenerated base-promoted synthesis of ring-opened carbamodithioate derivatives and cyclic carbamodithioates i.e. *N*-benzylic rhodanine was carried out by *Tissaoui et.al*. [19] A series of (2-alkylthiothiazolin-5-yl) methyl dodecanoates was synthesized from various alkyl N-allylcarbamodithioates and dilauroyl peroxide by *Kakaei et.al.* [20].*Shahvelayati et. al.* [21] synthesized

dithiobarbamates *via* one-pot three component reaction of maleic anhydride, CS_2 and primary amines in good to excellent yields.

Literature survey revealed that amongst dithiobarbamates of pyrazole or pyrazolones are very rarely studied. Hence, we focused our plan towards the synthesis of dithiobarbamates of pyrazoles. Inspired with literature reports, we envisioned in designing and further synthesis of novel (substituted phenylcarbamoyl)methyl 3-methyl-1-phenyl-1*H* pyrazol-5-ylcarbamodithioate derivatives, **5(a-g)** using literature protocol [22].

II. Results and discussion

A series of novel substituted phenylcarbamoyl)methyl 3-methyl-1-phenyl-1*H*-pyrazol-5-ylcarbamodithioate derivatives **5(a-f)** has been synthesized from 3-methyl-1-phenyl-1*H*-pyrazol-5-amine 1, anilines **2** (a-f), carbon disulfide **3** and chloroacetyl chloride **4** via one pot the multicomponent condition at room temperature. The reaction was carried out under mild conditions and afforded the desired products in good yields (80-85%) ***(Scheme 1).***



Ar = C_6H_5, 2-ClC_6H_4, 3-ClC_6H_4, 2-MeC_6H_4, 3-MeC_6H_4, 2-MeOC_6H_4

Scheme 1: Novel synthesis of (substituted phenylcarbamoyl)methyl 3-methyl-1-phenyl-1H-pyrazol-5-yl carbamodithioate derivatives, 5 (a-f)

The structure was elucidated by IR, ^{1}HNMR and ^{13}C NMR spectral methods. The ^{1}H NMR spectrum of compound **5b** showed singlet at δ 2.75 (pyrazole CH_3), singlet at δ 4.24 (SCH_2), singlet at δ 7.29 (pyrazole =CH), singlet at δ 8.38 (amide NH), singlet at δ 8.94 (thioamide CSNH) groups. All the five aromatic protons were appeared in their respective region at δ 7.10-7.12 as multiplets while all the four aromatic protons associated with chlorophenyl ring were observed at δ 7.32-7.42.

Similarly, ^{1}H NMR spectrum of compound **5c** showed singlet at δ 2.72 (pyrazole CH_3), singlet at δ 4.24 (SCH_2), singlet at δ 7.68 (amide NH), singlet at δ 8.24 (thioamide CSNH) groups. All the five aromatic protons of pyrazole ring were appeared in their respective region at δ 7.15-7.16 as multiplets while all the four aromatic protons associated with 3-cholorophenyl were observed at δ 7.26-7.30 and at δ 7.39-7.41ppm.^{1}H NMR spectrum of compound **5d**displayedsinglet at δ 2.36, singlet at δ 2.56, singlet at δ 4.18, singlet at δ 7.23, singlet at δ 8.19, singlet at δ 8.94 were assigned to Ar-CH_3, pyrazole CH_3, SCH_2, pyrazole =CH, amide NH and thioamide CSNH groups.The ^{13}C NMR spectrum of compound **5d** showed δ 163.76 (C=O), δ 200.0 (C=S) for their characteristic peaks. Rest of the signals were observed in the respective regions.

III. Antimicrobial Activity Evaluation

The antimicrobial assay evaluation of the newly synthesized (substituted phenylcarbamoyl)methyl 3-methyl-1-phenyl-1*H* pyrazol-5-ylcarbamodithioate derivatives **5(a-g)**,was done using agar well plate method [23]. The antibacterial and antifungal assays were performed in Muller-Hinton broth and Crazek Dox broth [23]. The standard strains used for the antimicrobial assay was procured from Microbial Culture Collection, Pune, India.

Antimicrobial evaluation was performed using the bacteria reseeded in Muller-Hinton broth for 24 hr at 37^{o}C and fungi reseeded in Crazek Dox broth for 48 hr at 25^{o}C. The antibacterial activity of tested samples were studied in triplicate against gram positive bacteria *Staphylococcus aureus* (ATCC 29737) and gram negative bacteria *Escherichia coli* (ATCC 25922). The same samples were tested for antifungal activity in triplicate against *Candida albicans* (MTCC 277) and *Aspergillus niger* (MCIM 545). The compounds were dissolved in DMSO at desired concentrations of 200, 100, 50 µg/ mL. DMSO was loaded as negative control. Gentamicin (10 µg/ mL) and Nystatine (10 µg/ mL) were used as standards for evaluating the antibacterial and antifungal activity. The zone of inhibition (mm) was determined from the diameter of the zone of inhibition using calliper. The lowest concentration that showed invisible growth after spot subculture was considered as Minimum Inhibitory

Concentration (MIC μg/mL) value for each sample after 24 hr incubation period at 37°C. (MIC μg/ mL) value for each sample were determined using agar plates by pouring the molten agar in unique sized petri dishes as per National Committee for Chemical Laboratory Standards (NCCLS, M7-A5, January 2000).

Table 1: Antimicrobial activity of compounds- *Zone of inhibition (mm)*

Comp. No.	Conc. (μg/ml)	*Zone of Inhibition (mm)*				
		S. aureus **ATCC 25923**	***E. coli*** **ATCC 25922**	***P. aeruginosa*** **ATCC 27853**	***A. niger*** **MCIM 745**	***C. albicans*** **MTCC 277**
5a	**200**	**14.7**	15.2	15.5	19.1	15.6
	100	14.5	**15**	**15.1**	**19.0**	**15.2**
	50	14.3	14.8	14.6	18.9	14.7
5b	**200**	19.3	20.7	15.4	22.7	20.1
	100	19.2	20.3	**15.2**	22.5	20
	50	**19.1**	**20.2**	14.9	**22.4**	**19.8**
5c	**200**	19.7	22.1	21.5	15.3	15.3
	100	19.4	21.8	21.3	**15.2**	**15.1**
	50	**19.1**	**21.6**	**21.2**	14.9	14.6
5d	**200**	**14.9**	**10.7**	**13.5**	20.8	15.6
	100	14.7	10.5	13.3	20.6	**15.2**
	50	14.4	10.2	13.2	**20.3**	14.7
5f	**200**	**12.8**	**14.8**	**15.2**	15.2	15.5
	100	12.5	14.4	14.9	**15.0**	**15.1**
	50	12.0	14	14.5	14.8	14.6
DMSO	-----	**12**	**14**	**12.5**	**10**	**10.5**
Gentamicin	**10**	**22**	**28**	**20**	-----	-----
Nystatine	**10**	-----	-----	-----	**20**	**24**

Compound **5b, 5e** and **5h** containing chloro (Cl) and nitro (NO_2) group showed excellent antibacterial activities against Gram negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*with MIC 50 μg/mL compared with standard antibiotic drug Gentamicin (10 μg/mL).Compounds **5a,5b, 5c**and **5f** with chloro (Cl), methoxy (OCH_3) functionalities showed moderate antibacterial activity against Gram positive bacteria *Staphylococcus aureus* with MIC 100μg/mL. Similarly, compounds **5b, 5c** and **5e** containing chloro (Cl) and nitro (NO_2)group showed excellent antifungal activity against *Aspergillus niger* and *Candida albicans* with MIC 50 μg/mL on comparison with standard drug Nystatine (10 μg/mL).

Table 2: Antimicrobial activity of compounds- *Minimum Inhibitory Concentration (MIC-μg/ml)*

Comp. No.	*Minimum Inhibitory Concentration (MIC-*μg/ml)				
	S. aureus **ATCC 25923**	***E. coli*** **ATCC 25922**	***P. aeruginosa*** **ATCC 27853**	***A. niger*** **MCIM 745**	***C.albicans*** **MTCC 277**
5a	200	200	100	200	100
5b	100	100	100	100	**50**
5c	100	**50**	100	**50**	**50**
5d	200	200	200	100	100
5f	100	100	200	100	100
Gentamicin	**10**	**10**	**10**	-----	-----
Nystatine	-----	-----	-----	**10**	**10**
MIC in μg / mL)= 50 μg / mL: excellent activity; 100 μg / mL: moderate activity; 200 μg / mL: slight activity					

IV. Conclusion

We have synthesized novel (substituted phenylcarbamoyl)methyl 3-methyl-1-phenyl-1*H*-pyrazol-5-yl carbamodithioate derivatives **5(a-f)** in good yields from 3-methyl-1-phenyl-1*H*-pyrazol-5-amine. Some of the compounds showed excellent to moderate antimicrobial activities against germs.

V. Materials and Methods

All the chemicals and solvents had been purified by standard literature procedures and moisture was removed from the glass apparatus using $CaCl_2$ drying tubes. The melting points determined in open capillary tubes with Gallenkamp melting point apparatus and are uncorrected. FT-IR spectra recorded on Bruker FTIR-TENSOR II spectrophotometer using Platinum ATR discs. ^{1}H NMR spectra of synthesized compounds recorded on Bruker

Ascend 500 NMR spectrophotometer at 500 MHz frequency in $CDCl_3$ or dimethyl sulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as internal standard. Chemical shifts recorded in δ ppm and multiplicities are given as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Mass spectra were recorded on a Shimadzu LC-MS QP 2010A mass spectrometer with an ionization potential of 70eV. Elemental analyses were performed on Thermo Quest Flash 1112 Series EA analyzer. Reactions monitored by thin layer chromatography using 0.2 mm silica gel 60 F_{254} (Merck) plates using UV light (254 and 366 nm) for detection. Common reagent grade available chemicals were utilized without further purification or prepared by standard literature procedures. All the compounds have been synthesized by conventional methods.

VI. Experimental

Synthesis of (Phenylcarbamoyl)methyl 3-methyl-1-phenyl-1*H*-pyrazol-5-yl carbamodithioate,5a

To a stirred solution of aniline,**5a** (0.011 mol, 1 mL) and chloroacetyl chloride **4** (0.0125 mol, 1.20 mL) which was stirred in 15 mL DMF for 20 min.3-methyl-1-phenyl-1*H*-pyrazol-5-amine, **1**(0.014 mol, 1.96g) was dissolved in 10 mL DMF and carbon disulphide (CS_2) **2** (0.05 mol, 3.1 mL) was dropwise added to it. The reaction mixture was allowed to stir for 2-3 h. Then, 20 mL of water was added and the solution was stirred for 10-15 min. The solid product was filtered and purified by recrystallization in ethanol.

White powder; Yield 75%; mp 115–117°C; IR (Platinum ATR, ν_{max}cm^{-1}): 3148 (NH), 3055 aromatic (CH), 1676, 1601, 1546,1518, 1497, 1442, 1356, 941, 831, 750; ^{1}H NMR (500MHz, $CDCl_3$): δ 2.75 (s, 3H, CH3),4.19 (s, 2H, CH_2S), 7.19 (s, 1H, Pyrazole),7.35-7.38 (m, 5H, pyrazole ArH), 7.54-7.56 (m, 5H, ArH), 8.23(s, 2H, NH); *Anal. calcd. for* $C_{19}H_{18}N_4OS_2$ (Mol. Wt. 382.5): C, 59.66; H, 4.74; N, 14.65; *found*: C, 59.69; H, 4.81; N, 14.

Similar reaction procedure was used for synthesis of compounds 5(b-g)

(2-Chlorophenylcarbamoyl)methyl 3-methyl-1-phenyl-1*H*-pyrazol-5-yl carbamo dithioate, 5b

Off White powder; Yield 79 %; mp 115–117°C; IR (Platinum ATR, ν_{max}cm^{-1}): 3148 (NH), 3055 aromatic (CH), 1676, 1601, 1546,1518, 1497, 1442, 1356, 941, 831, 750; ^{1}H NMR (500MHz, $CDCl_3$): δ 2.75 (s, 3H, CH_3),4.24 (s, 2H, CH_2S), 7.09 (d, 1H, ArH), 7.09 (d, 1H, ArH), 7.10-7.11 (d, 1H, ArH), 7.12 (d, 1H, ArH), 7.29 (s, 1H, Pyrazole), 7.31-7.32 (m, 5H, pyrazole ArH), 7.40-7.42 (d, 1H, ArH), 8.36 -8.38 (bs, 1H, NH), 8.94(s, 2H, NH). *Anal.calcd. for* $C_{19}H_{17}ClN_4OS_2$ (Mol. Wt.: 416.95): C, 54.73; H, 4.11; N, 13.44; *found*: C, 54.70; H, 4.18; N, 13.61.

(3-Chlorophenylcarbamoyl)methyl 3-methyl-1-phenyl-1*H*-pyrazol-5-yl carbamo dithioate, 5c

Pale yellow powder; Yield 82%; mp 115–117°C; IR (Platinum ATR, ν_{max}cm^{-1}): 3148 (NH), 3055 aromatic (CH), 1676, 1601, 1546,1518, 1497, 1442, 1356, 941, 831, 750; ^{1}H NMR (500MHz, $CDCl_3$): δ 2.72 (s, 3H, CH_3),4.19 (s, 2H, CH_2S), 7.15 (d, 1H, ArH), 7.16 (d, 1H, ArH), 7.28-7.30 (t,1H, ArH), 7.67-7.68 (t, 1H, ArH), 7.27 (s, 1H, Pyrazole), 7.39-7.41 (m, 5H, pyrazole ArH), 8.24(s, 2H, NH). *Anal.calcd. for* $C_{19}H_{17}ClN_4OS_2$ (Mol. Wt.: 416.95): C, 54.73; H, 4.11; N, 13.44; *found*: C, 54.8; H, 4.21; N, 13.53.

(2-Methylphenylcarbamoyl)methyl 3-methyl-1-phenyl-1*H*-pyrazol-5-yl carbamo dithioate, 5d

White powder; Yield 81%; mp 115–117°C; IR (Platinum ATR, ν_{max}cm^{-1}): 3148 (NH), 3055 aromatic (CH), 1676, 1601, 1546,1518, 1497, 1442, 1356, 941, 831, 750; ^{1}H NMR (500MHz, $CDCl_3$): δ 2.36 (s, 3H, $ArCH_3$), 2.73(s, 3H, CH_3 pyrazole),4.18 (s, 2H, CH_2S), 6.98-7.00 (d, 1H, ArH), 7.23 (s, 1H, Pyrazole), 7.24 (d, 1H, ArH), 7.33-7.35(m, 5H, pyrazole ArH), 7.38 (d 1H, ArH), 8.19(s, 2H, NH). *Anal. calcd. for*$C_{20}H_{20}N_4OS_2$ (Mol. Wt.: 396.53): C, 59.66; H, 4.74; N, 14.65; *found*: C, 59.69; H, 4.81; N, 14.74..

(3-Methylphenylcarbamoyl)methyl 3-methyl-1-phenyl-1*H*-pyrazol-5-ylcarbamo dithioate, 5e

White powder; Yield 85%; mp 115–117°C; IR (Platinum ATR, ν_{max}cm^{-1}): 3148 (NH), 3055 aromatic (CH), 1676, 1601, 1546,1518, 1497, 1442, 1356, 941, 831, 750; ^{1}H NMR (500MHz, $CDCl_3$): δ 2.36 (s, 3H, $ArCH_3$), 2.73(s, 3H, CH_3 pyrazole), 4.18 (s, 2H, CH_2S), 6.98-7.00 (d, 1H, ArH), 7.23 (s, 1H, Pyrazole),7.24 (d, 1H, ArH), 7.33-7.35(m, 5H, pyrazole ArH), 7.38 (d 1H, ArH), 8.19 (s, 2H, NH). ^{13}C NMR (125MHz, $CDCl_3$): δ 21.48 ($2CH_3$), 42.92, (CH_2S), 117.23, 120.76, 124.61 126.10, 128.98, 130.13, 136.57, 139.16, 163.76 (C=O), 199 (C=S).*Anal. calcd. for* $C_{20}H_{20}N_4OS_2$ (Mol. Wt.: 396.53): C, 59.66; H, 4.74; N, 14.65; found: C, 59.69; H, 4.81; N, 14.74.

(2-Methoxyphenylcarbamoyl)methyl 3-methyl-1-phenyl-1*H*-pyrazol-5-yl carbamodithioate, 5f

Faint yellow powder; Yield 83%; mp 115–117°C; IR (Platinum ATR, ν_{max}cm^{-1}): 3148 (NH), 3055 aromatic (CH), 1676, 1601, 1546,1518, 1497, 1442, 1356, 941, 831, 750 ^{1}H NMR (500MHz, $CDCl_3$): δ 2.75 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3),4.18 (s, 2H, CH_2S), 6.99 (d, 1H, ArH), 7.05 (d, 1H, ArH), 7.10 (d, 1H, ArH), 7.26 (s, 1H, pyrazole), 7.31-7.34 (m, 5H, pyrazole ArH), 7.54-7.56 (t, 1H, ArH), 8.23(s, 2H, NH). *Anal. calcd. for* $C_{20}H_{20}N_4O_2S_2$ (Mol. Wt.: 412.53): C, 58.23; H, 4.89; N, 13.58; *found*: C, 58.23; H, 4.89; N, 13.58

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