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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF SOME NOVEL PYRAZOLE DERIVATIVES

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ABSTRACT

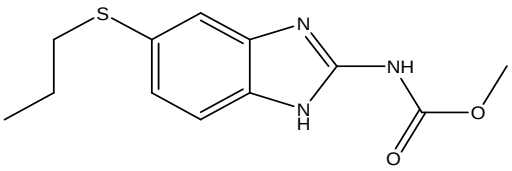
In this current work I made an effort near make new Pyrazole analogue (**5a-f)** and evaluate them for anthelmintic activity. In the initial step substituted acetophenone(**1a-f**) was react with substituted phenyl hydrazines(**2a-b**) in Ethanol solution and glacial acetic acid was added as catalyst to form Substituted 2-phenyl-1-(1-phenyl ethylidene) hydrazine (**3a-f**) as intermediate. This intermediate was further reacted with Dimethyl formamide *via* Vilsmeir hack reagent, in the presence of sodium bicarbonate, to neutralize the reaction mixture and form substituted formyl pyrazole (**4a-f).** Further to get desired product substituted derivative (**5a-f**), it was reacted with 3-hydrazinyl quinolone in presence of ethanol as solvent. The final conformation was confirmed by ^{1}HNMR and FTIR. Total value of FTIR, solubility, ^{1}HNMR, and TLC are found to be recorded. The biological activity was performed as anthelmintic, compound (**5a** and **5e**) has expressed maximum activity against standard drug Albendazole.

KEYWORDS: *Anthelmintic Activity, Albendazole, Pyrazole.*

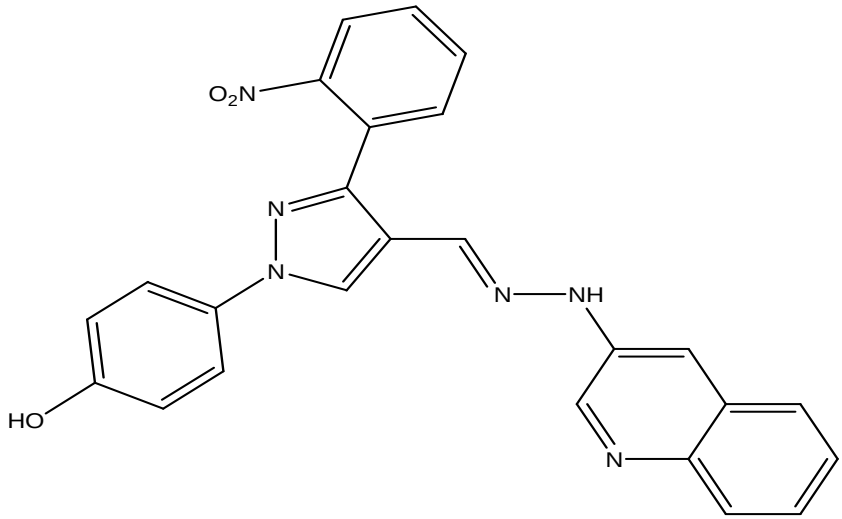
1 INTRODUCTION

According to the WHO report 2022, soil-transmitted helminth infections, the most prevalent disease worldwide, disproportionately affect the most underserved and underdeveloped areas. Eggs found in human faeces that pollute the soil in unclean locations spread their spores.[1] Ascaris lumbricoides (round, warm), trichuris trichiura (whipworms), Necator americanus,

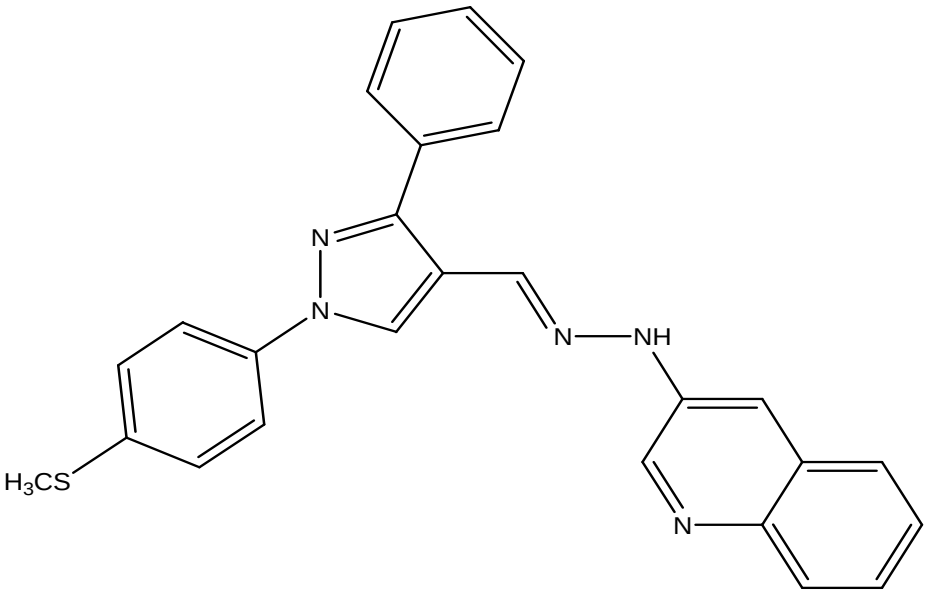
and Ancylostoma duodenale are the three main worm species that infect humans (hookworms,). Many STH species are often treated jointly due to their similar diagnostic needs and treatment responses.[2-3]



Albendazole



5a



5e

S. stercoralis is expected to infect more than 600 million people globally, but because it may also spread in filthy environments, its geographic range overlaps with that of another helminthiasis that is transmitted through the soil.[4-6] The drugs known as anthelmentics are used to treat parasitic worm infections in humans.[7] On pharmacological testing, pyrazole has a broad variety of effects, including antiviral, anticancer, antibacterial, antitubercular, antiviral, anti-inflammatory, antioxidant, and anthelmintic.[11]

2. RESULT AND DISCUSSION

2.1*Chemistry*

Our main purpose is to prepare an individual drug which have an anthelmintic activity**.** In first step of reaction we made **acetophenone phenyl hydrazine(3)** by the combination of **substituted acetophenone (1)** and **substituted phenyl hydrazines (2)** in presence of glacial acetic acid.

Table 2.1: Physicochemical properties of 2-phenyl-1-(1-phenylethylidene) hydrazine (3)

Code name	R	R’	Molecular formula	Molecular weight	R_f
3a	2-nitro	4-hydroxy	$C_{14}H_{15}N_3O_3$	273	0.68
3b	2-nitro	4-nitro	$C_{14}H_{14}N_4O_4$	302	0.73
3c	2-nitro	4-chloro	$C_{14}H_{14}N_3O_2Cl$	291.4	0.72
3d	H	2-bromo	$C_{14}H_{15}N_2Br$	290.9	0.71
3e	H	4-methylthio	$C_{15}H_{17}N_2S$	257	0.67
3f	H	4-bromophenyl	$C_{20}H_{20}N_2Br$	367.9	0.74

Our main intermediate **1,3-diphenyl-1H-pyrazole-4-carbaldehyde (4)** was prepared by Veilsmeyer- hack reaction in presence of phosphorous oxychloride and ethanol.

Further the compound **1,3-diphenyl-1H-pyrazole-4-carbaldehyde (4)** was condensed in presence of ethanol with 3-hydrazinyl quinoline to obtain our main compound **1-((1,3-diphenyl-1H-pyrazole-4-yl)methylene)-2-(quinoline-3-yl) hydrazine (5)**

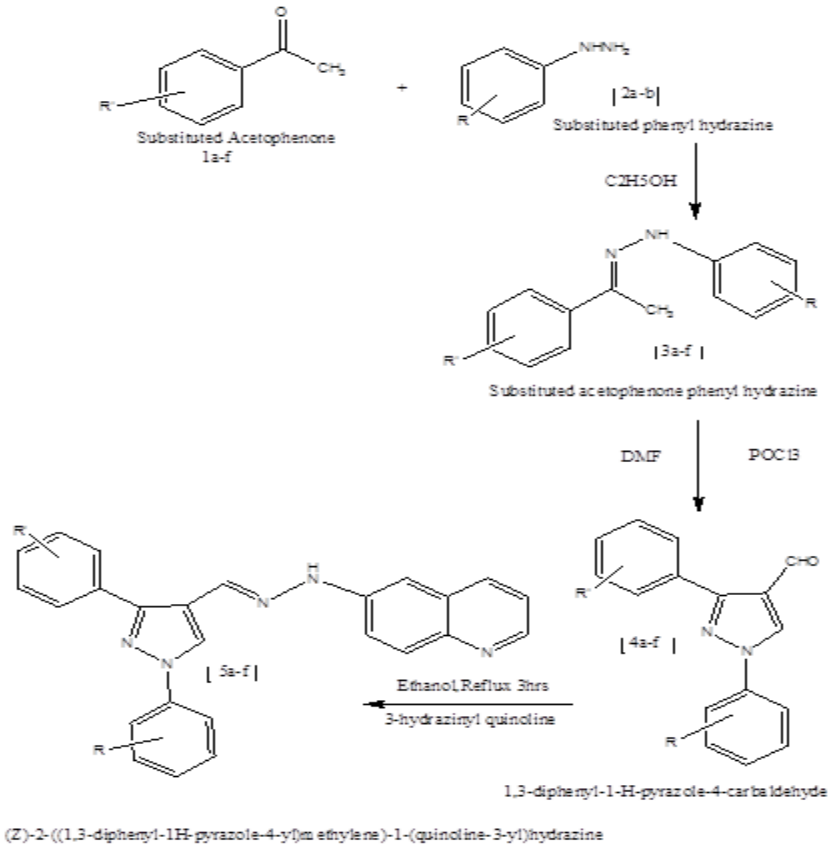


Table 2.2 Physicochemical properties of 1-((1,3-diphenyl-1H-pyrazole-4-yl)methylene)-2-(quinoline-3-yl) hydrazine (5)

Code name	R	R'	Molecular formula	Molecular weight	R_f	% yield
5a	2-nitro	4-hydroxy	$C_{25}H_{18}N_6O_3$	450	0.71	87%
5b	2-nitro	4-nitro	$C_{25}H_{17}N_7O_4$	479	0.76	71.12%
5c	2-nitro	4-chloro	$C_{25}H_{17}N_6O_2Cl$	468.4	0.66	69.23%
5d	H	2-bromo	$C_{25}H_{18}N_5Br$	467.9	0.73	73.33%
5e	H	4-methylthio	$C_{26}H_{21}N_5S$	435	0.79	78.12%
5f	H	4-bromophenyl	$C_{31}H_{22}N_5Br$	543.9	0.70	68.34%

This compound was characterized by TLC, melting point, solubility NMR and IR We have considered structure (**5a-f**) by spectral analysis.

In the IR spectrum of final pyrazole derivatives (**5a-f)** show strong peak in region of 3341-3353 cm-1 because of N-H stretching vibrations that indicate the presence of N-H in pyrazole. The intense peak in the region of 1591-1574 cm-1 confirm the aromatic C=C stretching. The region of 1477-1463 cm-1 is because of C=N stretch vibrations. In the 1H NMR band, Singlet value of hydroxyl group is 5.49 The methyl group protons are appeared to be a singlet at 2.43.

2.2 *Biological evaluation*

Anthelmintic activity

All novel synthesized compounds (5a-f) were examined for the activity of Anthelmintics using earth warm against Albendazole. All earth warms were dispersed into three main groups (standard, test and Control) .Each group contains thrice earth warms approximately having same sizes. Each test was operated at normal room temperature.

The samples and standard compounds are dissolved in very little amount of DMSO and then the volume will made to adjuste to 10ml with normal saline. The sample and standard solution are made in the concentration of 0.10%, 0.20%, 0.50 % w/v. To control group normal saline are used. The times are noted for both the conditions of study i.e. earthwarms paralysis and death.(Data mentioned in table 2.3).

Table 2.3: Anthelmintic activity of compounds(5a-f).

S. No.	Name	Time in minutes(mean±sem)					
		Forparalysis			Fordeath		
		%conc.			%conc.		
		0.1	0.2	0.5	0.1	0.2	0.5
1.	Control	-	-	-	-	-	-
2.	Albendazole	49±0.46	44±0.18	38±0.43	68±0.34	62±0.24	53±0.16
3.	**5a**	**53±0.36**	**48±0.49**	**42±0.25**	**145±0.38**	**137±0.19**	**124±0.24**
4.	5b	75±0.22	71±0.43	63±0.19	189±0.15	181±0.34	170±0.26
5.	5c	58±0.24	55±0.34	53±0.36	142±0.18	138±0.14	134±0.34
6.	5d	68±0.15	65±0.35	60±0.24	180±0.15	173±0.17	164±0.16
7.	**5e**	**50±0.41**	**45±0.25**	**39±0.15**	**107±0.13**	**103±0.24**	**101±0.38**
8.	5f	79±0.31	73±0.19	68±0.16	195±0.22	187±0.22	179±0.17

3. EXPERIMENTATION

3.1 Materials and Methods

Chemical and reagents used glacial acetic acid, phosphorous oxychloride, Dimethyl formamide (DMF), and 3-hydrazinyl quinoline were aquired from Spectro chem (Mumbai). n-hexane and ethyl acetate are from Aventor performance (Mumbai). NMR spectra were recorded on a Brucker 300 MHz spectrometer using CDCl3/DMSO as the solvent, and tetrametylsilane as an internal standard chemical shift value was listed in scale. The infrared spectra for the synthesised compounds were recorded on a SHIMADZU-FTIR 8400S spectrometer using KBr. Carlo Ebra 106 and Perkin Elmer model 240 analyzers were used for the elemental analysis.

3.2 General Procedure

Synthesis of 2-phenyl-1-(1-phenylethylidene) hydrazine.(3a-f)

Substituted acetophenones (0.01 mol) **(1)** were taken within a round bottom flask and substituted phenyl hydrazine (0.01 mol) **(2)** was added in it and both the compounds were added in 20 ml ethanol. After that the temperature was maintain at 0^0C with the help of ice cubes and then 2-3 drops of glacial acetic acid mixed and reflux 2 hr. (confirm TLC). following the conclusion of reaction the response combination were chilled with ice and solid particles was filtered and dry it to get the intermediate product.

Synthesis of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde.(4a-f)

Anhydrous N,N-dimethylformamide (DMF) (0.01 mol) was introduced dropwise to phosphorous oxychloride ($POCl_3$) (0.01 mol) with continuously stirr for fifteen minutes at similar temp. After the reaction was complete, 0.01 mol of the combination 2-phenyl-1-(1-phenylethylidene) hydrazine **(3)** were mix and refluxed for two hours at 100^0C. (Thin Layer Chromatography verified it.) After being neutralised with saturated sodium bicarbonate, the reaction mixture was put onto ice that had been crushed. The substance was collected, filtered, water-washed, and dried. compound re-crystallization from ethyl acetate.

Synthesis of 1-((1,3-diphenyl-1H-pyrazole-4-yl)methylene)-2-(quinoline-3-yl) hydrazine (5a-f)

Substituted 1,3-diphenyl 1H-pyrazoles 4-carbaldehyde **(4)** (0.01 mol) add to a solution of the 3-hydrazinyl quinoline (0.01 mol) in 30 ml C_2H_5OH, the combination heat and reflux for three hrs, when reaction mixture cooled and converted into crystals then solid formed. The final product **(5)** was obtained after filtration and drying, which was further recrystallize from dioxane.

(E)1-((1(4-hydroxyphenyl),3(2-nitrophenyl)-1H-pyrazole-4-yl)methylene)-2-(quinoline-3-yl) hydrazine (5a)

Yield: 87%, m.p.:131-133^0C; IR spectra [KBr; cm^{-1}]:3351 (N-H), 3255 (O-H), 1475 (C=N), 1587 (Ar C=C), 1333 (C-N), 1H NMR spectra [300 MHz; DMSO-d6/ ppm]:5.49 (s, 1H, -OH), 7.27-7.49 (m, 5H, Ar-H), 7.51-7.62 (m, 6H, Ar-H), 7.75-7.81 (m, 4H, Ar-H), 8.54 (s, 1H, N-H), 9.12(s, 1H, C-H)

(E)1-((1-(4-nitrophenyl)-3-(2-nitrophenyl)-1H-pyrazole-4-yl)methylene)-2-(quinoline-3-yl) hydrazine (5b)

Yield: 71.12%, m.p.:137-139^{0}C; IR spectra [KBr; cm^{-1}]: 3349 (N-H), 1473 (C=N), 1587 (Ar C=C), 1329 (C-N), 1475 (N=O), 1H NMR spectra [300 MHz; DMSO-d6/ ppm]:7.02-7.32 (m, 6H, Ar-H), 7.46-7.59 (m, 5H, Ar-H), 7.87-7.90 (m, 4H, Ar-H), 8.44(s, 1H, N-H), 9.10(s, 1H, C-H).

(E)1-((1-(4-chloroyphenyl)-3-(2-nitrophenyl)-1H-pyrazole-4-yl)methylene)-2-(quinoline-3-yl) hydrazine (5c)

Yield: 69.23%, m.p.:141-143^{0}C; IR spectra [KBr; cm^{-1}]: 3347 (N-H), 1471 (C=N), 1585 (Ar C=C), 1327 (C-N), 753 (C-Cl), 1H NMR spectra [300 MHz; DMSO-d6/ ppm]: 6.79-7.24 (m, 6H, Ar-H), 7.33-7.48 (m, 4H, Ar-H), 7.67-8.25 (m, 5H, Ar-H), 8.67(s, 1H, N-H) 9.53(s, 1H, C-H)

(E)1-((1-(2-bromophenyl)-3-phenyl-1H-pyrazole-4-yl)methylene)-2-(quinoline-3-yl) hydrazine (5d)

Yield: 73.33%, m.p.:129-131^{0}C; IR spectra [KBr; cm^{-1}]: 3346 (N-H), 1469 (C=N), 1575 (Ar C=C), 1323 (C-N), 632 (C-Br) 1H NMR spectra [300 MHz; DMSO-d6/ ppm]: 7.11-7.35 (m, 5H, Ar-H), 7.47-7.53 (m, 6H, Ar-H), 8.01-8.31 (m, 4H, Ar-H), 8.37(s, 1H, N-H), 9.13(s, 1H, C-H)

(E)1-((1-(4-methylthiophenyl)-3-phenyl-1H-pyrazole-4-yl)methylene)-2-(quinoline-3-yl) hydrazine (5e)

Yield: 78.12%, m.p.:150-152^{0}C; IR spectra [KBr; cm^{-1}]: 3345 (N-H), 2420 (S-H), 1468 (C=N), 1579 (Ar C=C), 1321 (C-N), 1H NMR spectra [300 MHz; DMSO-d6/ ppm]: 2.43 (s, 3H, -CH_3), 7.12-7.36 (m, 6H, Ar-H), 7.39-7.67 (m, 6H, Ar-H), 7.77-8.27 (m, 4H, Ar-H), 8.37(s, 1H, N-H), 9.11(s, 1H, C-H).

(E)1-((1-(4-(4-bromophenyl))-3-phenyl-1H-pyrazole-4-yl)methylene)-2-(quinoline-3-yl) hydrazine (5f)

Yield: 68.34%, m.p.:155-157^{0}C; IR spectra [KBr; cm^{-1}]: 3343 (N-H), 1467 (C=N), 1577 (Ar C=C), 1322 (C-N), 677 (C-Br) 1H NMR spectra [300 MHz; DMSO-d6/ ppm]: 7.01-7.37 (m, 6H, Ar-H), 7.44-7.79 (m, 8H, Ar-H), 8.13-8.33 (m, 6H, Ar-H), 8.83(s, 1H, N-H), 9.17 (s, 1H, C-H).

CONCLUSION

In the present study, six pyrazole analogues (**5a-f**) were synthesized by condensation of formyl pyrazole with hydrazinyl quinoline. Substituted phenyl hydrazine with substituted acetophenone was used as starting material to form intermediates. Newly Synthesized compounds were identified by m.p. range, solubility, R_f values, IR and ^{1}HNMR spectral analysis. IR and ^{1}HNMR spectral values confirmed the characters of the new compounds synthesize. All newly synthesized products were tested for anthelmintic activity and it was found that compound **5a** and **5e** has expressed the maximum anthelmintic activity against the standard drug Albendazole.

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REFERENCE

1. El Shehry, Mohamed F., Mostafa M. Ghorab, Samir Y. Abbas, Eman A. Fayed, Said A. Shedid, and Yousry A. Ammar. "Quinoline derivatives bearing pyrazole moiety: synthesis and biological evaluation as possible antibacterial and antifungal agents." *European journal of medicinal chemistry*, 2018; 143: 1463-1473.
2. Sangani, Chetan B., Jigar A. Makawana, Xin Zhang, Shashikant B. Teraiya, Lin Lin, and Hai-Liang Zhu. "Design, synthesis and molecular modeling of pyrazole–quinoline–pyridine hybrids as a new class of antimicrobial and anticancer agents." *European Journal of Medicinal Chemistry*, 2014; 76: 549-557.
3. Wang, Dun-Jia, Yan-Fang Kang, Chun-Yang Zheng, and Xian-Hong Wei. "Preparation and structures of some new 1H-pyrazole derivatives." *Research on Chemical Intermediates*, 2013; 39(6): 2311-2320.
4. Tınmaz, Feyza, İlhan Özer İlhan, and Senem Akkoç. "Preparation and Properties of Some New Pyrazole Derivatives." *Organic Preparations and Procedures International*, 2020; 53(1): 89-94.
5. Abrigach, F., and R. Touzani. "Pyrazole derivatives with NCN junction and their biological activity: A review." *Med. Chem*, 2016; 6: 292-298.

6. Alam, Md Jahangir, Ozair Alam, Perwaiz Alam, and Mohd Javed Naim. "A review on pyrazole chemical entity and biological activity." *Int. J. Pharm. Sci. Res,* 2015; 6: 1433-1442.
7. Ismail, A. H., A. M. Abdula, and M. T. Mohammed. "Al-Bayati. 1, 3, 5-Trisubstituted-1H-Pyrazole Derivatives as New Antimicrobial Agents: Synthesis, Characterization and Docking Study." *Int J Chem Sci* 2017; 15(2): 126.
8. Naim, Mohd Javed, Ozair Alam, Farah Nawaz, Md Jahangir Alam, and Perwaiz Alam. "Current status of pyrazole and its biological activities." *Journal of pharmacy & bioallied sciences*, 2016; 8(1): 2.
9. Ragavan RV, Vijayakumar V, Kumari NS. Synthesis and antimicrobial activities of novel 1,5-diaryl pyrazoles . Eur J Med Chem, 2010; 45: 1173-1180.
10. Sowmya DV, Teja GL, Padmaja A, Prasad VK, Padmavathi V. Green approach for the synthesis of thiophenyl pyrazoles and isoxazoles by adopting 1,3-dipolar cycloaddition methodology and their antimicrobial activity. Eur J Med Chem, 2018; 143: 891-898.
11. Karrouchi K, Radi S, Ramli Z, Taoufik J, Mabkhot ZN, et al. Synthesis and Pharmacological Activities of Pyrazole Derivatives: A Review Molecules, 2018; 23: 1-85.
12. Mu, Yangxiu, Zafar Iqbal, Rui Jiang, Jing Hou, Zhixiang Yang, Hongjun Li, and Dong Tang. "Synthesis of Fused pyrazolo [4, 3- c] quinolines through KI- Promoted Cyclization of Pyrazole- arylamines and Benzyl Bromide." *Chemistry Select*, 2022; 7(10): e202104337.
13. Dabholkar, Vijay V., and Faisal Y. Ansari. "Synthesis and characterization of selected fused isoxazole and pyrazole derivatives and their antimicrobial activity." *Journal of the Serbian Chemical Society*, 2009; 74(11): 1219-1228.
14. Wazalwar, Sachin S., Anita R. Banpurkar, and Franc Perdih. "Aqueous phase synthesis, crystal structure and biological study of isoxazole extensions of pyrazole-4-carbaldehyde derivatives." *Journal of Molecular Structure*, 2017; 1150: 258-267.
15. Abu-Hashem, Ameen Ali, and Ahmed S. Aly. "Synthesis of new pyrazole, triazole, and thiazolidine-pyrimido [4, 5-b] quinoline derivatives with potential antitumor activity." *Archives of pharmacal research*, 2012; 35(3): 437-445.
16. Bhat, Mahesh, and Shiddappa Lagamappa Belagali. "Synthesis, characterization and biological screening of pyrazole-conjugated benzothiazole analogs." *Future medicinal chemistry*, 2018; 10(1): 71-87.

17. Bhat, M., S. L. Belagali, NK Hemanth Kumar, and S. Jagannath. "Anti-mitotic Activity of the Benzothiazole-pyrazole Hybrid Derivatives." *Anti-Infective Agents*, 2019; 17(1): 66-73.
18. Ei-Sharief, Marwa AM Sh, Samir Y. Abbas, Ziad Moussa, Eman W. El-Gammal, and Ahmed M. Sh El-Sharief. "Synthesis and evaluation of antibacterial and antifungal activities of 1, 3-Disubstituted-4-Thioxoimidazolidin-2-One derivatives." *Croatica Chemica Acta*, 2018; 91(3): 335-341.
19. Abbas, Samir Y., and Marwa AM Sh. "El-Sharief, WM Basyouni, IMI Fakhr, EW El-Gammal." *Eur. J. Med. Chem*, 2013; 64(111): 10-1016.
20. Moussa, Ziad, Marwa AM Sh El-Sharief, and Samir Y. Abbas. "New imidazolidineiminothione derivatives: synthesis, spectral characterization and evaluation of antitumor, antiviral, antibacterial and antifungal activities." *European journal of medicinal chemistry*, 2016; 122: 419-428.
21. Farag, Awatef A., Mohamed F. El Shehry, Samir Y. Abbas, Safaa N. Abd-Alrahman, Abeer A. Atrees, Hiaat Z. Al-basheer, and Yousry A. Ammar. "Synthesis of pyrazoles containing benzofuran and trifluoromethyl moieties as possible anti-inflammatory and analgesic agents." *Zeitschrift für Naturforschung B*, 2015; 70(7): 519-526.
22. Farag, Awatef A., Mohamed F. El Shehry, Samir Y. Abbas, Safaa N. Abd-Alrahman, Abeer A. Atrees, Hiaat Z. Al-basheer, and Yousry A. Ammar. "Synthesis of pyrazoles containing benzofuran and trifluoromethyl moieties as possible anti-inflammatory and analgesic agents." *Zeitschrift für Naturforschung B*, 2015; 70(7): 519-526.
23. Kategaonkar, Amol H., Pravin V. Shinde, Atul H. Kategaonkar, Sharad K. Pasale, Bapurao B. Shingate, and Murlidhar S. Shingare. "Synthesis and biological evaluation of new 2-chloro-3-((4-phenyl-1H-1, 2, 3-triazol-1-yl) methyl) quinoline derivatives via click chemistry approach." *European journal of medicinal chemistry*, 2010; 45(7): 3142-3146..
24. Lilienkampf, Annamaria, Jialin Mao, Baojie Wan, Yuehong Wang, Scott G. Franzblau, and Alan P. Kozikowski. "Structure− activity relationships for a series of quinoline-based compounds active against replicating and nonreplicating Mycobacterium tuberculosis." *Journal of medicinal chemistry*, 2009; 52(7): 2109-2118.
25. Gümüş, Ayşegül, Veysi Okumuş, and Selçuk Gümüş. "Synthesis of 2-substituted 8-propargyloxyquinoline derivatives and determination of their antioxidant, antibacterial, and DNA binding activities." *Turkish Journal of Chemistry*, 2018; 42(5): 1358-1369.

26. Nasveld, Peter, and Scott Kitchener. "Treatment of acute vivax malaria with tafenoquine." *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2005; 99(1): 2-5.
27. Castillo, J. C., and J. Portilla. "Recent advances in the synthesis of new pyrazole derivatives." *Targets Heterocycl. Syst*, 2018; 22: 194-223.
28. Mustafa, Atif, Shaheen Siddiqui, Mohd Umar Khan, Abdulaziz Abdullah Qasem Ali, and Zeba N. Siddiqui. "Recent Advances in Synthesis of Pyrazole Derivatives using Functionalized Catalysts Immobilized on Silica." *ChemistrySelect*, 2021; 6(33): 8611-8629.
29. Saleh, Ibrahim, Hansa Raj Kc, Subrata Roy, Mohd Kotaiba Abugazleh, Hashim Ali, David Gilmore, and Mohammad A. Alam. "Design, synthesis, and antibacterial activity of N-(trifluoromethyl) phenyl substituted pyrazole derivatives." *RSC Medicinal Chemistry*, 2021; 12(10): 1690-1697.
30. Akbarpour, Tahereh, Jaber Yousefi Seyf, Ardeshir Khazaei, and Negin Sarmasti. "Synthesis of Pyrano [2, 3-c] Pyrazole Derivatives Using a Novel Ionic-Liquid Based Nano-Magnetic Catalyst (Fe3O4@ SiO2@(CH2) 3NH@ CC@ Imidazole@ SO3H+ Cl−)." *Polycyclic Aromatic Compounds*, 2021; 1-21.
31. Gosselin, Francis, Paul D. O'Shea, Robert A. Webster, Robert A. Reamer, Richard D. Tillyer, and Edward JJ Grabowski. "Highly regioselective synthesis of 1-aryl-3, 4, 5-substituted pyrazoles." *Synlett*, 2006; (19): 3267-3270.
32. Han- Song, Chen, and Li Zheng- Ming. "Synthesis of some heteroaryl pyrazole derivatives and their biological activities." *Chinese Journal of Chemistry*, 2000; 18(4): 596-602.
33. IKEDA, Masazumi, Kazumi MARUYAMA, Youichi NOBUHARA, Toshihiro YAMADA, and Susumu OKABE. "Synthesis and cytoprotective antiulcer activity of 2-or 4-(1H-pyrazol-1-yl) pyrimidine derivatives related to mepirizole and dulcerozine." *Chemical and pharmaceutical bulletin*, 1996; 44(9): 1700-1706.
34. Jiang, Jian-An, Cai-Yan Du, Chun-Hui Gu, and Ya-Fei Ji. "'"One-Pot" Synthesis of 4-Substituted 1, 5-Diaryl-1H-pyrazole-3-carboxylic Acids via a MeONa/LiCl-Mediated Sterically Hindered Claisen Condensation–Knorr Reaction–Hydrolysis Sequence." *Synlett*, 2012; 23(20): 2965-2968.
35. Khunt, R. C., V. M. Khedkar, R. S. Chawda, N. A. Chauhan, A. R. Parikh, and E. C. Coutinho. "Synthesis, antitubercular evaluation and 3D-QSAR study of N-phenyl-3-(4-

fluorophenyl)-4-substituted pyrazole derivatives." *Bioorganic & medicinal chemistry letters*, 2012; 22(1): 666-678.

36. Singh, Kiran, Yogender Kumar, Parvesh Puri, Mahender Kumar, and Chetan Sharma. "Cobalt, nickel, copper and zinc complexes with 1, 3-diphenyl-1H-pyrazole-4-carboxaldehyde Schiff bases: Antimicrobial, spectroscopic, thermal and fluorescence studies." *European Journal of Medicinal Chemistry*, 2012; 52: 313-321.
37. Renuka, Nagamallu, and Kariyappa Ajay Kumar. "Synthesis and biological evaluation of novel formyl-pyrazoles bearing coumarin moiety as potent antimicrobial and antioxidant agents." *Bioorganic & medicinal chemistry letters*, 2013; 23(23): 6406-6409.
38. Panda, Niranjan, and Ashis Kumar Jena. "Fe-catalyzed one-pot synthesis of 1, 3-di-and 1, 3, 5-trisubstituted pyrazoles from hydrazones and vicinal diols." *The Journal of Organic Chemistry*, 2012; 77(20): 9401-9406.
39. Yerragunta, Vishwanadham, Duggi Suman, V. Anusha, P. Patil, and M. Naresh. "Pyrazole and its biological activity." *PharmaTutor* 2, no. 1 (2014): 40-48.
40. Patil, Prathima, S. Sridhar, V. Anusha, Y. Vishwanatham, Kumara Swamy, and D. Suman. "Synthesis, Characterisaton and Evaluation of Anti-Inflammatory Activity of some new Aryl Pyrazole Derivatives." *Asian Journal of Research in Chemistry*, 2014; 7(3): 269.
41. A Khedkar, Samrat, and Pratibha B Auti. "1, 4-Dihydropyridines: a class of pharmacologically important molecules." *Mini reviews in medicinal chemistry*, 2014; 14(3): 282-290.
42. Pathan, Shahebaaz K., Satish Deshmukh, Santosh S. Chhajed, Aniruddha Chabukswar, and Jaiprakash Sangshetti. "Green Synthesis Of Methyl-6-Amino-5-Cyano-4-Aryl-2, 4-Dihydropyrano [2, 3-C] Pyrazole-3-Carboxylates using Dimethyl Acetylene dicarboxylate." *Chemical Data Collections*, 2020; 28: 100403.