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FACILE SYNTHESIS AND BROAD SPECTRUM PHARMACOLOGY OF NOVEL HETEROCYCLES: DERIVATIVES OF PYRAZOLO PYRIMIDINE WITH BENZOTHIAZOLES AND HYDRAZINO BENZOTHIAZOLES

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ABSTRACT

A series of novel bis (substituted benzothiazolo [2,3-*b*] 4H-imino-pyrimido) [4,3-*e*] pyrazolo [1,5-*a*] ,[6,5-*d*]-4H-oxo-pyrimidines (6a-6f) and 3,9-diamino-6N-phenyl-bis (R) pyrazolo [3,4-*c*] pyrazolo [1,5-*a*]-4H-oxo-pyrimidino [4,5-*d*] pyrazolines (7a-7e) were synthesized via facile condensation of pyrazolo pyrimidine (5) with different benzothiazoles and hydrazino benzothiazoles. The pyrazolo pyrimidine (5) was prepared via reaction between, simple condensation product of phenyl hydrazine (1) and bis(methylthio) methylene malanonitrile (2) that is 3-amino-4-cyano-5-(methylthio)-1-phenyl-1H-pyrazole (3) and ethyl-2-cyano-3,3-bis(methylthio) acrylate (4).These fused heterocycles were examined for their plausible antimycobacterium (against *mycobacterium smegmatis)*, antityphoid (against *S. typhi*) and antioxidant activity which were found to be more potent and biologically significant heterocycles with least cytotoxicity.

KEYWORDS: Antimycobacterium activity , Antityphoid activity, Antioxidant activity, Benzothiazoles, Ethyl-2-cyano-3,3-bis(methylthio) acrylate , Pyrazolo pyrimidine, Bis(methylthio) methylene malanonitrile.

INTRODUCTION

The broad spectrum biological importance of nitrogen containing heterocycles was continuously encouraged chemists to synthesize their large number of derivatives during last 3-4 decades. One of most important among them are pyrazole derivatives which was found to be potent with anti-microbial (Ritu Bhatt et al 2015, Essam Mohamed Sharshira et al 2012**)**, antibacterial and antifungal **(** Bhavna N. Amin et al 2014**,** P. Ashok et al 2013**)**, anti-cancer **(**Mohamed A Abdelgawad et al 2014**)**, anti-tuberculor **(**P. R. Kawale et al 2013**)**, anti-inflammatory **(** S. K. Sahu et al 2008 **)**, anti-oxidant **(**Tarun S. et al 2012**)** activities etc. Well known drugs containing pyrazole nucleus in pharmacophoric part such as Ruxolitinib for treatment of HIV, Tepoxalin as non-steroidal anti-inflammatory drug, Crizotinib, Celecoxib, Lonazolac, Pyrazofurin, Fezolamin, Rimonabant were well practiced by doctors. Another important heterocycle pyrimidine and its derivatives covered big class of biologically active moieties. Condensed pyrimidines have been reported as potent antimicrobial **(** Nirav M. Shah et al 2014**,** Neelam K. Yadav et al 2015 **)**, anticancer **(** Suparna S. De et al 2014**)**, anti-bacterial and anti-fungal **(** Vartale S.P et al 2013 **)**, anti-tuberculor **(** Harshlata D. et al 2015 **)**, anti-inflammatory **(** Y. Kotaiah et al 2012 **)**, anti-oxidant **(** M. Suresh et al 2010 **)** etc. Some marketed drugs which were found to be well and regularly practiced by pharmacist were Afloqualone, Epirizole (antiinflammatory, analgesic), Nilotinib, Dasatinib, Cytarabine, Capecitabine (anti-cancer) contains pyrimidine, pyrazole rings in their structures.

Another important class of heterocyclic compounds is of benzothiazoles which exhibit numerous biological activities such as anti-microbial **(**Abdel-Rahman et al 2008**)**, antifungal and antibacterial **(** G. M. Sreenivasa et al 2012**)**, anti-inflammatory and antioxidant **(** Vrushali Patil et al 2015**)**, anti-cancer **(**Livio Racané et al 2012**)** etc. By keeping in mind importance of above heterocyclic moieties here in this present investigation we report polycyclic heterocycles containing pyrazole, pyrimidine and benzothiazole rings, hoping that these polycyclic heterocycles will exhibit remarkable activities against different pathogens and for different pharmacological assistance.

EXPERIMENTAL

A) General Procedure

All reactions were carried out at room temperature and pressure by following synthetic procedures. All synthesis routes were monitored by thin layer chromatography where 0.2 mm silica gel-C plates were used and detection were carried out by using UV-VIS chamber.

Synthesis of 3-amino-4-cyano-5-(methylthio)-1-phenyl-1H-pyrazole[3]

A mixture of phenyl hydrazine[1] (0.01 mol) and bis(methylthio) methylene malanonitrile[2] (0.01 mol) in 15 ml of N, N'- dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 4 hours. The reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with water and recrystallized from ethanol to give pure.[3]

Synthesis of 3,6-dicyano-1,7-dihydro-2,5-bis(methylthio)-7-oxo-1-phenylpyrazolo[1,5-*a*]pyrimidine[5]

A mixture of 3-amino-4-cyano-5-(methylthio)-1-phenyl-1H-pyrazole[3] (0.01 mol) and ethyl-2-cyano-3,3-bis(methylthio) acrylate[4] (0.01 mol) in 20 ml of N, N'-dimethyl formamide and anhydrous potassium carbonate (10 mg) was refluxed for 5 hours. The reaction mixture was cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water and recrystallized from N, N'- dimethyl formamide- ethanol mixture (2:8) to give pure[5] with better yield.

Synthesis of bis (Benzothiazolo [2,3-*b*] 4H-imino-pyrimido) [4,3-*e*] pyrazolo [1,5-*a*] ,[6,5-*d*]-4H-oxo-pyrimidine (6a-6f)

A mixture of[5] (0.001 mol) treated independently with benzothiazoles (0.002 mol) in 15-20 ml of N, N'-dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 7-8 hours. The reaction mixture was cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water and recrystallized from N, N'- dimethyl formamide-ethanol mixture (2:8) to give pure (6a-6f) with good yield.

Synthesis of 3,9-Diamino-6N-phenyl-bis(R)pyrazolo [3,4-*c*] pyrazolo [1,5-*a*] -4H-oxo-pyrimidino [4,5-*d*] pyrazoline (7a-7e)

A mixture of[5] (0.001 mol) and independently with hydrazines and hydrazino benzothiazoles (0.002 mol) in 15-20 ml of N, N'- dimethyl formamide and anhydrous potassium carbonate (10 mg) was refluxed for 7-8 hours. The reaction mixture was cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water and recrystallized from N, N'- dimethyl formamide- ethanol mixture (2:8) to give pure (7a-7e) with good yield.

B) Analytical And Spectral Data

The resulted moieties were characterized by spectral analysis where IR spectra were taken on FT-IR spectrometer,followed by which some of them underwent Mass,Proton and Carbon NMR-spectral analysis which were shown following data.Melting points of resulted moieties were taken on digital melting point apparatus.

2-Amino-4-cyano-5-(methylthio)-1-phenyl-1*H*-pyrazole[3]

Greenish Yellow powder; MF :$C_{11}H_{10}N_4S_1$; Yield 98.63%, M.P: 100.9°C(dec.); IR(KBr/cm^{-1}) 3357.84 (NH_2), 2208.34 (CN); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.40 (s, 3H, SCH_3), 3.4(s,NH_2) 6.8-7.6(m, 5H,Ar-H);MS (m/z: RA %): 229 (M-1,100%) & 231(M+1,100%).

3,6-Dicyano-1,7-dihydro-2,5-bis(methylthio)-7-oxo-1-phenylpyrazolo[1,5-*a*]pyrimidine[5]

Brown powder;MF : $C_{16}H_{11}N_5OS_2$; Yield 78.36 %, M.P106.7 °C (dec.). IR (KBr / cm^{-1}) 1674.10 (CO), 2216.06 (CN); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.3 (s, 3H, SCH_3), δ 2.5 (s, 3H, SCH_3) 7.4-7.6 (m,5H,Ar-H); EI-MS (m/z:RA%): 353(M+.100%); ^{13}C-NMR ($CDCl_3$) δ:13.6265,14.1187,16.7382,60.6872,111.8846,116.813,123.7002,128.6622,129.
3962,137.1629,149.9628,163.7932,170.2251

Bis (6-methoxy benzothiazolo [2,3-*b*] 4H -imino-pyrimido) [4,3-*e*] pyrazolo [1,5-*a*] ,[6,5-*d*] -4*H*-oxo-pyrimidine (6a)

Brown powder, MF: $C_{30}H_{19}N_9O_3S_2$; Yield 81.46 %, M.P 149.0 °C (dec.)

Bis (6-methyl benzothiazolo [2,3-*b*] 4*H*-imino-pyrimido) [4,3-*e*] pyrazolo [1,5-*a*] ,[6,5-*d*] -4*H*-oxo-pyrimidine (6b)

Yellowish brown powder, MF: $C_{30}H_{19}N_9OS_2$; Yield 83.28%, M.P 133.1°C (dec.); IR (KBr /cm^{-1}), 1718.46(imino),1674.10(CO); ^{1}H NMR (400MHz,DMSO-d_6) δ 2.4-2.6 (s, 3H, CH_3), δ 2.6-2.7 (s, 3H, CH_3), δ 7.2-7.6(m, 11H,Ar-H), δ 11.2-11.4(s,2H,imino-H); MS (m/z: RA %): 584.4 (M-1,100%)

Bis (4,6-dichloro benzothiazolo [2,3-*b*] 4H-imino-pyrimido) [4,3-*e*] pyrazolo [1,5-a] ,[6,5-*d*] -4*H*-oxo-pyrimidine (6c)

Ash powder, MF: $C_{28}H_{11}N_9OS_2Cl_4$; Yield 80.73 %, M.P 139.2 °C (dec.).

Bis (4,6-dimethyl benzothiazolo [2,3-*b*] -4*H*-imino-pyrimido) [4,3-*e*] pyrazolo [1,5-*a*], [6,5-*d*] -4*H*-oxo-pyrimidine (6d)

Ash powder, MF: $C_{32}H_{23}N_9OS_2$; Yield 76.91 %, M.P 120.7 °C (dec.).

Bis (6-nitro benzothiazolo [2,3-*b*] -4*H*-imino-pyrimido) [4,3-*e*] pyrazolo [1,5-*a*] ,[6,5-*d*] -4*H*-oxo-pyrimidine (6e)

Brown powder, MF :$C_{28}H_{13}N_{11}O_5S_2$; Yield 71.94 %, M.P 127.2 °C (dec.).

Bis (6-chloro benzothiazolo [2,3-*b*] 4*H*-imino-pyrimido) [4,3-*e*] pyrazolo [1,5-*a*] ,[6,5-*d*] -4*H*-oxo-pyrimidine (6f)

Brown powder, MF: $C_{28}H_{13}N_9OS_2Cl_2$; Yield 85.3 %, M.P 147.1 °C (dec.).

3,9-Diamino -6N-phenyl bis(N-*H*)pyrazolo [3,4-*c*] pyrazolo [1,5-*a*] -4*H*- oxo-pyrimidino [4,5-*d*] pyrazoline (7a)
Yellowish green powder, MF : $C_{14}H_7N_9O$, Yield 70.23 %, M.P 122.7 °C (dec.).

3,9- Diamino -6N- phenyl bis(N-phenyl)pyrazolo [3,4-*c*] pyrazolo [1,5-*a*] -4*H*- oxo-pyrimidino [4,5-*d*] pyrazoline (7b)
Pale brown powder, MF : $C_{26}H_{19}N_9O$; Yield 73.87 %, M.P 131.7 °C (dec.).

3,9-Diamino -6N- phenyl bis(2',4'-dinitrophenyl) pyrazolo [3,4-*c*] pyrazolo [1,5-*a*] -4*H*- oxo-pyrimidino [4,5-*d*] pyrazoline (7c)
Yellowish brown powder; MF: $C_{26}H_{15}N_{13}O_9$; Yield 77.47 %, M.P 141.3 °C (dec.); IR (KBr /cm^{-1}) 1674.10(CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.070 (s, 2H, NH_2),4.093(s,2H,NH_2),7.440-7.629(m, 11H,Ar-H); MS (m/z: RA %): 652(M-1).

3,9-Diamino-6N- phenyl bis(benzothiazolo) pyrazolo[3,4-*c*] pyrazolo[1,5-*a*] -4*H*-oxo-pyrimidino [4,5- *d*] pyrazoline (7d)
Brown powder, MF : $C_{28}H_{15}N_9OS_2$; Yield 69.87 %, M.P 128.2 °C (dec.).

3,9-Diamino -6N- phenyl bis(6'-methoxybenzothiazolo) pyrazolo [3,4-*c*] pyrazolo [1,5-*a*] -4*H*-oxo-pyrimidino [4,5-*d*] pyrazoline (7e)
Yellowish brown powder, MF : $C_{30}H_{19}N_9O_3S_2$;Yield 76.13 %, M.P130.1 °C (dec.).

C) Pharmacological Study
The resulted products were screened for their antimicrobial, antityphoid, antioxidant activities and cytotoxicity by making use of following well known methods.

Antimycobacterial activity
The Mycobacterium smegmatis (MTCC 994) was obtained from Microbial Type Culture Collection and Gene Bank, Institute of Microbial Technology, Chandigarh (PB), India. The sensitivity of *Mycobacterium smegmatis* to the various test compounds was done using agar well method **(**Chaturvedi V. et al 2007**,** Tawde K. V. et al 2012**)**. In short, test compound 100 µl (5 mg/ mL) was filled in 8mm diameter agar well. Rifampicin is used as a reference standard. 100 µl (1 mg/mL) Rifampicin and control well was filled with respective solvent.

The media used was Middlebrook 7H 10 agar with No.1 McFarland standard inoculums of *m. smegmatis*. The plates were placed at 4ºC for 3 hrs for diffusion of compounds in agar medium and then shifted to the 37 ºC. After sufficient incubation, the zones of inhibition were measured by the zone scale (Himedia Pvt. Ltd. Mumbai).

Determination of Minimum Inhibitory Concentration (MIC)
The determination of MIC was done as per previously reported method **(**Tawde K. V. et al 2012**)**. The microtitre plates were inoculated with 10 µl of diluted 24-hr grown culture of *m. smegmatis* with a titer of equivalent to 0.5 McFarland standards. The inoculated microtitre plates were then incubated at 370C for 24 hr and the microbial growth was determined spectrophotometrically at 600 nm using Thermo make Automatic Ex-Microplate Reader (M51118170) microplate reader. Rifampicin was used as a standard drug.

Anti-typhoid activity of compounds
The culture of *Salmonella typhi* (MTCC-3224) to determine the anti-typhoid activity of tested compounds was purchased from Microbial Type Culture Collection and Gene Bank (MTCC), IMTECH, Chandigarh. Sterile tripticase soya agar was poured in to sterile standard petri plates (15ml). This was then inoculated with 0.1ml of each cultures of *S. typhi* (which was previously incubated for 24 hr in broth) the spreading were carried out by sterile glass spreader. After spreading cultures on medium, three cups of 8 mm diameter were prepared with the help of a sterile borer so that appropriate distance is made in each of well among three wells. The cups were filled by adding 50 µl of the different test compounds (10µg/ml), Penicilin 50 µl (10µg/ml) used as standard and 50 µl of solvent DMSO as control. The plates are allowed to diffuse in freeze for 30 min and then transferred to incubator and incubated for 24 h at 37˚c. After incubation the zones of inhibition around each cup were measured (including cup) in millimeter with the help of zone measuring scale (Himedia Pvt. India).

Antioxidant Activity.
a) DPPH Radical scavenging activity.
DPPH (1, 1-diphenyl-2-picryl hydrazine) radical scavenging assay was performed as per the earlier reported method. The reaction cocktail was prepared by mixing individual compounds with equal volume of DPPH radical (10-4 M in absolute ethanol) solution. After 20 min reaction time, the absorbance was recorded at 517 nm using UV-Visible spectrophotometer **(**Blois M.S. et al 1958**,** Roberta R et al 2006**)**.

b) OH Radical scavenging activity.
Hydroxyl radical (OH) scavenging activity was measured as per previously published protocol. The reaction mixture contained 60 µl of 1mM, $Fecl_3$, 90 µl of 1 M 1,10-phenanthroline, 2.4 ml of 0.2 M phosphate buffer (pH 7.8), 150 µl of 0.17 M H_2O_2 and 1.5 ml of individual brand. The reaction mixture was kept at room temperature for 5 minutes incubation and absorbance was recorded at 560 nm using UV-VIS spectrophotometer **(**Rollet-Labelle E et al 1998**)**.

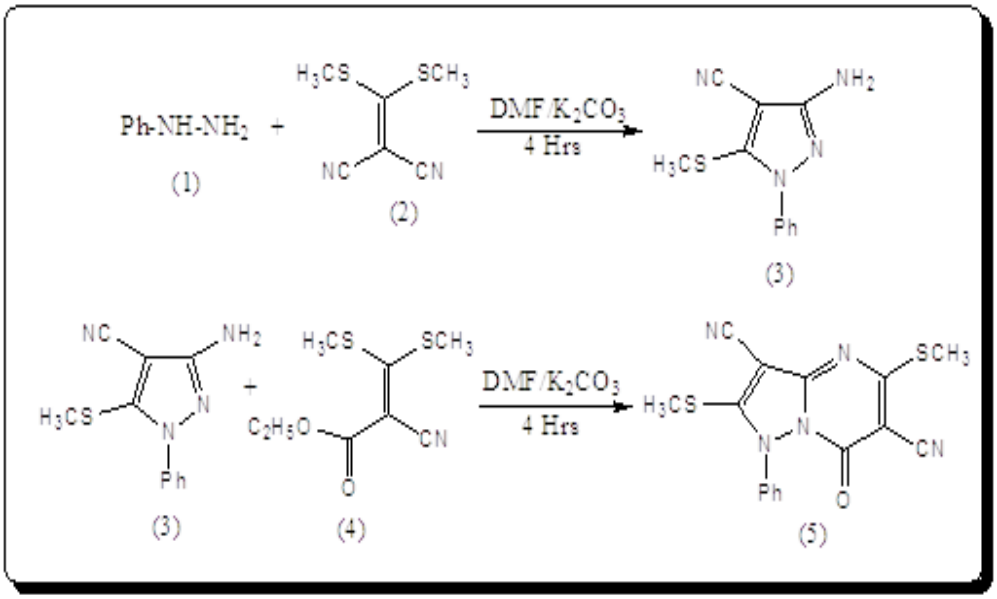
Cytotoxicity Evaluation

The MTT cytotoxicity assay was performed as per the reported method **(**Mosmann T. et al 1983**,** Kawase M et al 2003**)**. Normal human Chang liver cell line was purchased from NCCS (National Center for Cell Science), Pune (MS). The cells were harvested and inoculated in 96 well (4 x 104 cells/well) microtiter plates. The cells were washed with phosphate buffered saline (PBS) and the cultured cells were then inoculated with and without the selected compounds. After 72 hr incubation, the medium was aspirated followed by addition of 150 µl of MTT (3-(4, 5 dimethylthiazol-2-yl)-2, 5- diphenyltetrazolium bromide) solution (5 mg ml-1 In PBS, pH 7.2) to each well and the plates were incubated for 4 hr at 37° C. After incubation, 80 µl of DMSO was added to the wells followed by gentle shaking to solubalize the formazan dye for 15 min. Absorbance was read at 540 nm and the cytotoxicity (%) was calculated.

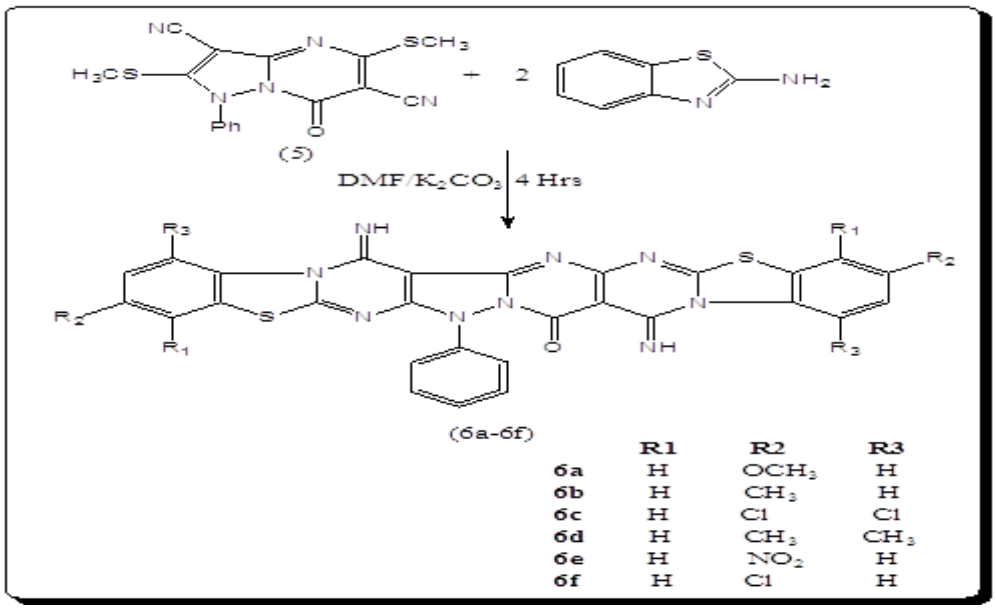
Activity (%) = 1 – T/C X 100

Where,T= Absorbance of the test sample & C= Absorbance of the control sample

REACTION SCHEME

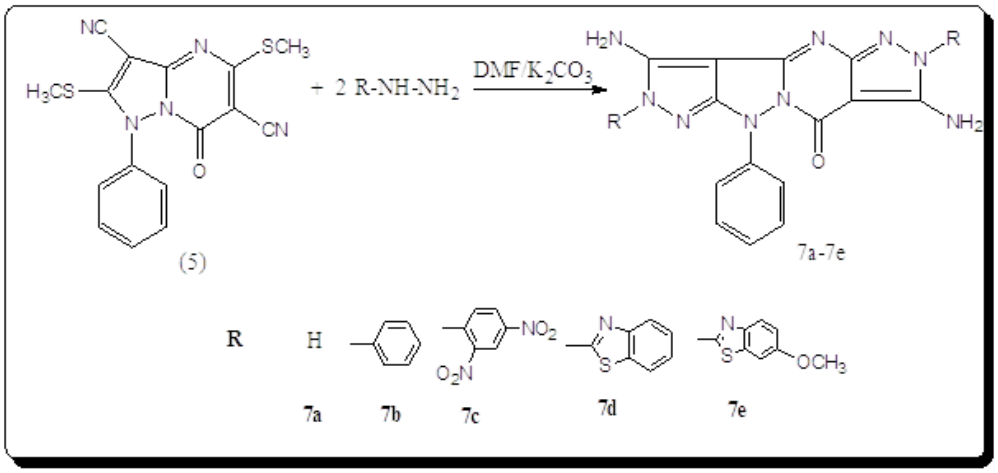


Scheme-A)



	R1	R2	R3
6a	H	OCH_3	H
6b	H	CH_3	H
6c	H	Cl	Cl
6d	H	CH_3	CH_3
6e	H	NO_2	H
6f	H	Cl	H

Scheme-B)



Scheme-C)

RESULTS AND DISCUSSION

A) Chemistry

In present study we reported facile synthesis of novel fused heterocycles, bis(substituted benzothiazolo[2,3-*b*]4H-imino-pyrimido)[4,3-*e*]pyrazolo[1,5-*a*] ,[6,5-*d*]-4H-oxo-pyrimidines (6a-6f) and 3,9-diamino-6N-phenyl-bis(substituted)pyrazolo[3,4-*c*]pyrazolo[1,5-*a*]-4H-oxo-pyrimidino[4,5-d] pyrazolines (7a-7e).These heterocycles were prepared by condensing different benzothiazoles (6a-6f),hydrazines (7a-7e) via addition-elimination followed by condensation with[5] which was synthesized using 3-amino-4-cyano-5-(methylthio)-1-phenyl-1H-pyrazole[3] and ethyl-2-cyano-3,3- bis (methylthio) acrylate[4] in DMF and anhydrous K_2CO_3. The compound[3] was prepared by reaction of phenyl hydrazine[1] with bis(methylthio) methylene malononitrile[2] in same reaction conditions. The presence of tautomerisable 1,3-nucleophilic nitrogen atoms in[3] made itself more facile for attack on[4] resulting in building of pyrimidine ring via elimination of simple thiomethyl and ethoxy group. The presence of nucleophilic centers on carbon which possess thiomethyl group and cyano group on adjacent carbon made cyclisation easier when attacked by 2-amino benzothiazoles and 2-hydrazino benzothiazoles, moreover this attack was supported by resonance stabilization of incoming electron density by carbonyl present adjacent to them.The cyclisation was confirmed by disappearance of IR-absorption band in the region 2216 cm^{-1} for cyano group which was present in. [5] All analytical and spectral data supports corresponding novel compounds which reveals that synthesis was in proper orientation.

B) Pharmacology

Anti-Mycobacterium activity

As shown in table no.1 all tested compounds shown moderate to good activity against M. smegmatis.They shown comparative zone of inhibition with standard rifampicin (22 + 0.33 mm) ranging between 05 ± 0.19 to 19 ± 0.71. The most potent zone of inhibition was shown by 6a (19 ± 0.71) and 7c (19 ± 0.41) with MIC value 500 ± 0.94 and 1000 ± 0.46 µg/mL respectively.

Antityphoid activity

These newly synthesized compounds were tested for their plausible anti-typhoid activities against Salmonella typi (MTCC-3224).The results formulated in table no.1 clearly reveals that results are promising as compared with standard antibiotics penicillin (14 + 0.65 mm). The compounds **6b,6e** and **7e** shown promising activity against tested pathogen while compounds 6c,6d and 6f were failed to become active.

Antioxidant activity

Efficiency of these new heterocycles as antioxidants in terms of percent DPPH and OH radical scavenging assay were tabulated in table no.1.

1) **DPPH radical scavenging assay:** From tested compounds **5** and **7c** had shown very good proton radical scavenging activity followed by all other tested derivatives in accordance with standard ascorbic acid.
2) **OH radical scavenging assay:** All tested compounds were found very much active in scavenging the most hyper reactive free radical is OH radicals amongst the relative oxygen species which affect almost all type of molecule in living cell when compared with standard ascorbic acid as shown in table no.1.All tested compounds shown % OH activity ranges in 14.96 ± 0.80 to 80.22 ± 0.28 which were far better as compared with standard (02.98 + 0.18 %). Interestingly the tested novel pyrazolo [1,5-*a*] pyrimidine derivatives were good in hydroxyl free radical stabilizing activity as compared with the proton radical stabilization.

Cytotoxicity analysis

The newly synthesized compounds were evaluated for their toxicity against chang liver cell lines using MTT assay and results are presented in table no. 1. All the tested compounds were found to be nontoxic when compared with the toxicity of H_2O_2 as a reference (04.85 + 0.08 %)

Table No. 1: Anti-mycobacterium, Anti-typhoid, Anti-oxidant activity and Cytotoxic analysis of selected derivatives

Compound	Antimycobacterium activity		Antityphoid activity		Antioxidant Activity		Cytotoxicity
	Zone of inhibition (mm)At 5mg/mL	MIC µg/mL (1mg/ml)	Zone of inhibition (mm)	MIC (µg)	% DPPH activity	% OH activity	Inhibition of Cell Viability (%) at 1mg/ml
5	NR	NR	NR	NR	87.05 ± 0.49	80.22 ±0.28	-2.95 ± 0.23
6a	19 ± 0.71	500 ± 0.94	06 ± 0.12	250 ± 1.17	NR	15.42 ± 0.43	-1.8 ± 0.17
6b	14 ±0.41	1000 ± 0.47	08 ± 0.42	125 ± 0.43	79.23 ± 0.51	65.85 ± 0.73	--
6c	15 ± 0.82	250 ± 0.67	--	--	75.19 ± 0.63	57.65 ± 0.49	--
6d	14 ± 0.27	500 ± 1.28	--	--	NR	NR	-1.9 ± 0.27
6e	05 ± 0.19	500 ± 0.64	08 ± 0.39	125 ± 1.28	79.10 ± 0.42	68.12 ± 1.01	-2.1 ± 0.42
6f	15 ± 0.81	250 ± 0.31	--	--	77.12 ± 0.37	58.97 ± 0.37	-2.2 ± 0.09
7a	18 ± 0.63	250 ± 0.39	06 ± 0.35	250 ± 1.19	77.57 ± 0.69	59.10 ± 0.62	-3.1 ± 0.30
7b	13 ± 0.17	250 ± 0.47	02 ± 0.09	500 ± 0.31	NR	33.65 ± 0.44	-2.1 ± 0.16
7c	19 ± 0.41	1000 ± 0.46	06 ± 0.73	250 ± 0.49	80.22 ± 0.17	18.36 ± 0.49	-2.7 ± 0.21
7d	10 ± 0.34	250 ± 0.61	02 ± 0.41	250 ± 0.62	74.34 ± 0.19	14.96 ± 0.80	-1.8 ± 0.44
7e	18 ± 0.72	500 ± 1.17	08 ± 0.55	252 ± 1.07	78.09 ± 0.13	44.12 ± 0.14	-2.0 ± 0.05
Standard	22 ± 0.33	31.25 ± 0.20	14 ± 0.65	15.62 ± 0.54	84.32 ± 0.20	02.98 ± 0.18	04.85 ± 0.08
	Rifampicin (1mg/ml)		Penicillin		Ascorbic Acid		Hydrogen peroxide

CONCLUSION

The steps followed in preparation of (6a-6f) and (7a-7e) clearly reveal that we reported incorporation of pyrazole,pyrimidine and benzothiazole one by one in promisingly facile way. From pharmacology,it can be concluded that all synthesized compounds were found to be potent against tested typhoid pathogen and in scavenging DPPH radical,but nearly all of the newly synthesized heterocycles were very comparative with standard in their antimycobacterial activity and results were very enthusiastic for us when we went for OH radical scavenging properties. Nevertheless, the findings of the present work may serve as a guideline for the synthesis and screening of new compounds which will be raised towards the development of new drugs in current MDR crisis.

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