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A COMPREHENSIVE UPDATE ON PYRIMIDINE, COUMARIN AND BENZIMIDAZOLE (PCB)-VERSATILE ANALOGS WITH BIOLOGICAL POTENCY

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Keywords:

Pyrimidine, Coumarin, Benzimidazole, SAR, and Biological significance

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ABSTRACT: All three versatile heterocyclic compounds (PCB) are majorly contributing to the field of medicine due to their unique medicinal activities like antimicrobial, anti-inflammatory, anticancer, antioxidant, analgesic, anti-diabetic, anti-viral, anti-ulcer, anti-HIV, and as an anti-protozoal agent (Fig. 1). Many novel PCB analogs are already being used commercially as medicines. Further, the structure-activity relationship and the recent medicinal significance of all three (pyrimidine, coumarin, and benzimidazole) derivatives were discussed. Finally, this comprehensive update may attract synthetic chemists and biologists for further design and development of a novel molecule.

INTRODUCTION:

Pyrimidine: The pyrimidine skeleton is a versatile scaffold for its synthesis and medicinal significance. The pyrimidine associated with other heterocyclic compounds attracted the chemists such as antimicrobial [1] Samvel N S *et al*. 2018, anticancer [2] Safinaz *et al*. 2019, anti-inflammatory [3] Haroonur Rashid *et al*. 2021, anti-malarial [4] Mohammad M A *et al*. 2021, anti-diabetic [5] Fariba Peytam *et al*. 2021, anti- HIV [6] Roberto Romeo *et al*. 2019, Anthelmintic [7] David I U *et al.* 2018., CNS depressants [8] Marek Krol *et al*. 2021, cardiac agents [9] Fatma Bassyouni *et al*. 2021 & the thiouracil analogs observed anti-thyroid activity [10] Samir M A *et al*. 2018. In addition, pyrimidine fused heterocyles observed inhibitor potential against protein kinase [11] Kaled R. A A *et al* 2021.

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Coumarin: Coumarins, popularly known as benzopyrone, are found in nature (tonka bean, woodruff, and bison grass).

Coumarin and coumarin fused other heterocycles showed various medicinal potential, such as antimicrobial [12] (Phutdhawong W *et al.* 2021), anti-inflammatory [13] (Hanan M Alshibl *et al.* 2020), anti-cancer [14] (E K Akkol *et al*. 2020), anti-tubercular [15] (Dinesh S Reddy et al. 2021), antithrombotic [16] (Leilei Gao *et al.* 2021), and antioxidant [17] (Anum Sahar *et al*. 2017).

Benzimidazole: The fusion of benzene with imidazole is popularly known as benzimidazole. Benzimidazoles are known for their wide spectrum of biological activities and also for their clinical applications, such as antimicrobial [18] (Hasan Küçükbay *et al*. 2021), Anticancer [19] (Eman A. Abd El-Meguid *et al.* 2020), antioxidant [20] (Rahman Basaranet *et al.* 2020), anti-inflammatory [21] (Sathyanarayana R *et al.* 2022), analgesi [22] (Shejuti Rahman Brishty *et al.* 2020), anti-diabetic [23] (Burak Dik *et al.* 2021), anti-ulcer [24] (Avinash Patil *et al.* 2009), anti-viral [25] (Mei Chen *et al.*

2021) and as an anti-protozoal agent [26] (Karen Rodríguez Villar *et al.* 2021) **Fig. 1.**

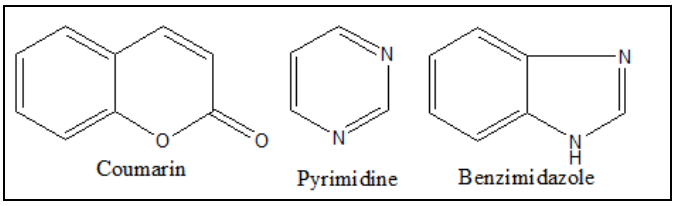

FIG. 1: STRUCTURES OF PYRIMIDNE, COUMARIN AND BENZIMIDAZOLE

Clinical Significance of Pyrimidine, Coumarin, and Benzimidazole (PCB) Analogs:

As Antimicrobial agents: The Contribution of **a**ntibiotics is significant after the discovery of penicillin in 1928 [27] (M.A. Radwan *et al*. 2020). Further novel inventions are required to prevent multidrug resistance. Every year, the resistance of bacterial strains is affected very badly in European countries. Compound (1), inventor: Wenneng Wu *et al*. 2021, Activity: Good, EC50: 10.5 µg/ml against microbial strains compared with standard (32.1 µg/ml), SAR: Observed potential may be the presence of $–NH_2$,-F, and -Br groups in different positions of the aromatic ring [28]. Compound (2), inventor: Rongcui Zhong *et al*. 2021, Activity: Potent, Fungal strain: gram-positive bacteria, SAR: The coumarin bearing hydrophobic and cationic moiety may be responsible for the enhanced activity [29]. Compound 3 and 4, inventor: Bassyouni F *et al.* 2021, Activity: Good, MIC: 10-17, 5 µL against microbial strains, *SAR:* The existence of sulfur, methyl, and amine in the pyrimidine skeleton may be responsible for the enhanced potential [30]. Compound (5), inventor: M. Nibin Joy *et al.* 2020, Activity: Higher, MIC: 5-150 µg/ml, Bacterial strains: *P. aeruginosa* and *E. coli*, standard: pyrimethanil, MIC: 0.2-0.6 µg/ml, 32.1 µg/ml, SAR: Pyrimidine ring bearings with fluoro groups may be responsible for the activity [31] **Fig. 2.**

Compound (6), inventor: Mostafa *et al.* 2020, Activity: Good, Inhibition zone: 19, 19, 18 and 17 & 17, 18 & 18 mm against microbial strains compared with standard (26, 25 & 21 mm), SAR: Substituted pyridine and pyrimidine scaffold may be responsible [32]. Compound (7 and 8), inventor: Chintakunta R *et al*. 2020, Activity: satisfactory potency, Microbial strains: *B. subtilis* (100, 50, 25, 12.5, 6.25, 3.12, 1.6, 0.8, and 0.4 µg/ml) and *P. aeruginosa* (100, 50, 25, & 12.5 µg/ml), standard: Ciprofloxacin, SAR: The observed potency may be due the presence of amine and carboxylic acid groups at the specific position [33].

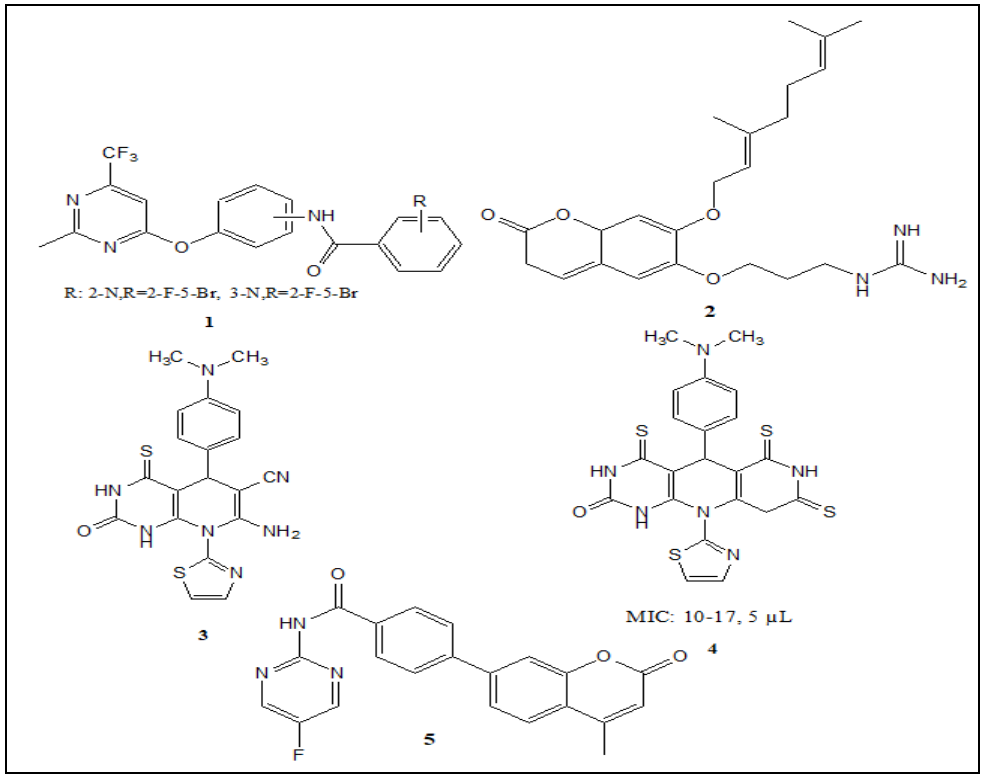

FIG. 2: THE ANTIMICROBIAL POTENTIAL OF PYRIMIDINE, BENZIMIDAZOLE AND COUMARIN DERIVATIVES

Compound (9 and 10), inventor: Moustafa A. H *et al*. 2020, Activity: Good potency, MIC: 0.07 µg/mL against microbial strains compared with standard (0.67 µg/mL), SAR: The existence of the –OH, -ClC_6H_5 and pyrimidine skeleton may be responsible for the activity [34].

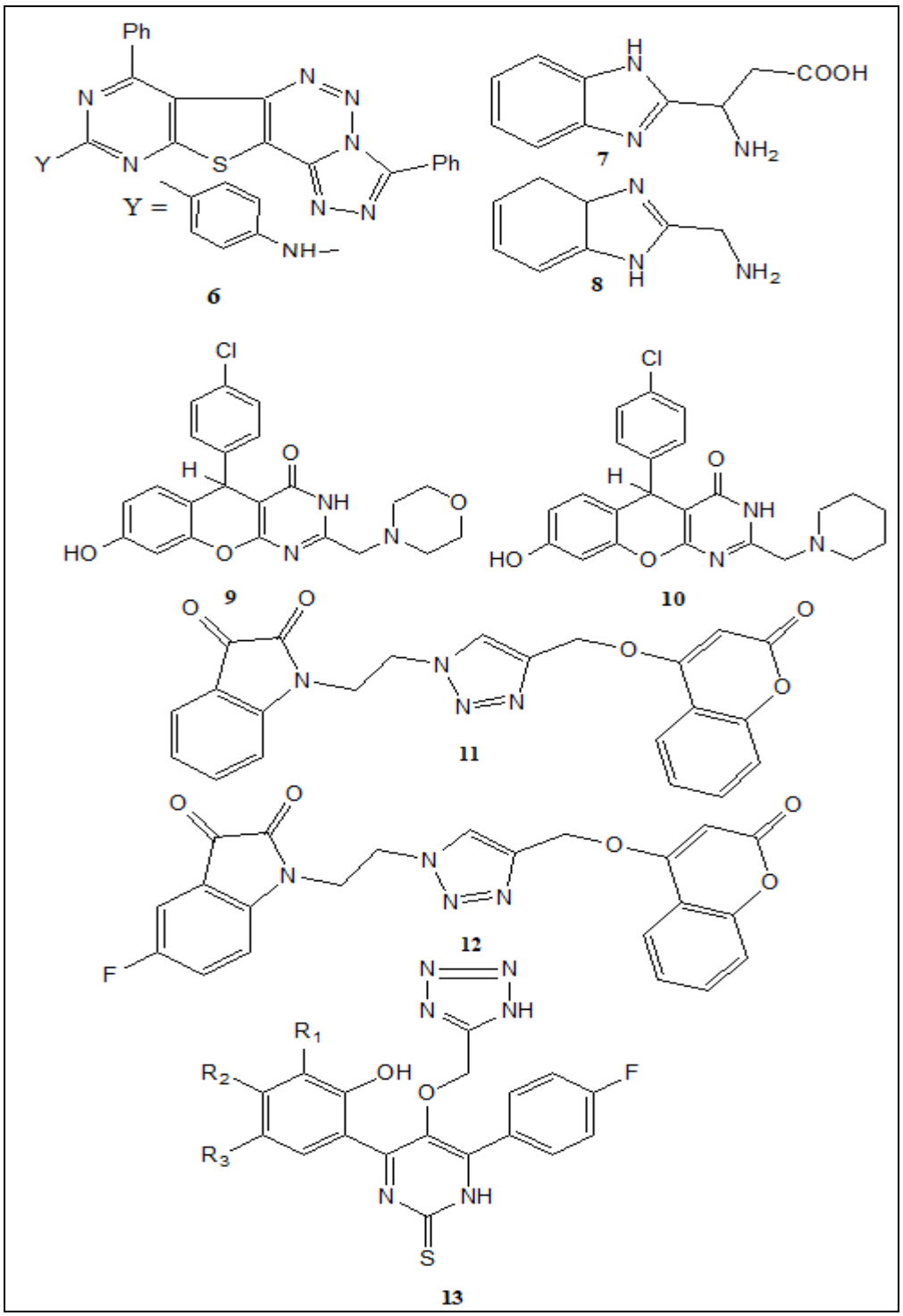

FIG. 3: THE ANTIMICROBIAL POTENTIAL OF PYRIMIDINE, BENZIMIDAZOLE AND COUMARIN DERIVATIVES

Compound (11 and 12), inventor: Kavita Bhagat *et al*. 2019, Activity: potent, MIC: 30 and 312 µg/mL against microbial strains compared with standard. SAR: The existence of carbon chain length and the presence of an electronic medium may be responsible for the activity [35]. Compound (13), inventor: D. Vidya S *et al*. 2018, Activity: satisfactory potency, MIC: 25, 200, 175, 150

µg/mL, 75, and 25 µg/mL against microbial strains. SAR: The fluorophenyl and thione-pyrimidine scaffolds may be responsible for the high potency [36] **Fig. 3.**

As Anticancer agents: The anticancer potential is responsible for the presence of di, tri, and tetra substituted pyrimidines, substituted pyrazole and thieno pyrimidines, and quinazoline, coumarin, and benzimidazole bearing other heterocylic compounds, which represent potent anticancer activity.

Compound (14), inventor: Phutdhawong W. *et al.* 2021, Activity: High potency, IC50 = 2.62–4.85 µM, 0.39–0.75 µM against cancer cell lines. SAR: Because of the presence of the fluorobenzamide moiety, high potency was observed [37].

Compound (15), inventor: Bakare Safyah *et al.* 2021, Activity: potent, IC50: 83.69 µM against cancer cell lines. SAR: The existence of bromo and methoxy groups in the fifth and eighth positions may be responsible for the activity [38].

Compound (16), inventor: Mrugesh Patel *et al.* 2021, Activity: potent, IC50: 12.59, 11.36 µM, and 11.26, 9.13 µM against cancer cell linge. SAR: The phenyl pyrazoline bearing chloro- methoxy group may be responsible for the enhanced activity [39].

Compound (17, 18, and 19), inventor: N. M Ahmed *et al.* 2021, Activity: Good potency, IC_{50}: 5.1, 5.02, and 6.6 µM against cancer cell lines. SAR: The existence of thiazolidine and pyrimidine associated with other heterocyles may be responsible for the activity [40] **Fig. 4.**

Compound (20), inventor: Yichang Ren *et al.* 2021, Activity: Satisfactory, Cancer cell lines: IC50: 9.7 nM, A2780/T, and 6.2 nM, A2780S, SAR: Phenyl ring, indole, and benzimidazole scaffold presence may be responsible for the high potency [41].

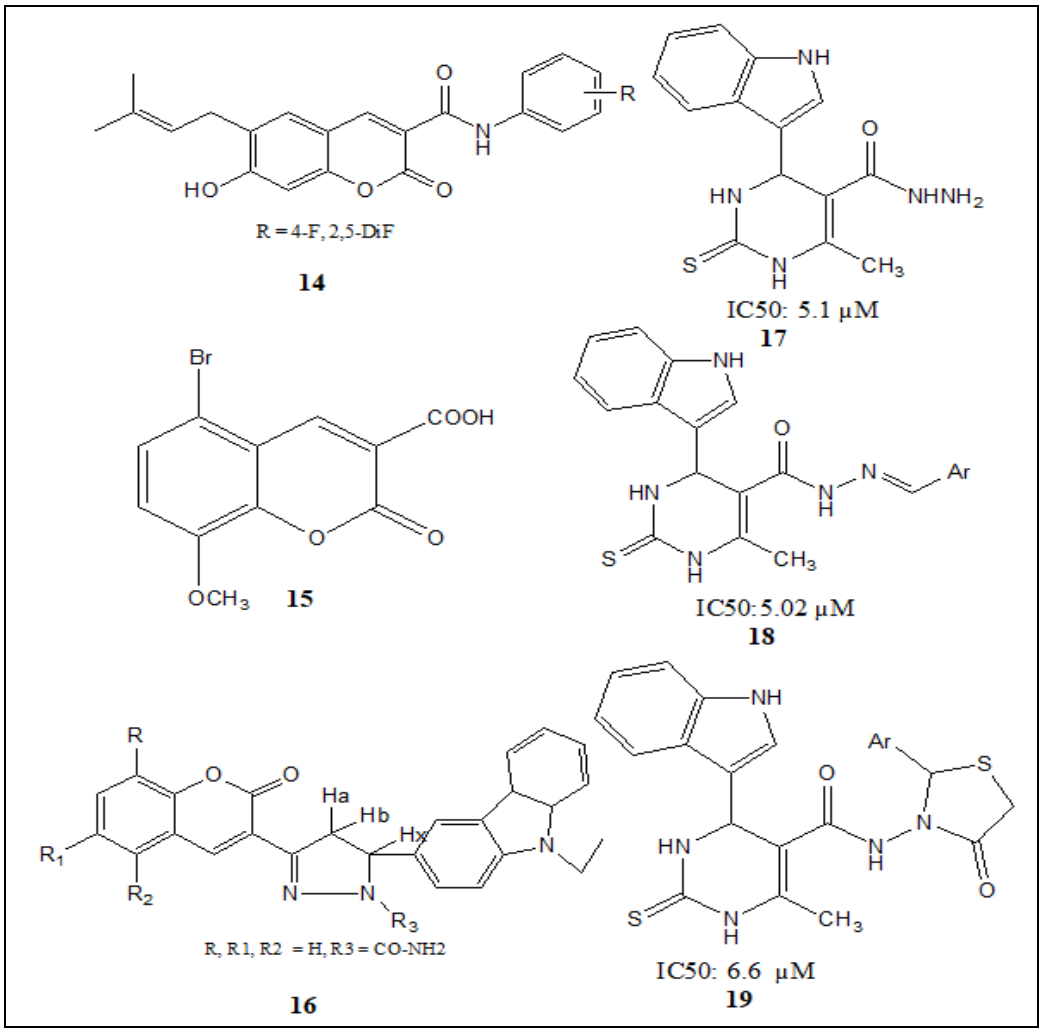

FIG. 4: THE ANTICANCER POTENTIAL OF PYRIMIDINE, COUMARIN AND BENZIMIDAZOLE ANALOGS

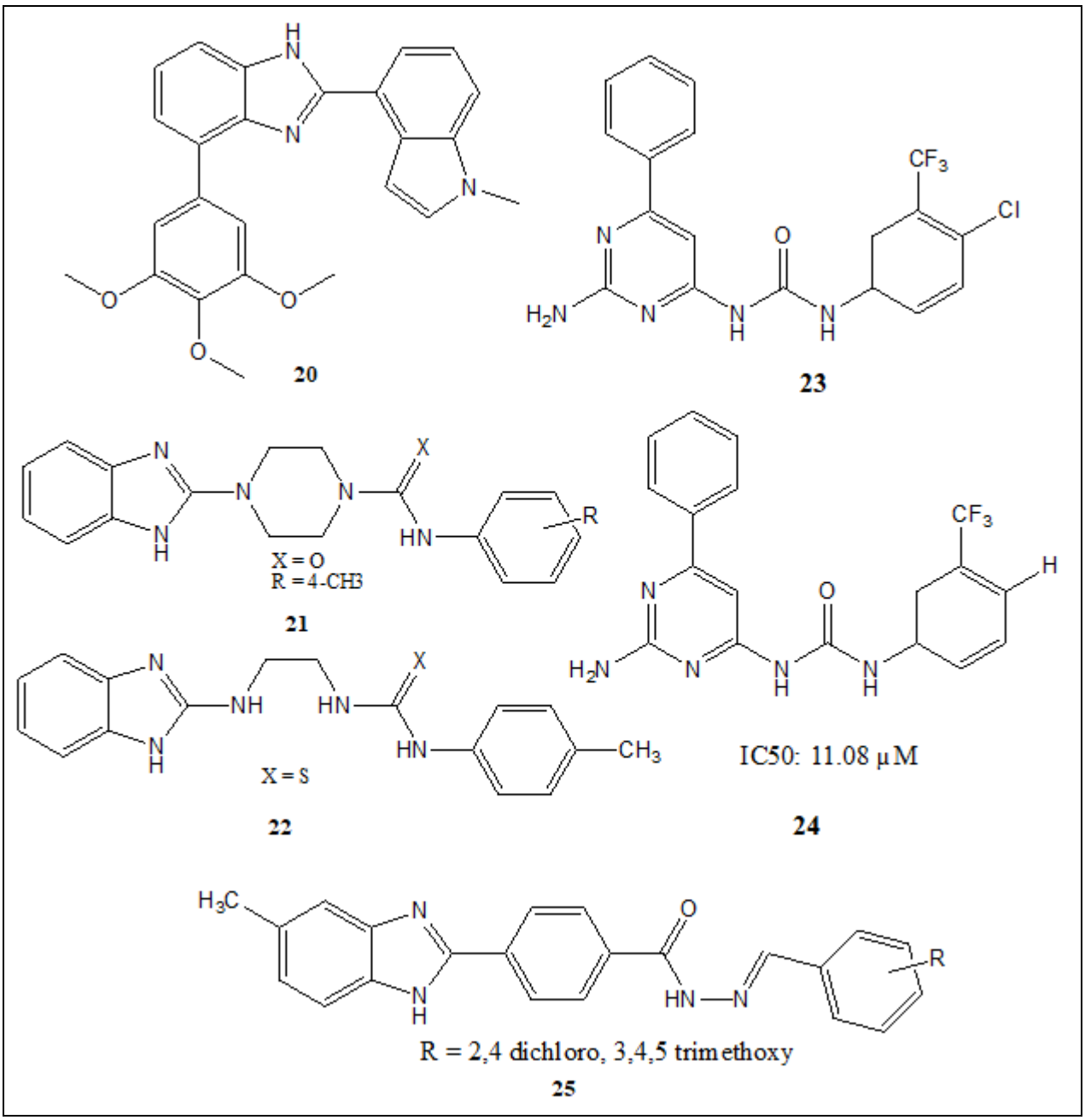

FIG. 5: THE ANTICANCER POTENTIAL OF PYRIMIDINE, COUMARIN AND BENZIMIDAZOLE ANALOGS

Compound (21 and 22), inventor: Lamia A. Siddig *et al.* 2021, Activity: Good, Cancer cell lines: MCF-7, IC50: 25.8 and 48.3 µM, SAR: The chlorine, methyl, and sulfur groups are the key groups for the enhanced activity[42].

Compound (23 and 24), inventor: Zuhal K. Kurt *et al.* 2020, Activity: Satisfactory, Cell lines: IC_{50}: 11.08 µM, SW480, SAR: The CF3, Cl, and amino-pyrimidine scaffold may be responsible for the activity [43].

Compound (25), inventor: Martha M. Morcoss *et al*. 2020, Activity: satisfactory, cancer cell lines: GI%: 50-84 %, SAR: The hydrazone group and benzimidazole moiety presence observed the high potencty [44] **Fig. 5.**

Compounds (26 and 27), inventor: Huang T *et al.* 2019, Activity: Good, Cancer cell lines: Inhibition rates: HeLa & A549: 45.08% & 41.69% & HeLa, HepG-2 & MCF7, IC_{50}: 20.30, 12.37 & 13.18 µM, SAR: The ethanolamine and pyrimidine moiety presence observed the enhanced activity [45].

Compound (28 and 29), inventor: Safinaz *et al.* 2019, Activity: Significant, IC_{50} = 0.01 µM against cancer cell lines compared with standard (0.04

µM). SAR: The existence of the –Cl and -CH_3 groups associated with hetercycles may be responsible for the activity [46] **Fig. 6.**

As Anti-tubercular agent: If we observed various diseases caused by Mycobacterium. Among them Tuberculosis is one creating a bad impact on human health [47] (Claudia TA Pires *et al*, 2020).

Compound (30), Inventor: Godge R *et al* 2018, Activity: Potent, MIC: 1.6 mcg/ml against M tuberculosis. SAR: The existence of pyrazole ring and methoxy group may be responsible for the activity [48].

Compound (31), Inventor: Kumbar S S *et al* 2018, Activity: Good, Mycobacterium tuberculosis: H37Rv strain, Standard: Isoniazid, MIC: 0.02 µg, SAR: The chloro group presence in specific position on the phenyl ring may responsible for the enhanced potency [49] **Fig. 7.**

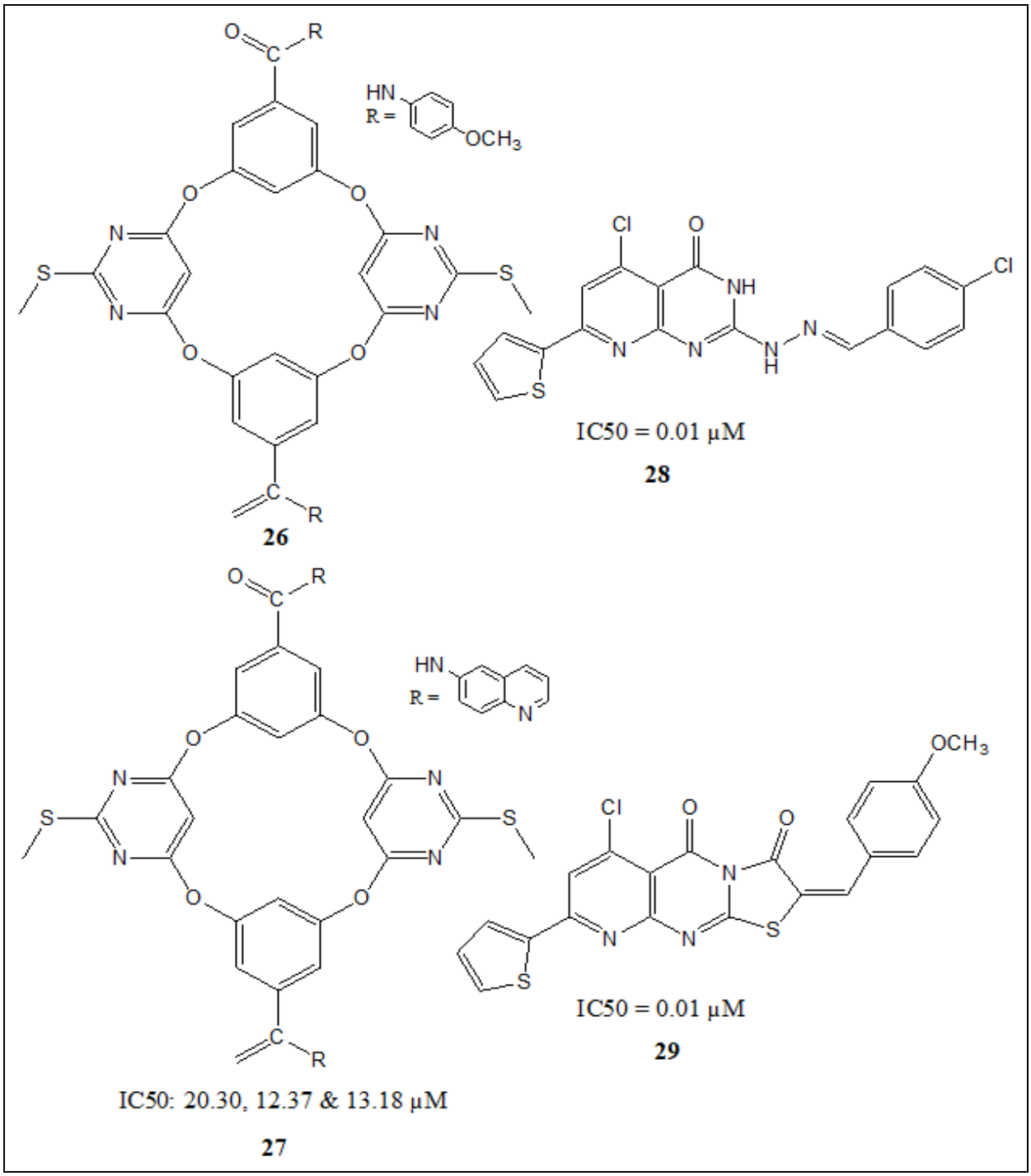

FIG. 6: THE ANTICANCER POTENTIAL OF PYRIMIDINE, COUMARIN AND BENZIMIDAZOLE ANALOGS

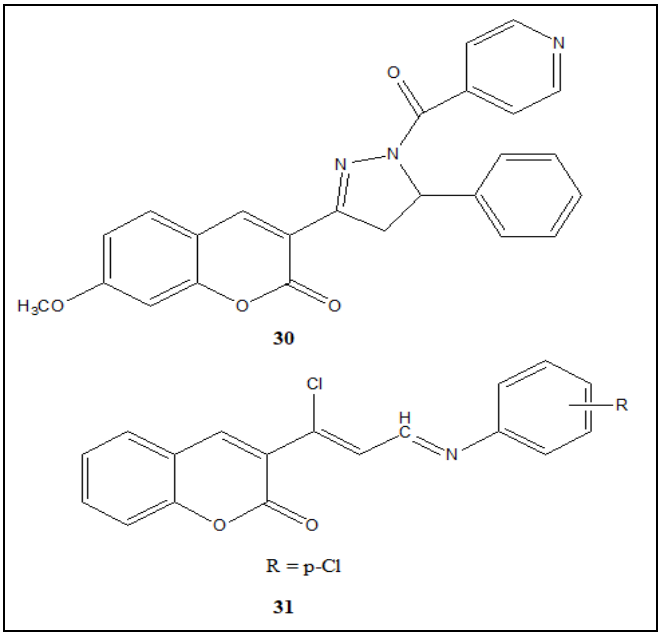

FIG. 7: THE ANTI-TUBERCULAR POTENTIAL OF COUMARIN ANALOGS

As an Anti-inflammatory and Analgesic agent: Human beings are suffering due to various inflammatory diseases. The drugs (commercial) are not always effective and are also associated with major adverse effects [50] (Alshibl Hanan M *et al.* 2020). Anti-inflammatory agents are popularly used to treat and prevent inflammation. The anti-inflammatory drugs inhibit the prostaglandin synthesis at the site of injury [51] (L. V Ganji *et al.* 2019). Compound (32 and 33), inventor: Helmy M. Sakr *et al.* 2021, Activity: Significant, Percentage increase in latency time: 286.7 and 255.6%, 100 mg/kg, which was compared to Indomethacin (percentage increase in latency time: 91 %), SAR: The methoxy group & pyrimidine scaffold may play a key role in the enhanced activity [52].

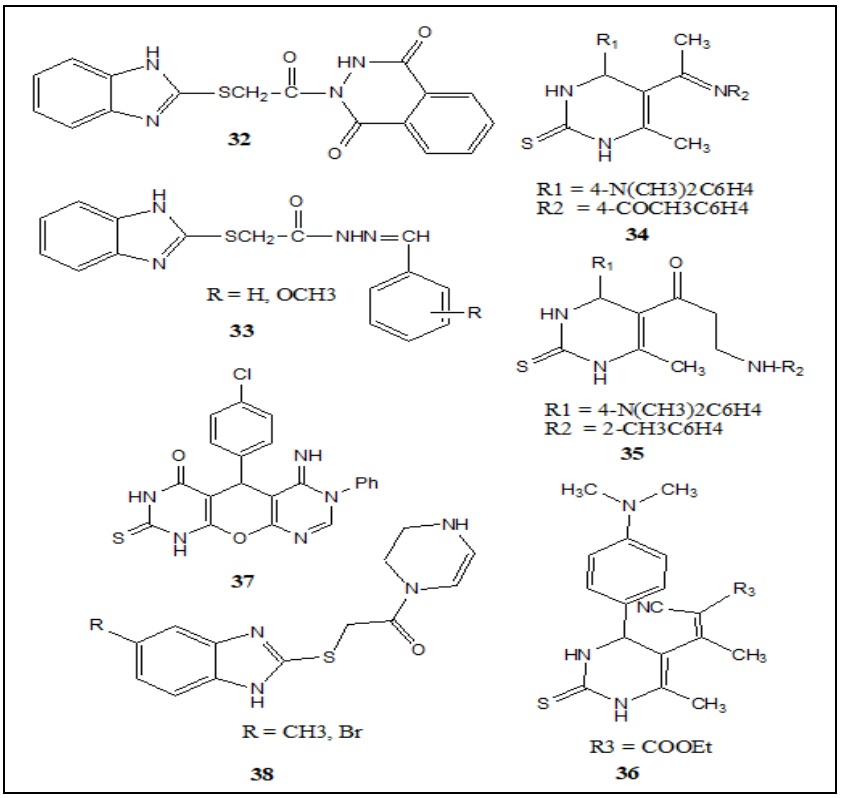

FIG. 8: THE ANTI-INFLAMMATORY & ANALGESIC POTENTIAL OF PYRIMIDINE, BENZIMIDAZOLE AND COUMARIN ANALOGS

Compound (34, 35 & 36), Inventor: N M Ahmed *et al.* 2020, Activity: Significant (61-86%), Standard: Ibuprofen, 69% at 1 hr interval, 22-74%, SAR: The thieno-pyrimidine moiety may be responsible for the observed high potency [53] **Fig. 8.** Compound (37), inventor: Mohamed H. M Abd El-Azim *et al.* 2020, Activity: Remarkable, Cox-1 IC_{50} (µm) = 13.13 ± 0.15m and Cox-2 IC_{50} (µm), 0.04 ± 0.02) compared with standard (0.04 ± 0.01, 3.34 ± 0.12, and 6.90 ± 0.26). SAR: Chloro group and thino-pyrimidine moiety existence may be responsible for the enhanced activity [54].

Compound (38), inventor: L. V Ganji *et al.* 2019, Activity: Significant, (% inhibition of paw volume: 66.59 & 71.99 %), standard: Diclofenac Sodium (% inhibition of paw volume: 36.72 %), SAR: The enhanced activity may be due to substitution at 5(6) with -Br and -CH_3 [55]. Compound (39), inventor: Chavan Rakesh *et al.* 2018, Activity: Good, Inhibition: 53.65% and 67.27% compared with standard (5.50%), SAR: Observed activity may be the presence of methoxy and hydroxyl groups on the heterocyclic skeleton [56]. Compound (40), inventor: Karam Ahmed *et al.* 2018, Activity: Good, (%inhibition): 2.38±0.08, 3.18±0.08, 2.43±0.03, 125.1±1.68 and 97.56±0.55 & 0.82±0.02, 0.84±0.01, 29.34±2.97, 32.08±2.05), SAR: The coumarin and 4-methoxyphenylpyridine moiety presence may be observed high potency [57].

Compound (41), inventor: Siham Lahsani *et al.* 2018, Activity: satisfactory, (RBC= 0.179 ± 0.01775, 101.6216 ± 0.0005) compared with standard (0.132 ± 0.002251, 102.851 ± 0.00076). SAR: Thiazolo-pyrimidine scaffold existence observed enhanced activity [58].

Compound (42), inventor: Ritchu Sethi *et al.* 2018, Activity: Significant, Percentage (%) reduction in edema at (4^{th} hr) 66.66±2.45, 100 mg/kg), Standard: Diclofenac Sodium, percentage (%) reduction in edema at (4^{th} hr) 76.25±2.75). SAR: The existence of the chloromethyl group on the benzimidazole scaffold may play a key role in the high potency [59] **Fig. 9.**

As an Anti-malarial agent: Malaria causes a severe threat to humankind caused by Anopheles mosquito [60] (Mziyanda Mbaba *et al.* 2021). Compound (43), inventor: Lorena Coronado *et al.* 2021, Activity: Potent, *P. falciparum*, CC50/IC50 = 675. SAR: The methoxy group's existence may be observed to enhance activity [61].

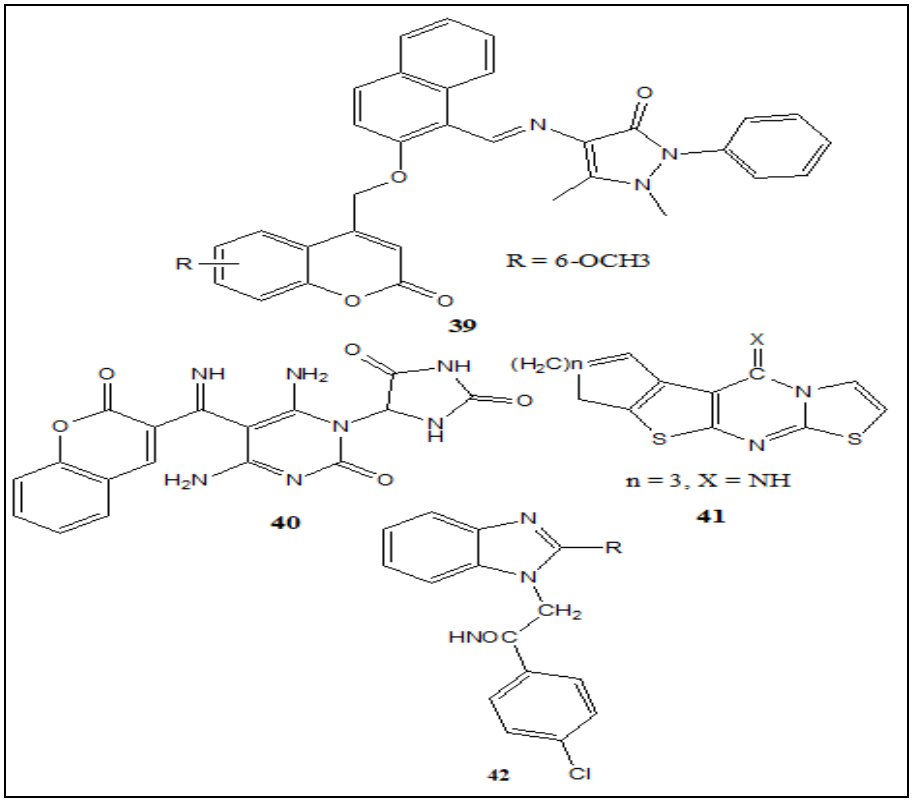

FIG. 9: THE ANTI-INFLAMMATORY & ANALGESIC POTENTIAL OF PYRIMIDINE, BENZIMIDAZOLE AND COUMARIN ANALOGS

Compound (44), inventor: Neha Batra *et al.* 2020, Activity: Potent, *P. falciparum* (3D7) IC50 = 3.64 µM, SAR: The sulfonamide group existence observed the enhanced activity [62] **Fig. 10.**

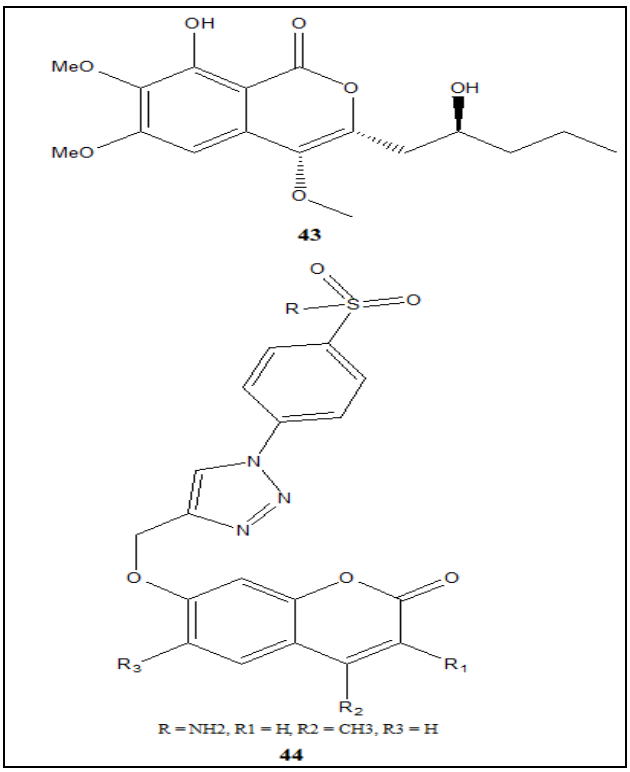

FIG. 10: THE ANTI-MALARIAL POTENTIAL OF COUMARIN ANALOGS

As an anti-HIV agent: a major percentage of humankind suffers from AIDS caused by HIV-1. The enhanced treatment procedure with potential antiretroviral therapies has resulted in a remarkable increase in the survival rate.

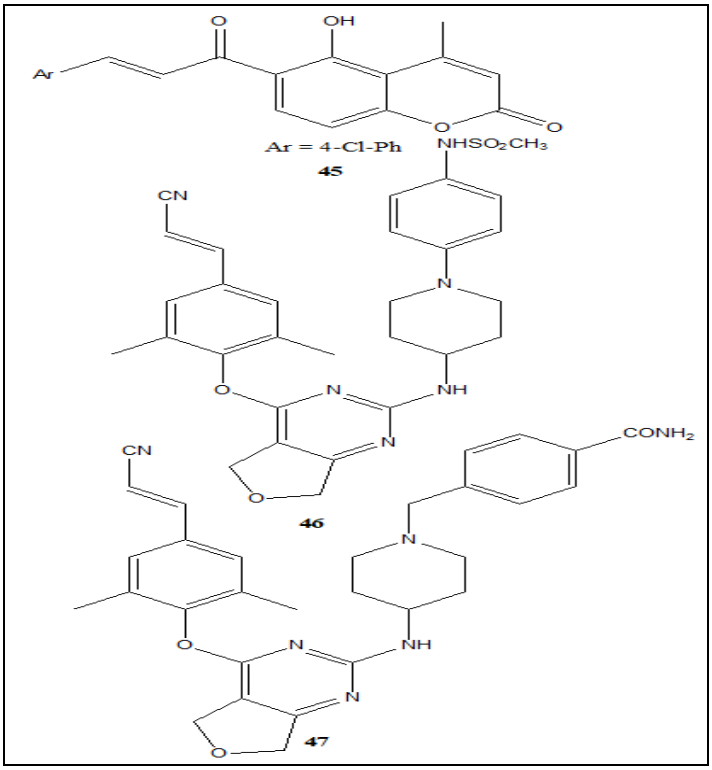

FIG. 11: ANTI-HIV POTENTIAL OF PYRIMIDINE AND COUMARIN ANALOGS

Compound (45), inventor: Srivastav V. K. *et al.* 2018, Activity: Good, IC 50: 4.7 µM against the T cell line (C8166). SAR: The phenyl ring bearing chloro group may be responsible for activity [63].

Compound (46 and 47), inventor: Dongwei Kang *et al.* 2022, Activity: Superior potency, EC50 = 5.79-28.3 nM and 2.85-18.0 nM compared with standard: etravirine & rilpivirine, SAR: The existence of the -CN, -$CONH_2$ group, and pyrimidine skeleton may be responsible for the activity [64] **Fig. 11.**

As an Anti-oxidant agent: Antioxidants are the drugs that will help the hosts against injurious factors [24]. Oxidative stress can be prevented by active, novel antioxidants [65]. Therefore, there is a need to synthesize novel active analogs with free radical scavenging properties.

Compound (48), inventor: Esvet Akbas *et al.* 2019, Activity: satisfactory, IC_{50}: 155.80 µm compared with standard (145.59 µm). SAR: Pyrimidine skeleton existence may be responsible for the activity [66].

Compound (49), inventor: Ahmed A. Hadi *et al.* 2020, Activity: Good, Inhibition: 82%, Standard: Inhibition: 94%, SAR: The substituted naphthalene and pyrimidine scaffold skeleton may be responsible for the enhanced activity [67].

Compound (50 and 51), inventor: Hatem A. Abuelizz *et al.* 2019, Activity: Good, FRAP: 973 & 1143 µmol compared with standard. SAR: sulfur group and pyrimidine scaffold presence may be observed to enhance activity [68].

Compound (52), inventor: Bhadraiah U. K *et al.* 2021, Activity: Strong, IC_{50}: 2.50±0.65 µg/ml compared with standard (5.35±0.68 µg/ml). SAR: Substituted pyrimidine skeletons with -Cl and -OCH_3 groups may be responsible for the activity [69] **Fig. 12.** Compound (53 and 54), inventor: Abrar A. Bayazeed *et al.* 2020, Activity: Good, Inhibition: 86.07% and 85.29% compared with standard (88.23%). SAR: The substituted pyran moiety with the acetyl and benzoyl groups may be responsible for the activity [70]. Compound (55), Inventor: Maria A. Argirova *et al.* 2021, Activity: Satisfactory, Percentage of activity: 40-50%, SAR: The existence of the hydroxyl group on the phenyl moiety may be responsible for the enhanced activity [71].

Compound (56 and 57), inventor: Muhmmad Taha *et al.* 2020, Activity: Good, $IC_{50} = 29.14 \pm 0.47$ µM, 22.42 ± 0.26 µM compared with standard (29.20 ± 1.25 µM). SAR: Hydroxyl group-bearing aromatic compounds may have high potency [72].

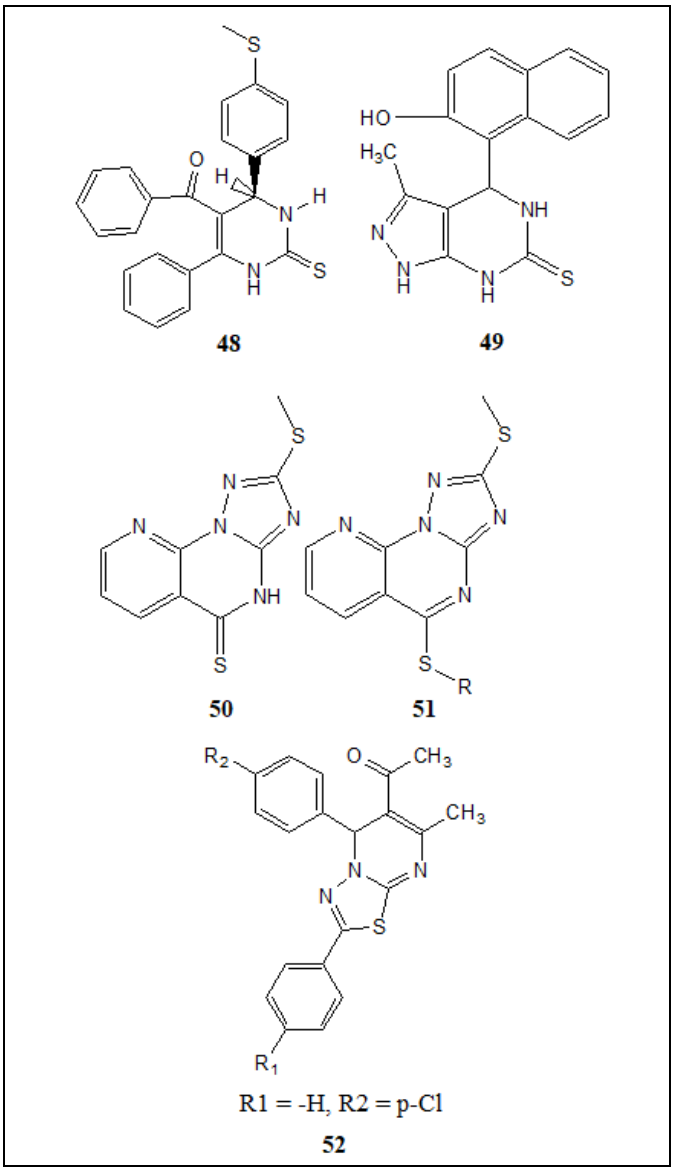

FIG. 12: ANTI-OXIDANT POTENTIAL OF PYRIMIDINE ANALOGS

Compound (58 and 59), inventor: Vineet Kumar Singh *et al.* 2020, Activity: satisfactory, percentage scavenging of DPPH radical: 40-100 µg/ml, 48.02-85.03%, and 53.02–88.53%, Standard: ascorbic acid (percentage scavenging of DPPH radical: 40-100 µg/ml, 64.49– 92.34%). SAR: The existence of electron-donating groups on the ring may be responsible for the enhanced activity [73] **Fig. 13.**

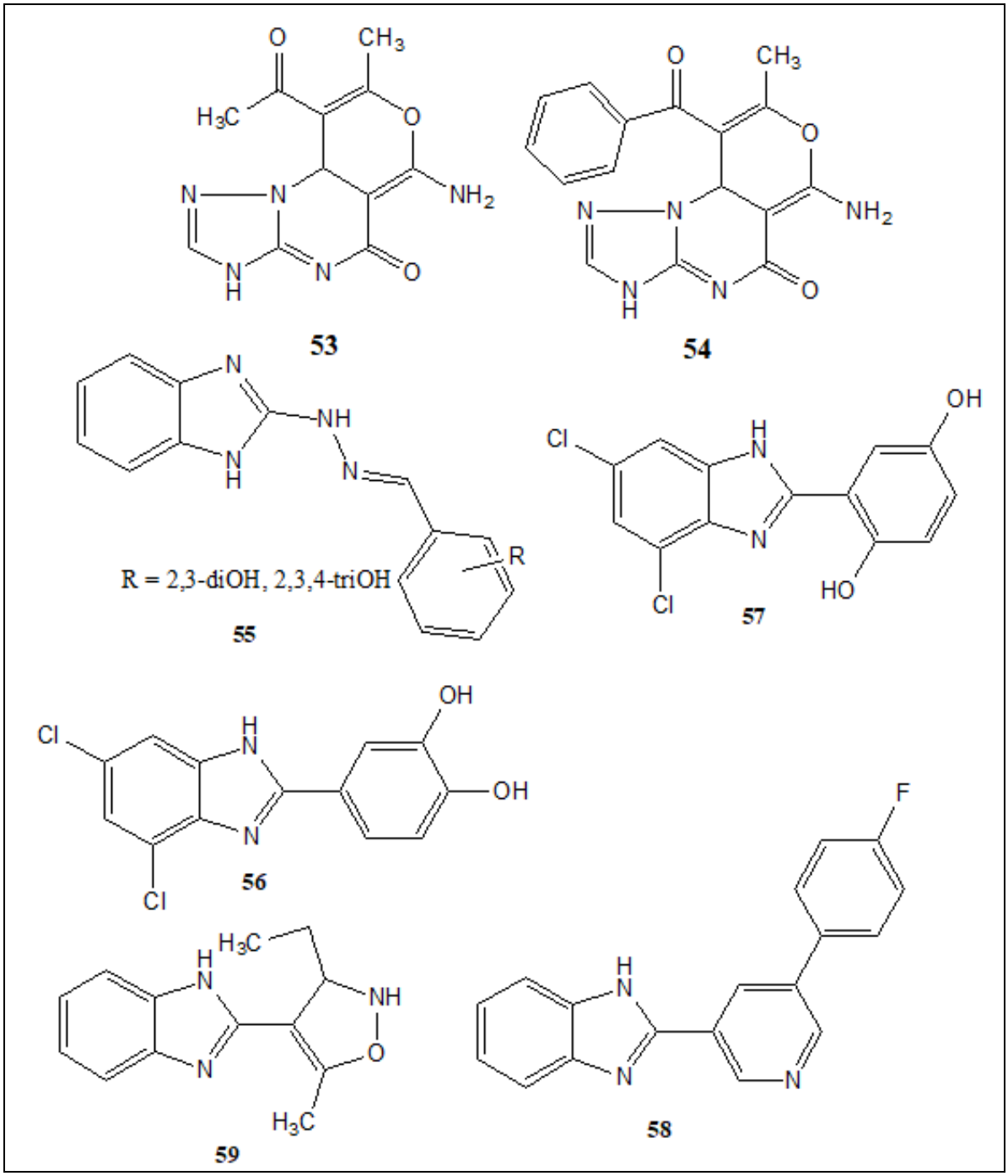

FIG. 13: ANTI-OXIDANT POTENTIAL OF PYRIMIDINE AND BENZIMIDAZOLE ANALOGS

As a Cardiac agent: The increased death rate due to hypertension is worldwide, and many people are suffering from hypertension. Treatment and prevention of cardiovascular-diseases is a big challenge.

Compound (60, 61 and 62), inventor: Nadeem Irshad *et al.* 2021, Activity: Good, 45 ± 0.5, 56 ± 0.5, 64 ± 0.4 mmHg, 373 ± 0.5 bpm and 50 ± 0.6, 61 ± 0.6, 60 ± 0.3 mmHg, 381 ± 0.5 bpm and 51 ± 0.4, 43 ± 0.5, 67 ± 0.5 mmHg, 378 ± 0.4 bpm compared with standard (43 ± 0.5, 39 ± 0.4, 59 ± 0.4 mmHg and 381 ± 0.6 bpm). SAR: -Cl and -OH group-bearing pyrimidine scaffold existence may be responsible for the activity [74] **Fig. 14.**

As an Anti-diabetic agent: Major humankind suffers from diabetes mellitus, and the treatment and prevention of the disease is a challenging task, and soon it may rise to five hundred seventy eight million (Approximate estimation) by 2030 (Suri Babu Patchipala *et al*. 2022) [75].

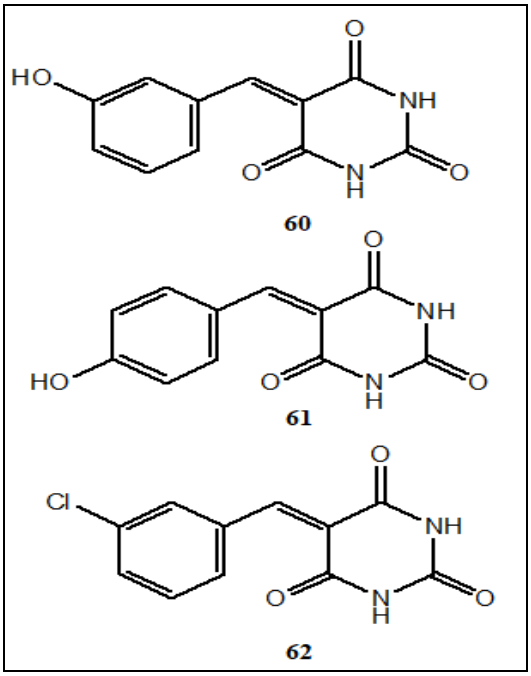

FIG. 14: CARDIAC POTENTIAL OF PYRIMIDINE ANALOGS

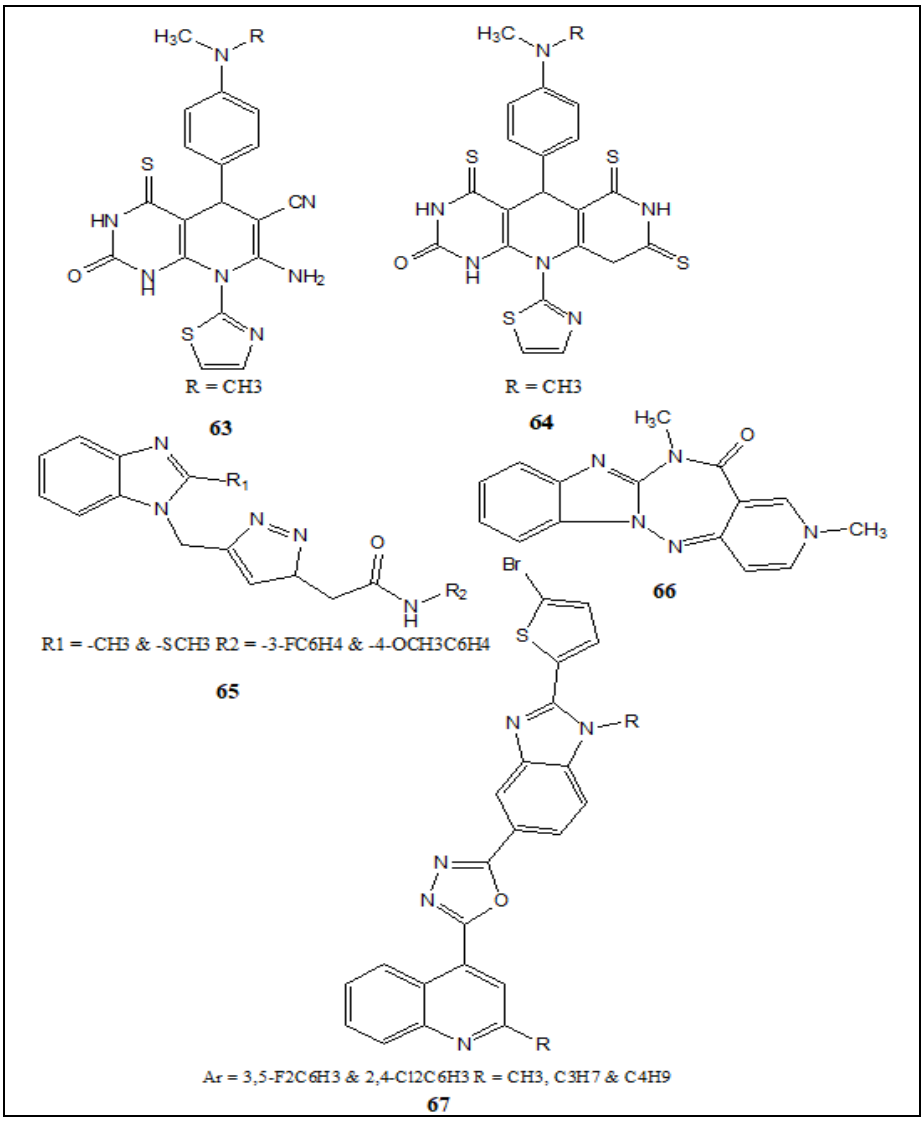

FIG. 15: ANTI-DIABETIC POTENTIAL OF PYRIMIDINE AND BENZIMIDAZOLE ANALOGS

Compound (63 and 64), inventor: Bassyouni F *et al.* 2021. Activity: Good, Glucose Level: 122.4 ± 3.2, mg/dL and 116.5 ± 7.2, α-amylase Level: 117.6 ± 1.51 and 78.41 ± 1.04 U/L. SAR: The observed activity may be due to the presence of pyridine and thino-pyrimidine scaffolds [76].

Compound (65), inventor: Laxmi Deswal *et al.* 2020. Activity: Good, IC50: 0.0410-0.0916 µmol/ml & 0.0146-0.0732 µmol/ml, α-amylase & α-glucosidase. SAR: The enhanced activity may be due to the presence of the -F, $-CH_3$, $-SCH_3$ and $-OCH_3$ groups [77].

Compound (66), inventor: El Bakri *et al.* 2018. Activity: Good, α-Amylase, α-Glucosidase, and β-Galactosidase: (343.83± µM), standard: Acarbose (618.87± 31.76 µM). SAR: The enhanced activity may be due to the presence of methyl and benzimidazole scaffolds [78].

Compound (67), inventor: S. Shashidhar *et al.* 2018. Activity: Good, IC 50 = 0.66 ± 0.05–3.79 ± 0.46 µg/L. SAR: The observed activity may be due to the presence of substituted quinolinyl oxadiazole and the benzimidazole moiety [79] **Fig. 15.**

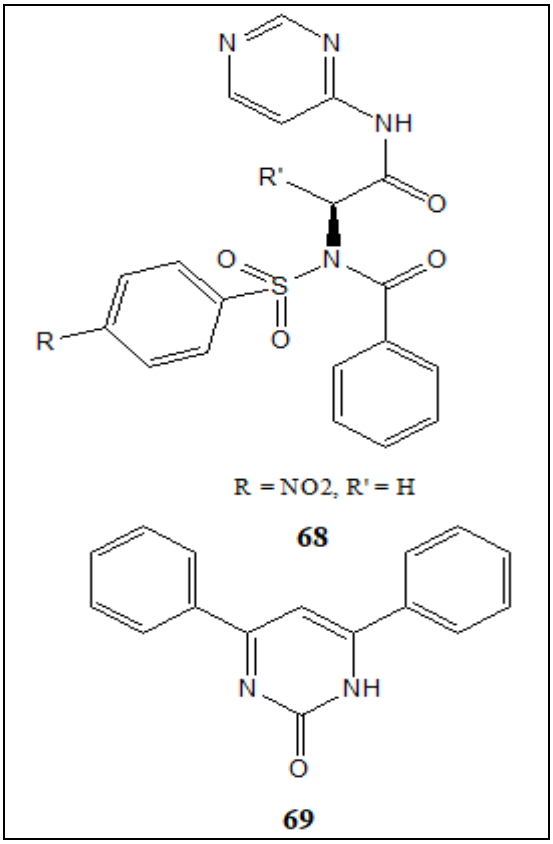

FIG. 16: ANTHELMINTIC POTENTIAL OF PYRIMIDINE ANALOGS

As an Anthelmintic agent: The anthelmintic agent kills the parasitic worms by preventing the host, and the treatment and prevention of this disease are the challenging.

Compound (68), inventor: David I Ugwu *et al.* 2018. Activity: Satisfactory, Paralyzing time: 37, 26 & 19, min compared with standard (28, 20 & 10, min). SAR: The existence of the pyrimidine and nitrophenyl skeletons may be responsible for the activity [80].

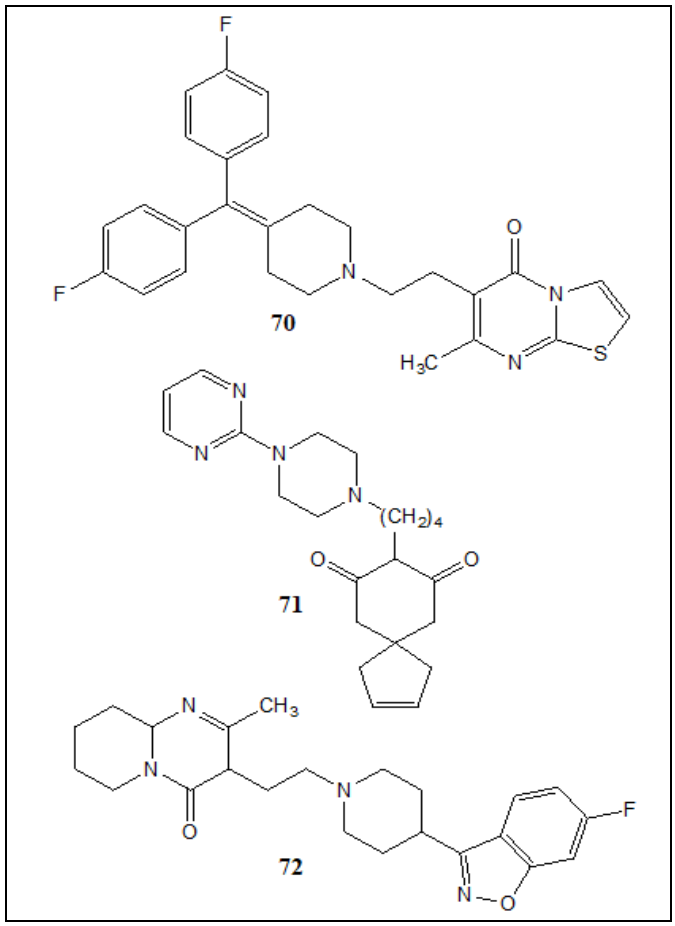

FIG. 17: ANXIOLYTIC POTENTIAL OF PYRIMIDINE ANALOGS

Compound (69), inventor: Sudha Rani K *et al.* 2018. Activity: High potential, paralysis and death time: 7 ± 0.763 min and 11 ± 0.611 min compared with standard (2.51± 1.1 min and 18 ± 2.1 min). SAR: Phenyl-pyrimidine scaffold existence may be responsible for the activity [81] **Fig. 16.**

As Anxiolytic agents: Jeelan B. N *et al.* 2021 reported that some pyrimidine-bearing other heterocyles (compounds: 70, 71, and 72) act as anxiolytic agents [82] **Fig. 17.**

As an Anti-ulcer agent: Khan Farhan *et al.* 2021. Prepared novel benzimidazole derivatives and tested for antiulcer and H^+K^+ ATPase Inhibitor. Compound (73) Activity: Good, % inhibition of ulcer: 74.03, 72.87, and 75.15%, Standard: Pantoprazole, % inhibition of ulcer: 76.16%. The existence of propyl substitution on the pyrimidine scaffold may be responsible for the enhanced potency [83].

Compound (74), inventor: Abida Noor *et al.* 2017. Activity: satisfactory, % inhibition of ulcer: 83.1% at 500 µg/kg dose, Standarad: omeprazole, % inhibition of ulcer: 83.1%, SAR: The aromatic and pyrazole moiety presence may be observed to have high potency [84] **Fig. 18.**

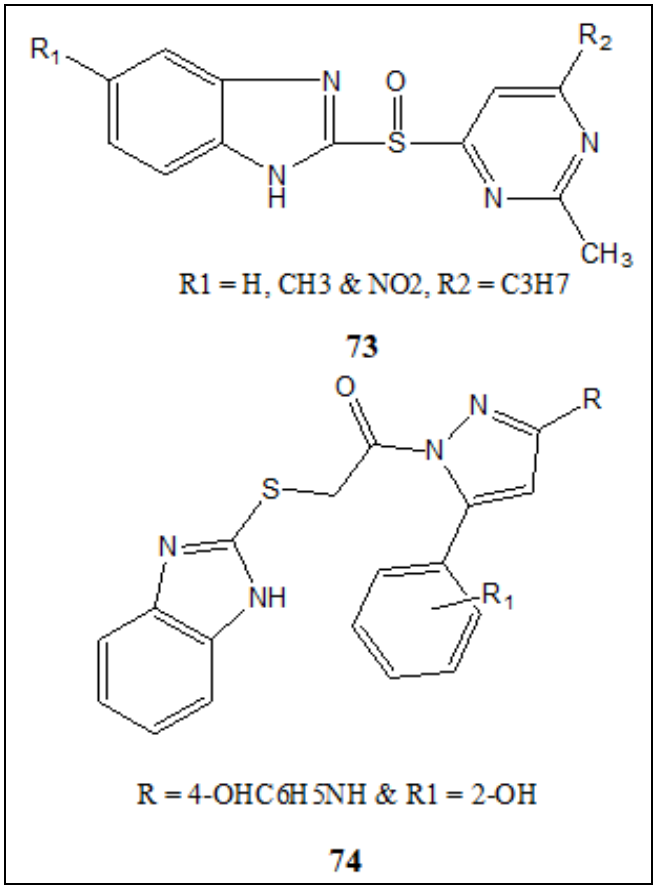

FIG. 18: ANTI-ULCER POTENTIAL OF PYRIMIDINE ANALOGS

As an Anti-viral agent: Compound (75 and 76), inventor: Francesconi V *et al.* 2020, Activity: Good, EC50: 7.0 & 2.4 µM & EC50: 25–86 µM, syncytial, influenza A, and coronavirus virus, Standard: Ribavirin, EC_{50} of 6.7 µM, SAR: The presence of thiosemicarbazone and benzimidazole scaffolds may be responsible for enhanced activity [85] **Fig. 19.**

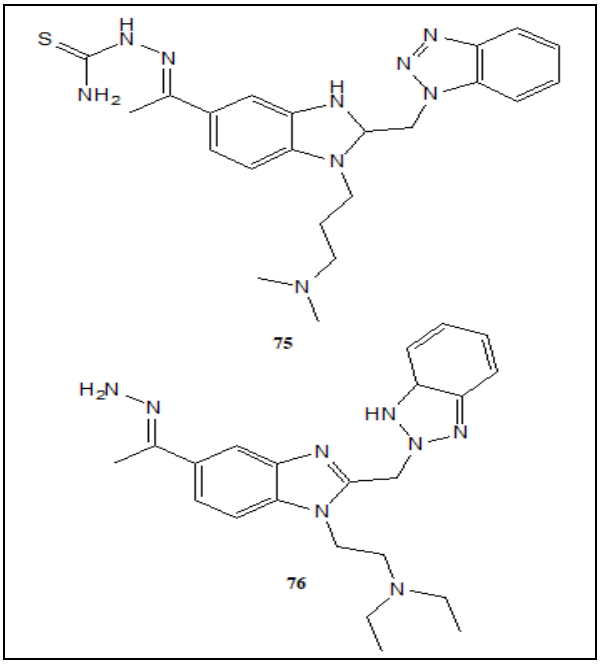

FIG. 19: AS ANTI-VIRAL POTENTIAL OF BENZIMIDAZOLE ANALOGS

As an Anti-protozoal agent: Compound (77), inventor: Andrea Bistrovic *et al.* 2018, Activity: Good, $IC_{50} = 1.1$ µM compared with the standard (4.4 µM). SAR: The presence of a *p*-methoxyphenyl moiety may be responsible for activity [86]. Compound (78 and 79), inventor: Paulina Flores-Carrillo *et al.* 2017, Activity: Good, $IC_{50} = 0.0120 \pm 0.0050$ µM and $IC_{50} = 0.3455 \pm 0.0170$ µM, *T. vaginalis* and *G. intestinalis* compared with the standard (0.0370 ± 0.0030 µM, 1.5905 ± 0.0113 µM). SAR: The presence of a methyl group on the benzimidazole nucleus may increase the activity [87] **Fig. 20.**

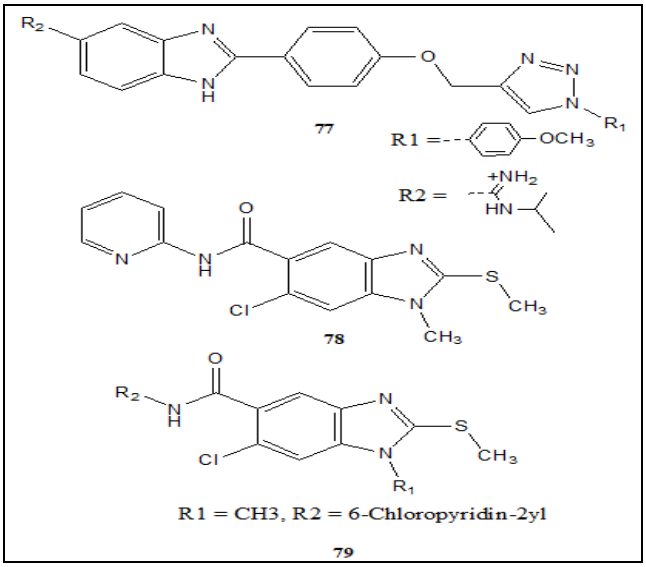

FIG. 20: AS ANTI-PROTOZOAL POTENTIAL OF BENZIMIDAZOLE ANALOGS

Commercially Available Drugs: Dinesh S. R *et al.* 2021. Reviewed the commercially available drugs of coumarin (compounds: 80, 81, 82 and 83) [88] **Fig. 21.**

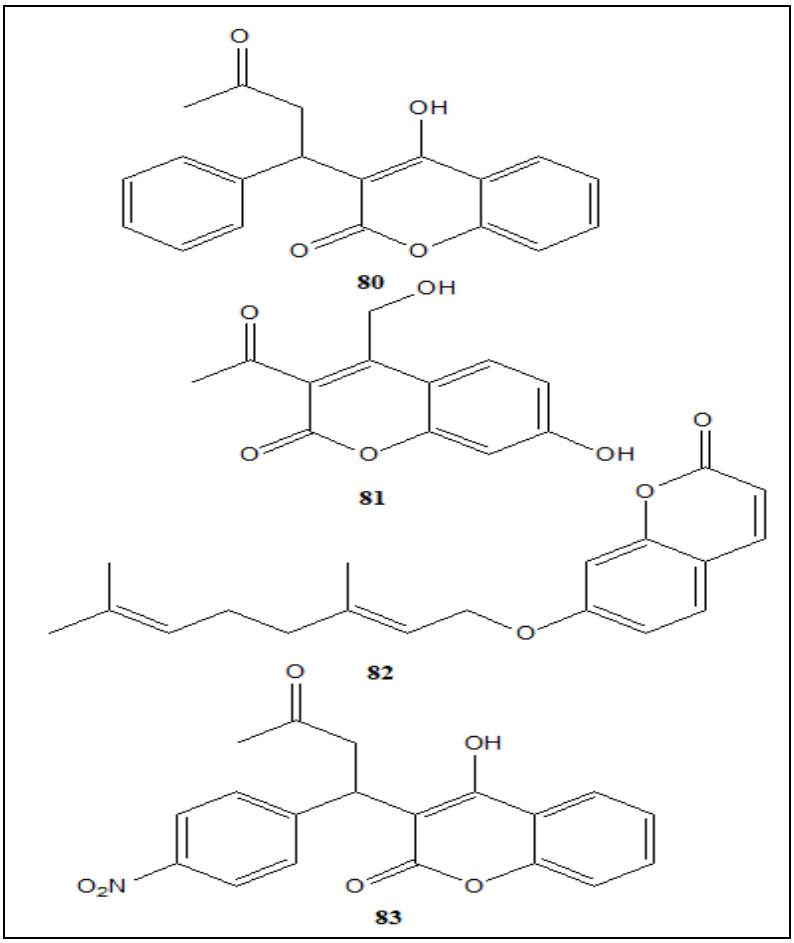

FIG. 21: COMMERCIALLY AVAILABLE COUMARIN DRUGS

Compound: 84 (Dosatinib) is used to treat chronic leukemia & lymphoblastic leukemia. Etravirine (85) and Rilpivirine (86) both meant for the treatment of HIV-1 (NNRTI) [89] **Fig. 22.**

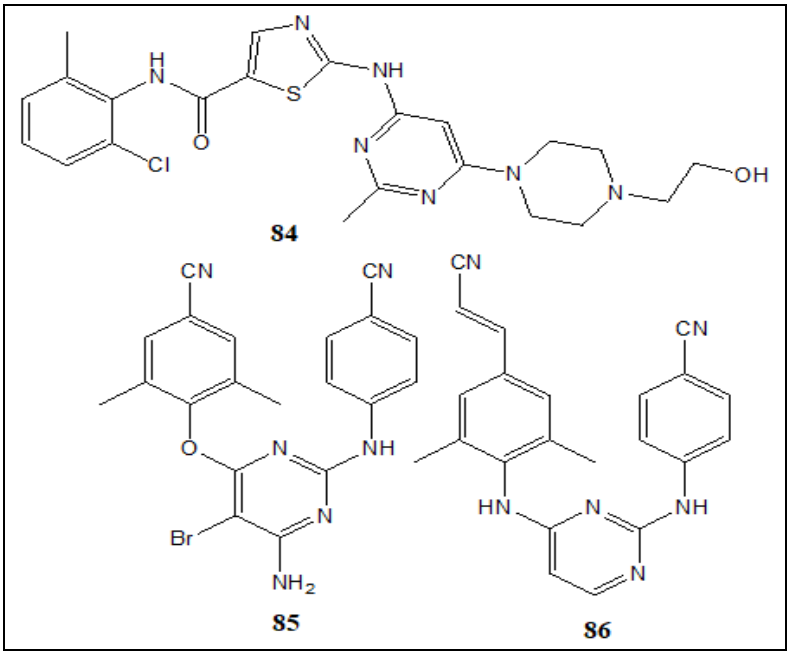

FIG. 22: COMMERCIALLY AVAILABLE PYRIMIDINE SCAFFOLD ASSOCIATED DRUGS

Veerasamy R. Roy *et al.* 2021. recently reviewed the commercially available drugs of benzimidazole analogs such as Astemizole, Albendazole, Mebendazole, Oxibedazole, Thiabendazole, Oxfendazole, Pimobenden & Enviroxime, Irtemazole, Omeprazole, Lansoprazole, Pantoprazole Rabeprazole, candesartan, cilexitil and telmisartan as well as the various targets for benzimidazole, are shown in [90] **Fig. 23.** Various synthetic and biological activities of novel heterocylic compounds and recent updates of novel pyrimidine, coumarin, and benzimidazole analogs may be useful for the new researcher in designing new active drugs [91-102].

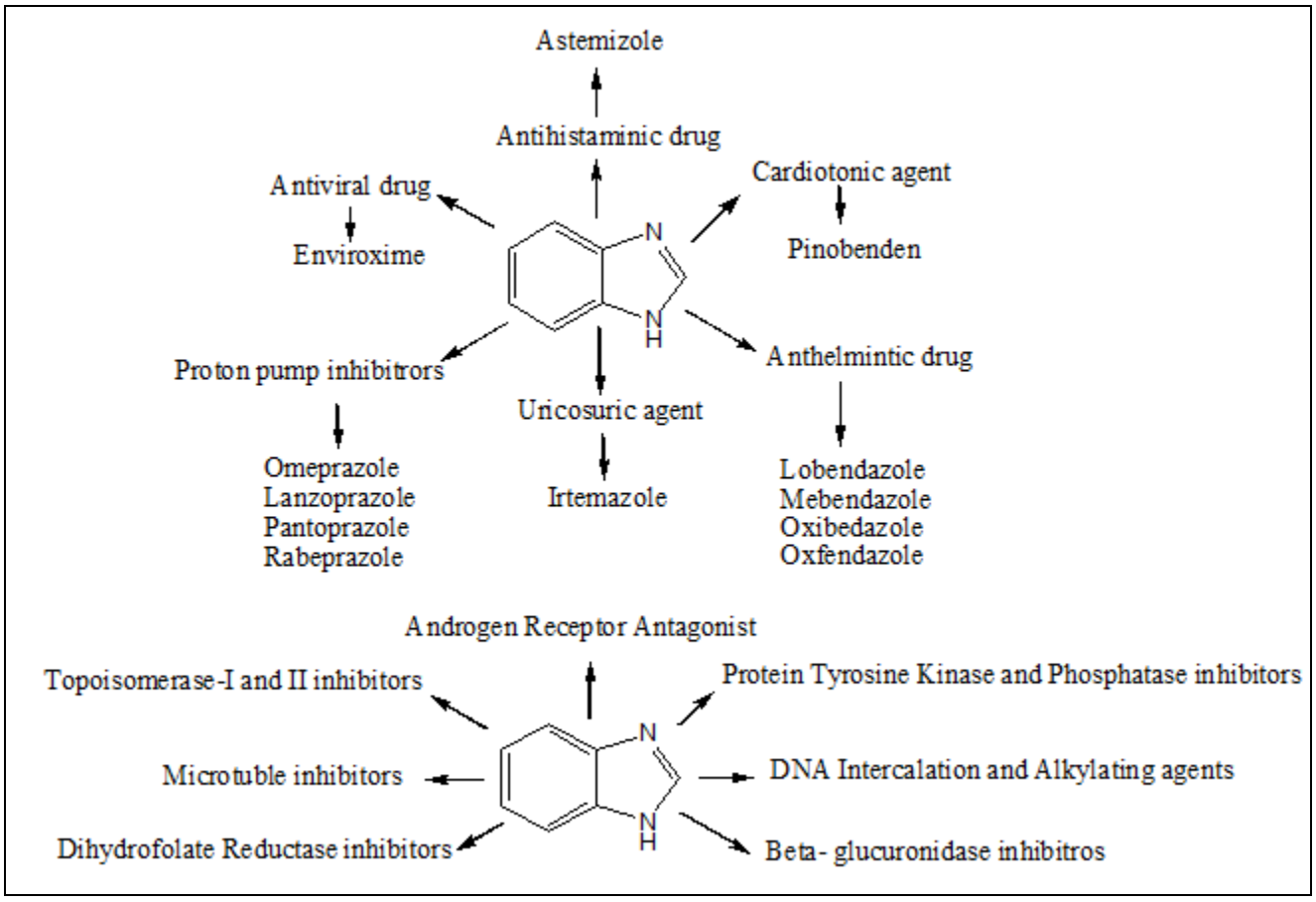

FIG. 23: BENZIMIDAZOLE SCAFFOLD BEARING CLINICALLY APPROVED DRUGS & POSSIBLE BIOLOGICAL TARGETS

CONCLUSION: All three PCB heterocyclic compounds are very popular for their versatile medicinal significance in the field of medicine, such as anti-microbial, inflammatory, cancer, oxidant, diabetic, viral, ulcer, and HIV, and as an anti-protozoal agent. Many novel PCB analogs are already being used commercially as medicines. In this manuscript, the activity relationship and its recent medicinal significance are mainly highlighted. Further the observed potency may be due to the existence of amine, fluorine, bromine, methyl, pyrimidine ring associated with fluro group, substituted pyridine, carboxylic acid group, hydroxyl group, chloro-phenyl ring, electronic environment presence, fluorophenyl, fluorobezamide moiety, bromo, methoxy group, chloro substituted phenyl pyrazoline, phenyl ring, indole, chlorine, methyl & sulfur groups on the aromatic ring, amino-pyrimidine scaffold, hydrazone group, ethanolamine, 4-methylbezylidene, pyrazole ring, thieno-pyrimidine moiety, 4-methoxyphenylpyridine moiety, thiazolo-pyrimidine scaffold, chloromethyl group,, sulfonamide group, para chloro substitution on the phenyl ring, CN, $CONH_2$ group, hydroxyl groups on the phenyl moiety, hydroxyl group bearing aromatic compounds, thino-pyrimidine scaffold, quinolinyl oxadiazole, nitrophenyl, *p*-methoxyphenyl moiety, thiosemicarbazone, pyrimidine, benzimidazole coumarin scaffold. Finally, this review may be helpful for designing and developing new active molecules for the new researcher.

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