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Review article

Synthetic approaches and pharmaceutical applications of chloro-containing molecules for drug discovery: A critical review

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ABSTRACT

At present more than 250 FDA approved chlorine containing drugs were available in the market and many pharmaceutically important drug candidates in pre-clinical trials. Thus, it is quite obvious to expect that in coming decades there will be an even greater number of new chlorine-containing pharmaceuticals in market. Chlorinated compounds represent the family of compounds promising for use in medicinal chemistry. This review describes the recent advances in the synthesis of chlorine containing heterocyclic compounds as diverse biological agents and drugs in the pharmaceutical industries for the inspiration of the discovery and development of more potent and effective chlorinated drugs against numerous death-causing diseases.

Contents

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1. Introduction

1.1. Chlorine in pharmaceuticals

Chlorine is one of the most vital industrial chemicals, which was utilized by various end-users of industries. And it has been tremendous sprite in pharmaceuticals as the major key ingredients in drugs to treat many diseases such as meningitis, cholera, plague, typhoid, bacterial skin infections, respiratory and nervous system problems etc., as per the Business Wire and A Berkshire Hathaway Company reports. The therapeutics and percentage of sales were presented to address the importance of chlorine chemistry in pharmaceutical drugs as what have been reported by HIS Applied Economics, Canada (Table 1**)**. In United States, more than 88% of the pharmaceuticals were depended on chlorine chemistry including the drugs those have been used for the treatment of stomach ulcer, cancer, anemia, high cholesterol, depression, and epilepsy. As per statistics, the benefit from the chlorine chemistry was estimated to $450 billion per year. The net gain of the pharmaceuticals in the U.S. and Canada using chlorine is as high as $640 billion per year from the health care system reported by HIS Applied Economics, Canada [1]. According to the Business Wire and A Berkshire Hathaway Company reports, the estimating chlorine market for the period of 2018–2023 is approximately 4.8%. Some of the drugs presented with chemical structures containing chlorine (number of groups are different). One of the studies detailed that, 163 compounds among 233 approved drugs; nearly 73% of them contained single chlorine atom [2]. Of which, 23% of them possessed by two chlorines, 2.6% of them possessed by three chlorine atoms, 1.4% of them possessed by four chlorines, and 2.5% of them possessed by six chlorines in the compounds. Surprisingly, none of the drugs had been approved with five chlorine atoms yet. Also, among them, 98% were monosubstituted (CCl), only four were disubstituted (CCl_2), and none of the approved drugs has trisubstituted (CCl_3) groups. This interesting research gap suggests that, chlorine will further continue its industry ruler role to provide and benefit consumers of the pharmaceuticals in the future [1]. To improve the quality and advantage of chlorinated chemistry, scientists need to an advance understanding of the chlorine in the view of medicinal chemistry in the future (see Table 2).

1.2. How important is the chlorine atom to improve the biological properties?

The presence of chlorine atom played a pivotal role in a number of natural products such as the antibiotics clindamycin [3], vancomycin [4], chloramphenicol [5], and griseofulvin. Over the course of time it has been found empirically that the introduction of a chlorine atom into one or more specific positions of a biologically active molecule may substantially improve the intrinsic biological activity [6]. The properties of the carbon-chlorine bond (C-Cl) in organochlorines have been analysed by Henschler [4,5]. However, in the low-molecular-weight chemicals investigated in that analysis, the electrophilic reactivity of the carbon centre adjacent to the chlorine atom, which facilitates displacement of chlorine by (bio) nucleophiles, determines the observed biological properties [4,5]. The increase of lipophilicity of the whole molecule by a chlorine substituent leads to a higher partitioning of a chlorinated compound into the lipophilic phase of a cell membrane or lipophilic domains of a protein. This causes a higher local concentration of the compound near a biological target site, but, not necessarily a higher biological activity. The most important effect of a non-reactive chlorine atom in the biological activity of many compounds comes from chlorine as a substituent on an aromatic, heteroaromatic or olefinic moiety.

The properties mentioned above will give rise steric and/or electronic effects of the chlorine substituents and lead to local electronic attraction or repulsion or to steric interference with any amino acid residue surrounding the position of the chlorine atom in the binding pocket of the protein. This in turn may cause a tighter interaction or a loosening of the contacts to the amino acids close to the chlorine or in other parts of the active molecule. Either one may affect the function of the target protein and cause an increase or decrease of biological activity. In other cases however a chlorine substituent may have no specific effect on the primary biological properties of the molecule to which it is attached [7]. Chlorinated compounds are not necessarily toxic or dangerous. Highly reactive chemicals or polychlorinated compounds cannot be compared with regard to toxicological properties with unreactive compounds having a low degree of chlorination. The chlorine atom, as one of many possible substituents used in synthetic organic chemistry, will remain in the future one of the important tools for probing structure-activity relationships in life science research and as a molecular component in commercialized compounds, in order to provide safer, more selective and more environmentally compatible products with higher activity for medicine and agriculture [7].

The application of chlorine in medicinal chemistry is one of the fastest growing hot areas in chemistry as its fascinating and instructive role of halogens distribution in the field of drug development. Surprisingly, among four halogens, chlorine (Cl) is the one which is more frequently found in drugs than others, even fluorine (F). Interestingly, in drugs, the elements of sulphur, chlorine, and fluorine were placed as 5–7 respectively after C, H, O, and N. The remaining phosphorous (P), bromine (Br), and iodine (I) are the rest of the top 10 elements in approved drugs, and remarkably, the Cl and F are the heavy hitters ($Cl > F \gg Br > I$) [8–10].

Table 1
The chlorine based drugs against categories of the diseases.

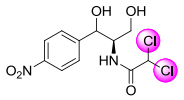
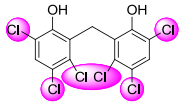
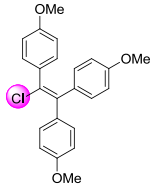
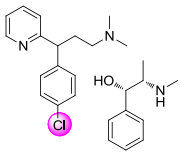
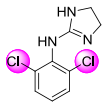
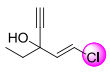
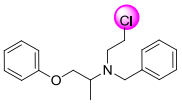
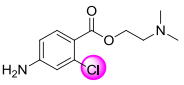
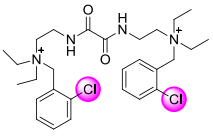
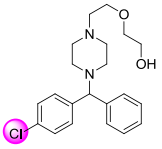
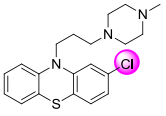
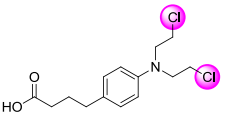
Therapeutic category	Sales in billons
Cardiovascular disease	$4.7
Central nervous system	$4.9
Alimentary-metabolism	$26.5
Respiratory	$19.4
Anti-infectives	$9.5
Musculo-skeleta	$19.8
Genito-urinary	$2.7
Cytostatics	$12.7
Blood agents	$10.4
Hormones	$13.6
Antiretrovirals and miscellaneous	$8.3
Total, all categories	**$168.5**

2. Synthesis and biological applications of chlorinated analogues

2.1. Synthesis of chlorine containing antimicrobial agents

The problem of antibiotic resistance among pathogenic bacteria is as old as antibiotics itself [11]. The antibiotic resistance which accelerated by the use and misuse of antimicrobial drugs has been a major universal challenge for public health. Remarkable increase of human pathogenic bacteria was observed from the past decades due to their resistance to one or more antibiotics. A number of infections caused by resistant organisms not succeed at responding to the conventional treatment and even the last choice antibiotics were also lost their power [12]. After all, loss of effectiveness and resistance power of old antibiotics against new and upcoming bacterial pathogens prompt us to develop novel, less toxic and highly effective antimicrobial agents with diverse structures to

Table 2
List out the FDA approved chlorine containing drugs in market (1949–2012).

Sl.No	Drug Name	Structure	Diseases	Approved Year
1	Chloromycetin		AIN/DER/GUS/SEN	1949
2	pHisoHex		Dermatological	1949
3	Tace		Genito-Urinary and Sex hormone	1950
4	Chloro-Trimeton		NES/RES	1950
5	Clonidine		NER/CAR/SEN	1950
6	Ethchlorvynol		Nervous System	1950
7	Phenoxybenzamine		Cardiovascular	1953
8	Nesacaine		Nervous System	1955
9	Ambenonium		Nervous System	1956
10	Halothane		Nervous System	1956
11	Atarax		Nervous System	1956
12	Compazine		Nervous System	1956
13	Leukeran		Oncological	1957

(*continued on next page*)

Table 2 (*continued*)

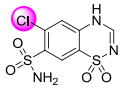
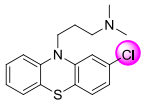
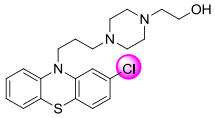
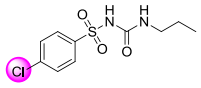
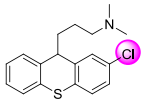
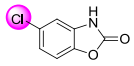
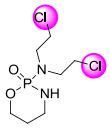
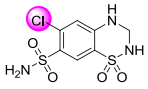
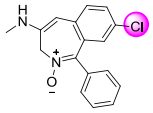
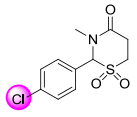
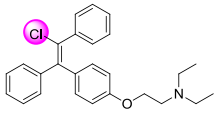
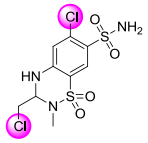
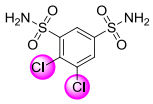
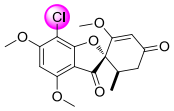
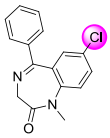
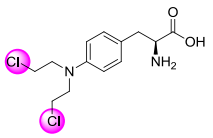
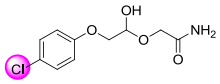
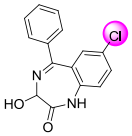
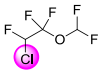
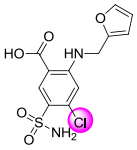
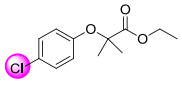
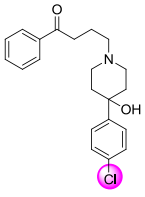
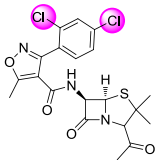
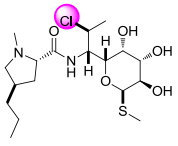
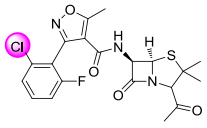
Sl.No	Drug Name	Structure	Diseases	Approved Year
14	Diuril		Cardiovascular	1957
15	Thorazine		Nervous System	1957
16	Trilafon		Nervous System	1957
17	Diabinese		Alimentary tract and metabolism	1958
18	Chlorprothixene		Nervous System	1958
19	Parafon		Musculo-skeletal	1958
20	Cytoxan		Oncological	1959
21	Hydrochlorothiazide		CAR/END	1959
22	Librium		Nervous System	1960
23	Trancopal		Musculo-skeletal	1960
24	Clomifene		Genito-Urinary and Sex hormone	1960
25	Clomipramine		NER/END	1960
26	Methoxyflurane		Nervous System	1960
27	Enduron		Cardiovascular	1960
28	Daranide		Sensory organ	1960

Table 2 (*continued*)

Sl.No	Drug Name	Structure	Diseases	Approved Year
29	Grisactin		Dermatological	1962
30	Valium		Nervous System	1963
31	Alkeran		Oncological	1964
32	Maolate		Dermatological	1965
33	Serax		Nervous System	1965
34	Enflurane		Nervous System	1966
35	Lasix		Cardiovascular	1966
36	Atromid-S		CAR	1967
37	Haldol		Nervous System	1967
38	Pathocil		Anti-infective	1968
39	Cleocin		AIN/DER/GUS	1970
40	Floxapen		Anti-infective	1970

(*continued on next page*)

Table 2 (*continued*)

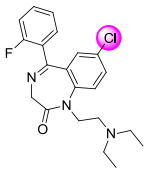
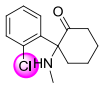
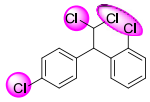
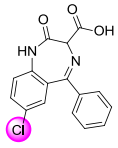
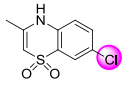
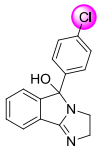
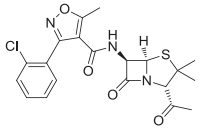
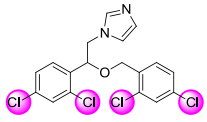
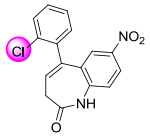
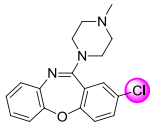
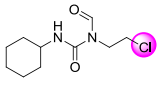
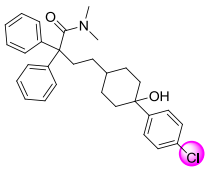
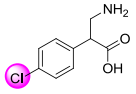
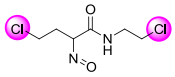
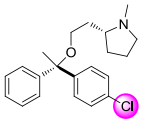
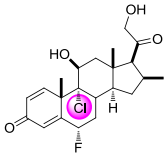
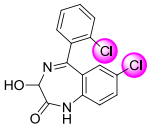
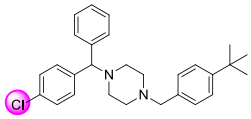
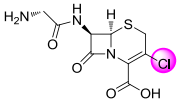
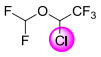
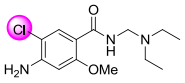
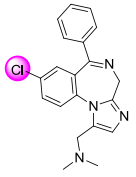
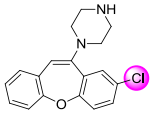
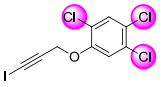
Sl.No	Drug Name	Structure	Diseases	Approved Year
41	Dalmane		Nervous System	1970
42	Ketalas		Nervous System	1970
43	Lysodren		Oncological	1970
44	Tranxene		Nervous System	1972
45	Hyperstat		Cardiovascular	1973
46	Sanorex		Alimentary tract and Metabolism	1973
47	Closapen		Anti-infective	1974
48	Monistat 7		AIN/ALM/DER/GUS	1974
49	Klonopin		Nervous system	1975
50	Lotrimin		AIN/ALM/DER/GUS	1975
51	Loxitane		Nervous system	1975
52	CeeNU		Oncological	1976

Table 2 (*continued*)

Sl.No	Drug Name	Structure	Diseases	Approved Year
53	Imodium		Alimentary tract and Metabolism	1976
54	Lioresal		Musculo-skeletal	1977
55	BiCNU		Oncological	1977
56	Tavist		RES/NER	1977
57	Cloderm		Dermatological	1977
58	Ativan		Nervous system	1977
59	Buclizine		Respiratory System	1979
60	Ceclor		Anti-infective	1979
61	Forane		Nervous system	1979
62	Reglan		Alimentary tract and Metabolism	1979
63	Adinazolam		Nervous system	1980
64	Asendin		Nervous system	1980
65	Halotex		Dermatological	1980

(*continued on next page*)

Table 2 (*continued*)

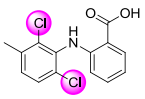
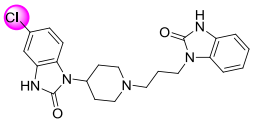
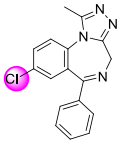
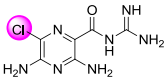
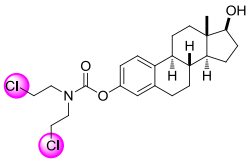
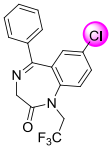
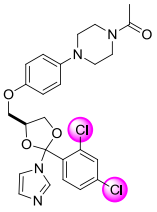
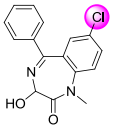
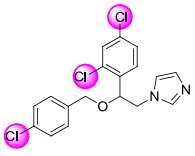
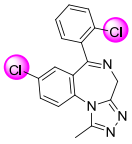
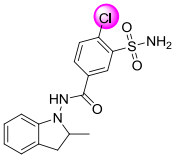
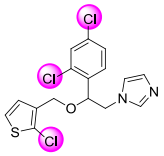
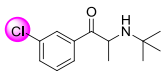
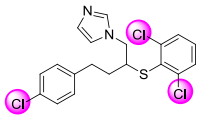
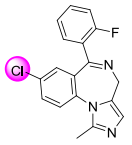
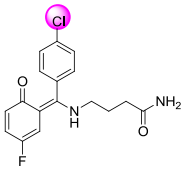
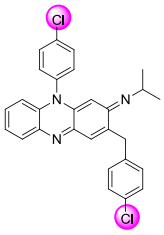
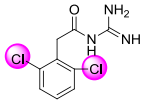
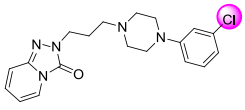
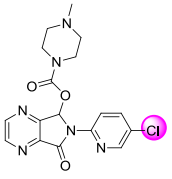
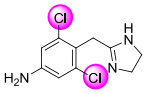
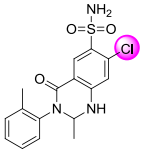
Sl.No	Drug Name	Structure	Diseases	Approved Year
66	Meclomen		Musculo-skeletal	1980
67	Domperidone		ALT/Met	1980
68	Xanax		Nervous system	1981
69	Midamor		Cardiovascular	1981
70	Emeyt		Oncological	1981
71	Paxipam		Nervous system	1981
72	Nizoral		AIN/DER/GUS	1981
73	Restoril		Nervous system	1981
74	Spectazole		DER/GUS	1982
75	Halcion		Nervous system	1982
76	Lozol		Cardiovascular	1983

Table 2 (*continued*)

Sl.No	Drug Name	Structure	Diseases	Approved Year
77	TZ-3		DER/GUS	1983
78	Wellbutrin		Nervous system	1985
79	Femstat		Genito-Urinary and Sex hormone	1985
80	Versed		Nervous system	1985
81	Progabide		Nervous system	1985
82	Lamprene		Anti-infective	1986
83	Tenex		Cardiovascular	1986
84	Trazodone		NER/END	1986
85	Zopiclone		Nervous system	1986
86	Lopidine		Sensory organ	1987
87	Mykrox		Cardiovascular	1987

(*continued on next page*)

Table 2 (*continued*)

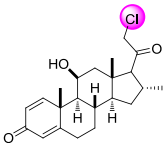
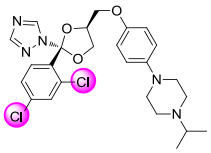
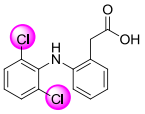
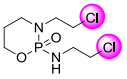
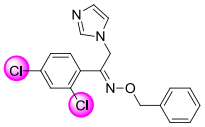
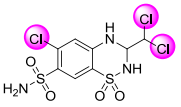
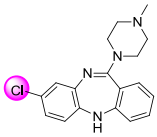
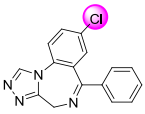
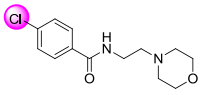
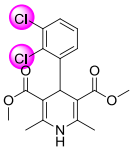
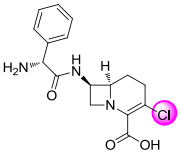
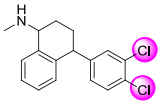
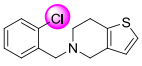
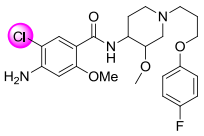
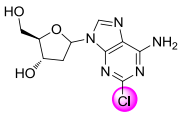
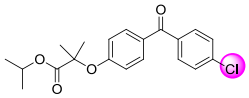
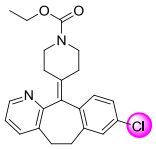
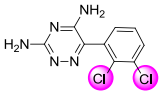
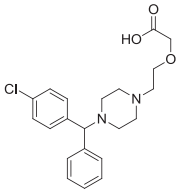
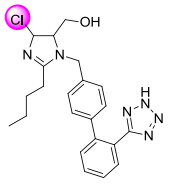
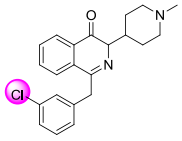
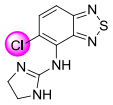
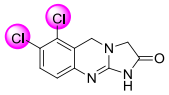
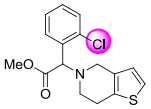
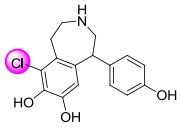
Sl.No	Drug Name	Structure	Diseases	Approved Year
88	Elocon		DER/RES	1987
89	Terazol 7		Genito-Urinary and Sex hormone	1987
90	Voltaren		MSK/SEN	1988
91	Ifex		Oncological	1988
92	Oxistat		DER/GUS	1988
93	Metahydrin		Cardiovascular	1988
94	Clozaril		Nervous system	1989
95	Prosom		Nervous system	1990
96	Moclobemide		Nervous system	1990
97	Plendil		Cardiovascular	1991
98	Lorabid		Anti-infective	1991
99	Zoloft		NER/GUS	1991
100	Tilid		Boold and blood forming organ	1991

Table 2 (*continued*)

Sl.No	Drug Name	Structure	Diseases	Approved Year
101	Propulsid		Alimentary tract and Metabolism	1993
102	Leustatin		Oncological	1993
103	Lipidil		CAR/END	1993
104	Claritin		Respiratory system	1993
105	Lamictal		Nervous system	1994
106	Zyrtec		Respiratory system	1995
107	Cozaar		Cardiovascular	1995
108	Astelin		RES/SEN	1996
109	Zanaflex		Musculo-skeletal	1996
110	Agrylin		BBO/ONC	1997
111	Plavix		BBO/END/CAR	1997
112	Corlopam		Cardiovascular	1997

(*continued on next page*)

Table 2 (*continued*)

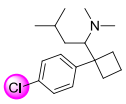
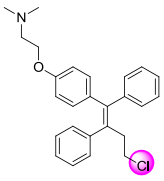
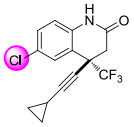
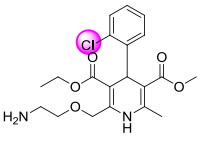
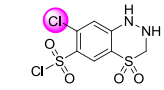
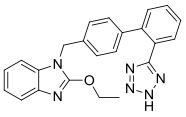
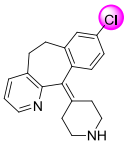
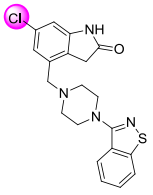
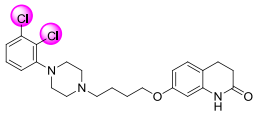
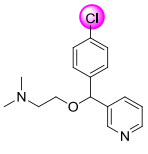
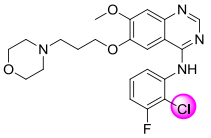
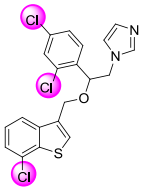
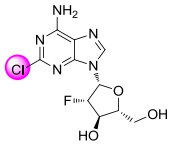
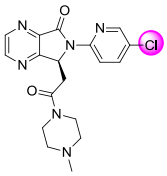
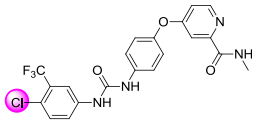
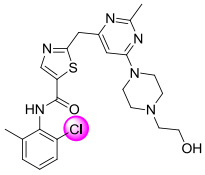
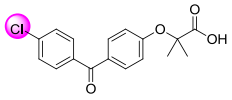
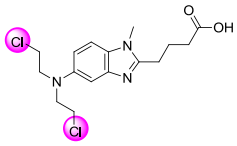
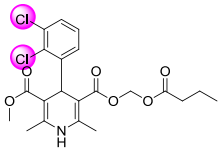
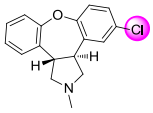
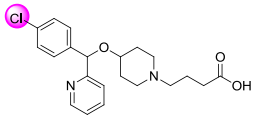
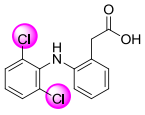
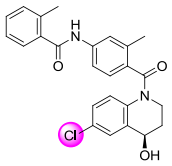
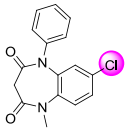
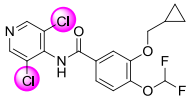
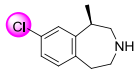
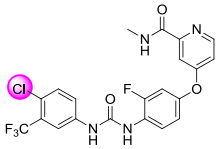
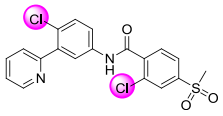
Sl.No	Drug Name	Structure	Diseases	Approved Year
113	Meridia		ALM/END	1997
114	Fareston		END/ONC	1997
115	Sustiva		Anti-infective	1998
116	Norvase		Cardiovascular	1999
117	Atacand HCT	 	Cardiovascular	2000
118	Clarinex		Respiratory system	2001
119	Geodon		Nervous system	2001
120	Abilify		Nervous system	2002
121	Carbinoxamine		Respiratory system	2003
122	Iressa		ONC/RES	2003

Table 2 (*continued*)

Sl.No	Drug Name	Structure	Diseases	Approved Year
123	Ertaczo		Dermatalogical	2003
124	Clolar		Oncological	2004
125	Lunesta		Nervous system	2004
126	Nexavar		Oncological	2005
127	Sprycel		Oncological	2006
128	Fenofibric acid		Cardiovascular	2007
129	Xyzal		DER/RES	2007
130	Cleviprerx		Cardiovascular	2008
131	Saphris		Nervous system	2009
132	Bepreve		Sensory organ	2009
133	Zipsor		Nervous system	2009

(*continued on next page*)

Table 2 (*continued*)

Sl.No	Drug Name	Structure	Diseases	Approved Year
134	Samsca		Blood and blood forming organ	2009
135	Onfi		Nervous system	2011
136	Daliresp		Respiratory system	2011
137	Belviq		Endocrime system	2012
138	Stivarga		ALM/ONC	2012
139	Erivedge		DER/ONC	2012

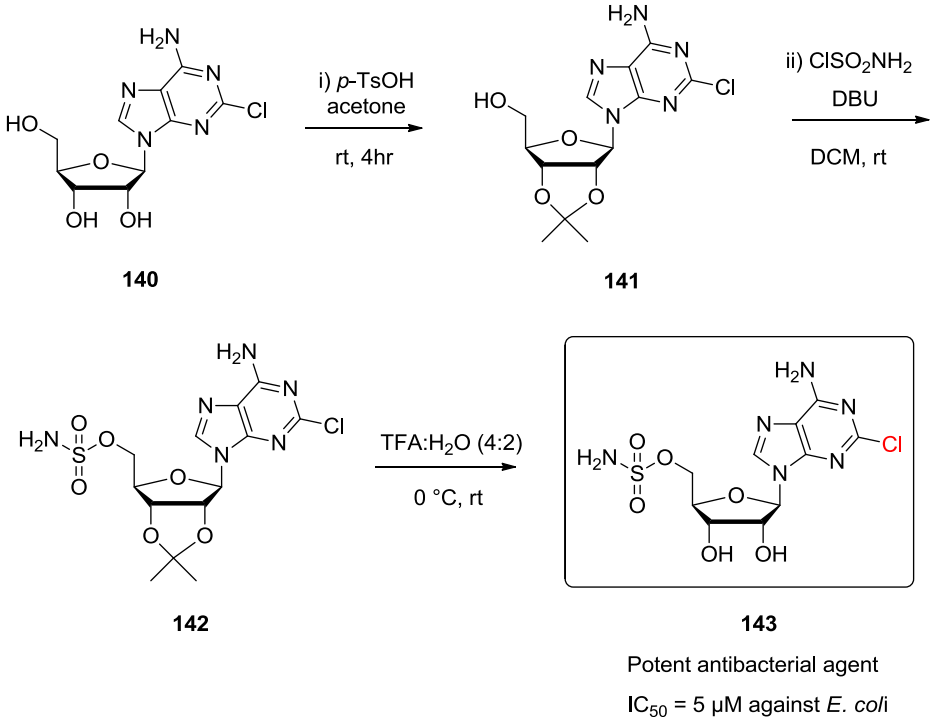
fight with an emerging antibiotic-resistant bacterial infections. In this review article, we have focused on chlorine containing analogues as a core substituent of antibacterial agents for drug development.

Mujumdar and co-workers synthesized a novel class of sulfamate-containing natural products and screened for their *in vitro* antibacterial properties. Title compound **143** was synthesized according to the literature reported as shown in Scheme 1. Commercially available 2-chloroadenosine **140** was reacted with tosylic acid under the optimal reaction condition to afford 2′,3′-*O*-isopropylidene protected adenosine precursors **141**, which then reacted with chlorosulfonyl amine in the presence of DBU as base to obtain the corresponding 5′-*o*-sulfamoyl adenosine **142** in moderate to good yields. The protecting group of compound **142** was removed by using a mixture solution of TFA and water (v/v = 4:2) to afford the target compound **143**. *In vitro* antimicrobial activity evaluation showed that the compound **143** possessed highest antibacterial activity with a MIC of 5 μM against *E. coli* [13]. The structure-activity relationship (SAR) revealed that the presence of chlorine atom highly enhanced the antibacterial properties of compound **143**. In addition, the presences of sulfonamide group also most favour to increases the antibacterial activity of potent compound **143**. The compound **143** as the lead compound need to be designed and synthesized for further investigation.

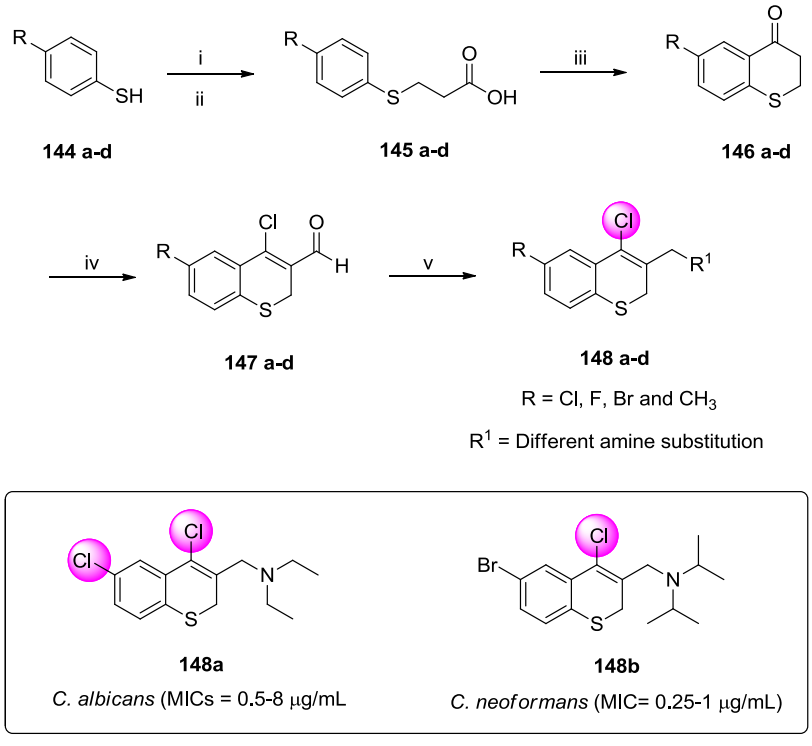
Wang and co-workers developed the chlorine containing thiochrome derivatives and screened for their *in vitro* antimicrobial activity. Substituted thiophenols (**144a-d)** were reacted with KOH and ethanol in the presence of water at 60 °C to yield the compounds **145a-d**. Compounds **145a-d** were reacted with *β*-chloropropionic acid and then cyclized in the presence of concentrated H_2SO_4 to afford thiochroman-4-ones **146a-d** via intra-molecular Friedel-Crafts reaction. Later, compounds **146a-d** were treated under Vilsmeier-Haack conditions to produce the key intermediates of **147a-d**. Then, compounds **147a-d** were reacted with various substituted amines and treated with $NaBH(OAc)_3$ in 1,2-dichloroethane at room temperature to yield the final target compounds **148a-d** (Scheme 2) [14]. All the synthesized compounds were tested for *in vitro* antifungal activities against different fungal strains. Based on the *in vitro* antimicrobial results, two compounds (**148a** and **148b)** were showed an excellent antifungal activities against *C. albicans* (MICs = 0.5–8 μg/mL) and *C. neoformans* (MIC = 0.25–1 μg/mL) respectively [15].

Karthikeyan et al. synthesized the novel chlorine containing potent antimicrobial compounds **154a-f.** From the beginning, starting material **149** was reacted with various substituted aldehydes (**150a-f**) in the presence of ethanol and Aq. KOH under reflux conditions to yield 1,3-diaryl-2-propen-1-ones (**151a-f**) in good yields. Then, compounds **151a-f** underwent bromination in chloroform to give bromo substituted compounds **152a-f**. Chalcone dibromides (**152a-f**) further treated with aryloxy acid hydrazides (**153a-f**) in the presence of triethylamine in absolute ethanol to furnish 1-aryloxy-3-aryl-5-hydroxy-5-aryl pyrazolines (**154a-f,** Scheme 3) in good yields. Compounds **154a** (zone of inhibition was 22 mm against *P. aeruginosa*) and **154b** (zone of inhibition was 21 mm against *P. aeruginosa*) turned out to be the most potent antibacterial agents. Compounds **154a** (zone of inhibition was 21 mm against *A. fumigatus*) and **154b** (zone of inhibition was 20 mm against *P. marneffei*) turned out to be the most potent antifungal agents [16].

Very recently, Zha and co-workers synthesized benzo[*d*]thiazole-hydrazones and tested for their *in vitro* antimicrobial activities. The synthetic route was depicted in Scheme 4. The intermediate 7-methylbenzo[*d*]thiazol-2-amine (**156**) was synthesized according to the literature of reported method [17,18]. Then,

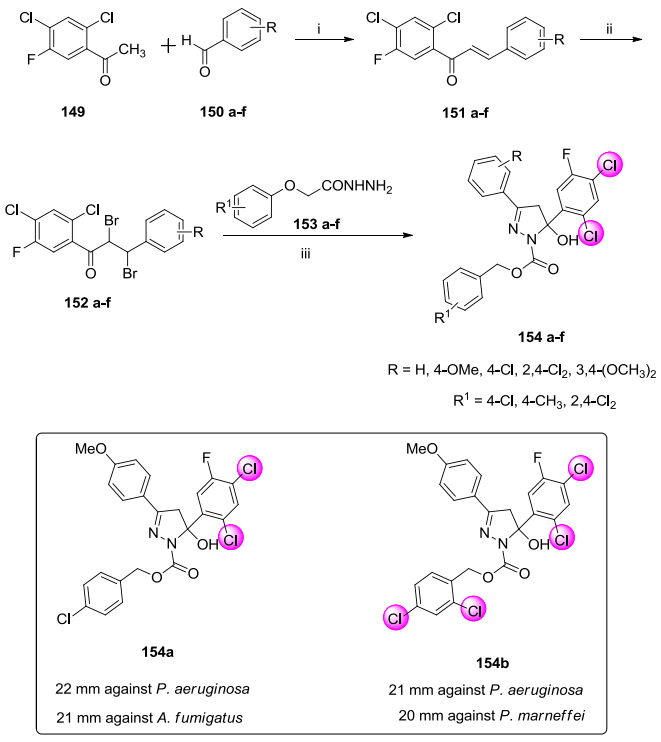


Scheme 1. Synthesis of chlorine containing sulfamate-containing natural products as potent antibacterial agent.



Reagents and conditions: (i) KOH, H_2O, EtOH, 60 °C; (ii) *β*-chloropropionic acid, 30% K_2CO_3 aqueous solution, reflux; (iii) H_2SO_4; (iv) $POCl_3$, DMF, 50 °C, (v) $NaBH(OAc)_3$, amine, DCE, N_2, rt.

Scheme 2. Synthesis of potent chlorine containing thiochromenes as antifungal agents. Reagents and conditions: (i) KOH, H_2O, EtOH, 60 °C; (ii) *β*-chloropropionic acid, 30% K_2CO_3 aqueous solution, reflux; (iii) H_2SO_4; (iv) $POCl_3$, DMF, 50 °C, (v) $NaBH(OAc)_3$, amine, DCE, N_2, rt.

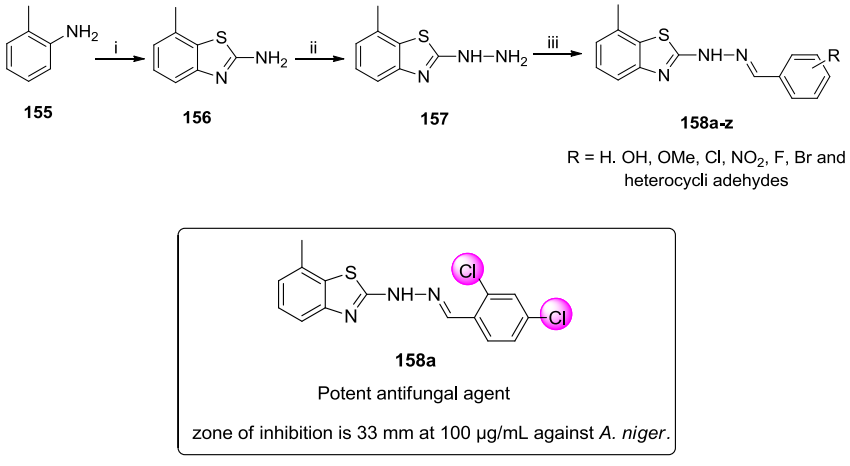


Scheme 3. Synthesis of chlorine containing pyrazoline analogues as potent antimicrobial agents. Reagents and conditions: (i) EtOH, aq. KOH, (ii) Br_2, $CHCl_3$, (iii) EtOH, Et_3N.

compound **156** was converted into hydrazides in the presence of hydrazine hydrate, catalytic amount of concentrated HCl and ethylene glycol under optimal reaction conditions for 3–4 h to afford the compound **157**. The benzo[*d*]thiazole-hydrazones (**158a-z**) were obtained by the reaction of **157** with different aldehydes in the presence of catalytic amount of glacial acetic acid. All the derivatives were obtained in good to excellent yield. All the obtained derivatives were evaluated for *in vitro* antimicrobial activities against various bacterial and fungal pathogens. Compound **158a** was found to be the most potent antifungal agent with 33 mm inhibition zone at 100 μg/mL against *A. niger*. The structure-activity relationship (SAR) revealed that, the presence of electron withdrawing groups (EWGs) (Cl, Br, NO_2 and F) on the phenyl ring increased the antifungal properties and the presence of electron donating groups (EDGs) (OH and OCH_3) diminished the antifungal properties [19]. Compound **158a** may serve as new potential antibacterial candidate in the future.

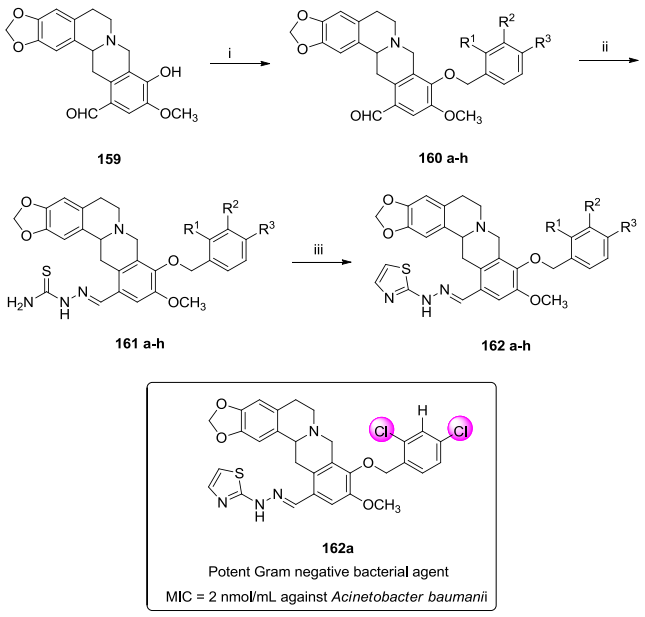
Very recently, Goa et al. have developed the potent antimicrobial aminothiazolyl berberine derivatives (**162a-h**) as illustrated in <sb>Scheme 5. Initial compound **159** was reacted with hydrazinecarbothioamide in the presence of glacial acetic acid and ethanol under optimal reaction conditions to afford the compounds **160a-h** in moderate to good yields. Subsequently, compounds **160a-h** were reacted with 2-chloroacetaldehyde to yield **161a-h**. Finally, compounds **161a-h** were converted into aminothiazolyl berberine derivatives (**162a-h**) by using substituted benzyl chlorides under optimal reaction conditions. Among all the synthesized derivatives, compound **162a** showed excellent antibacterial activity with MIC value of 2 mmol/mL against Gram-negative *A. baumanii*. The SAR revealed that the introduction of chlorine atom significantly improved the antibacterial effect. The EWGs (Cl) was useful to improve antibacterial activity. Molecular docking showed that hydrogen bonds existed in the supramolecular interaction between DNA gyrase and the active molecule **162a** (Fig. 1). [20].

The synthesis of novel class of antimicrobial quinoline bearing benzimidazole hybrids had been carried out by Garudachari et al. The targeted final compounds were synthesized through two steps. In the first step, isatin (**163**) was reacted with α-methylketone (**164**) in aqueous ethanol to yielded 4-carboxyquinoline (**165**) in good yield [21–23]. In the second step, **165** was reacted with various aromatic-1,2-diamines in polyphosphoric acid media to afford quinoline incorporated benzimidazole derivatives (**166a-f**, Scheme 6). Compound **166b** was found to be potent antibacterial agent



Reagents and conditions: (i) NH_4SCN, Br_2, glacial acetic acid, NH_3, (ii) hydrazine hydrate, Con. HCl, ethylene glycol, 3-4 h, rt, (iii) R-CHO, catalytic amount of acetic acid, EtOH, reflux, 8-10 h

Scheme 4. Synthesis of benzo[*d*]thiazole-hydrazones as potent antifungal agent. Reagents and conditions: (i) NH_4SCN, Br_2, glacial acetic acid, NH_3, (ii) hydrazine hydrate, Con. HCl, ethylene glycol, 3–4 h, rt, (iii) R-CHO, catalytic amount of acetic acid, EtOH, reflux, 8–10 h.



Reagents and conditions: (i) substituted benzyl chlorides, K_2CO_3, DMF, 80 °C; (ii) hydrazinecarbothioamide, glacial acetic acid, EtOH, 80 °C; (iii) 2-chloroacetaldehyde, EtOH, 80 °C;

Scheme 5. Synthesis of chlorine containing aminothiazolyl berberine derivatives as potent antibacterial agents. Reagents and conditions: (i) substituted benzyl chlorides, K_2CO_3, DMF, 80 °C; (ii) hydrazinecarbothioamide, glacial acetic acid, EtOH, 80 °C; (iii) 2-chloroacetaldehyde, EtOH, 80 °C.

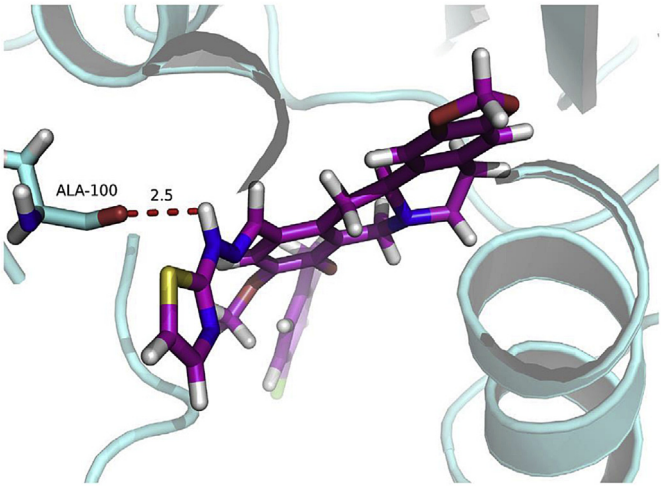
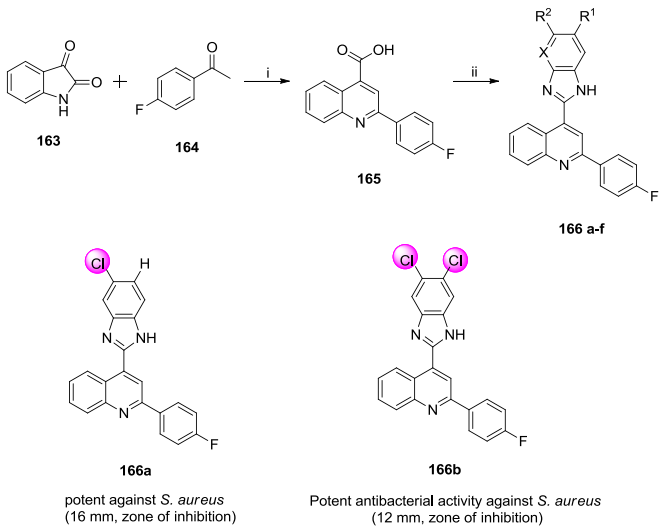


Fig. 1. Three-dimensional conformations of compound **162a** docked in DNA gyrase B (PDB code: 4DUH).

against *S. aureus* (12 mm inhibition zone) and compound **166a** was found to be more potent against *S. aureus* (16 mm inhibition zone). The SAR results revealed that the presence of fused pyridine ring in benzimidazole moiety as well as 4-fluorophenyl group on second position of quinoline ring has some relationship with their antibacterial activity. The presence of two chlorine atoms on benzimidazole ring along with 4-fluorophenyl group on second position of quinoline ring account for the enhanced activity of compound **166b** [24].

Karthikeyan et al. have synthesized a new series of triazole substituted compounds which were acted as potent antimicrobial



Reagents and conditions: (i) 33 % KOH, EtOH, (ii) Aromatic,1-2-diamine, PPA

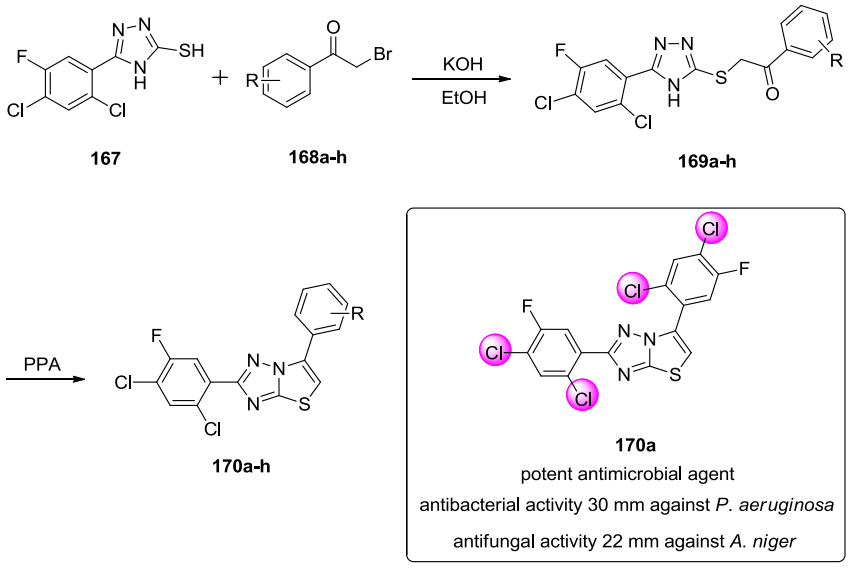
Scheme 6. Synthesis of chlorine containing potent antibacterial quinoline hybrids. Reagents and conditions: (i) 33% KOH, EtOH, (ii) Aromatic, 1-2-diamine, PPA.

agents. Starting material **167** was reacted with substituted phenacyl bromides (**168a-h**) in the presence of base under optimal reaction conditions to yield 2-[5-(2,4-dichloro-5-fluorophenyl)-4H-1,2,4-triazol-3-yl]thio-1-(substituted phenyl) ethanone (**169a-h**) which underwent further cyclization in the presence of PPA to obtain a series of 2,4-dichloro-5-fluorophenyl containing thiazolotriazoles (**170a-h**) in good yields (Scheme 7). Compound **170a** with triazole and chloro substituent was found to be the most active antibacterial agent (30 mm inhibition zone against *P. aeruginosa*) and antifungal agent (22 mm inhibition zone against *A. niger*) among all the synthesized series [25].

2.2. Synthesis of chlorine derived anticancer agent

Development in the area of anticancer therapeutic agents is one of the key challenges in medicinal chemistry. Cancer, a universal name for a group of diseases which characterized by uncontrolled cell proliferation, is found all over the world [26]. Cancer is the second major cause of death worldwide [27]. In the year of 2014 alone, it was estimated that about 585720 Americans were died from cancer, which refers to about 1600 deaths per day [28]. According to the assessment of the world health organization (WHO), global cancer rates could increase by 50% in the year 2020, which is approximately to 15 million. Cancers of the lung and bronchus, prostate, and colorectal continue to be the most common causes of cancer death [29].

A cancer consists of a group of cells that originated from a single cell with uncontrolled growth and rapid proliferation properties [30]. Presently, a wide range of cytotoxic drugs, either alone or in combination, are used to treat cancer, and several of these drugs are in different phases of clinical trials. These cytotoxic drugs suffer from several drawbacks and are not able to differentiate between cancerous and normal cell types; consequently, they can cause serious side effects that are often cumulative and dose-limiting. The anticancer drugs in recent clinical trials exhibited unnecessary organ toxicity, lack of cell specificity, short circulating half-life, and a noticeable tendency to induce resistance in the target cells [31]. Hence, in order to save the lives of millions of people globally, continuous efforts are being made to develop effective anti-cancer drug candidates with minimal side effects and less cost.

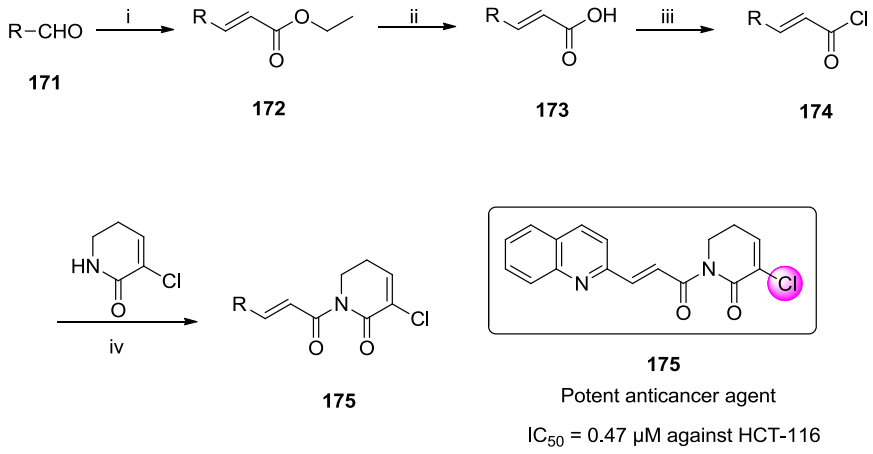


Scheme 7. Synthesis of chlorine containing triazole hybrids as potent antimicrobial agents.

Zou et al. have prepared dihydropyridine substituted chalcones and screened for their *in vitro* anticancer activity against different cell lines. The synthetic protocol was illustrated in Scheme 8. Initially, substituted aldehydes **171** were converted to esters **172** using Wittig-Horner reaction. Then, hydrolysis of **172** led to free acid **173** by using KOH, and compound **173** was reacted with pivaloyl chloride in DMF under the optimal reaction conditions to yield acylchloride **174**. Without isolation, compound **174** directly treated with 6-chloro-5,6-dihydro- pyridin-2(1*H*)-one, base and *n*-butyllithium to afford compound **175** in good yields (Scheme 8). Compound **175** showed excellent anticancer activity against HT-29 ($IC_{50} = 0.92\ \mu M$), HCT-8 ($IC_{50} = 1.79\ \mu M$) and HCT-116 ($IC_{50} = 0.47\ \mu M$) cell lines. The SAR results revealed that, the presence of EWG, namely chlorine atom, on the dihydropyridine ring would contribute to the enhanced anticancer activity [32].

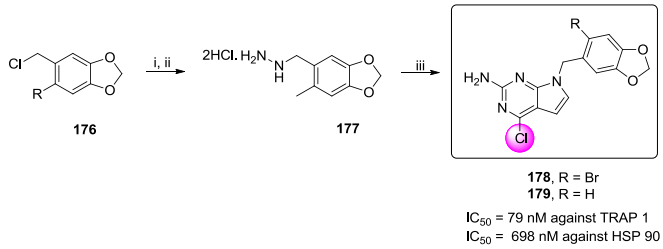
Park et al. have developed the synthetic route of a large number of pyrazolopyrimidin derivatives from **176** through a two-step reaction**.** Firstly, compound **176** was reacted with hydrazine hydrate in methanol under reflux conditions for 3 h. After cooled to room temperature, HCl in dichloromethane was added into the reaction mixture at −2 °C and then stirred for 13–14 h to yield intermediate compound **177** in moderate yield. The benzylhydrazine **177** was treated with 2-amino-4,6-dichloropyrimi-dine-5-carbaldehyde in the presence of TEA to afford target compounds **178** and **179** (Scheme 9). All the synthesized compounds were screened for their *in vitro* anticancer activity as TRAP1 Inhibitors. Among them, compound **178** was found to be the most potent TRAP1 inhibitors with the IC_{50} values of 79 nM [33].

Solomon and co-workers reported the syntheses of N-alkylated 4-aminoquinoline compounds (**183a-n**) which were showed in Scheme 10. An aromatic nucleophilic substitution of 4-chloro-7-substituted-quinoline (**180**) with excess amount of propanol



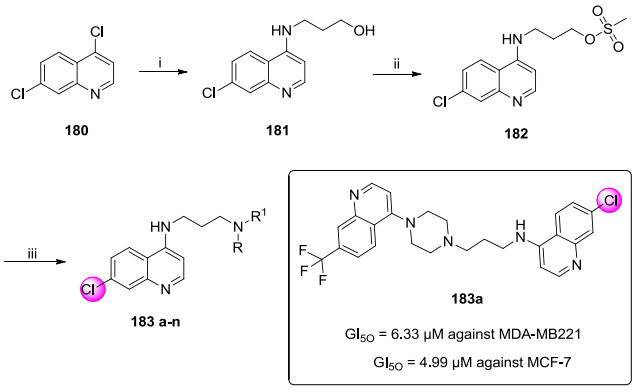
Reagents and conditions: (i) Wittig-Hornor reaction; (ii) KOH, 16 h; (iii) anhydrous DCM, pivaloyl chloride, one drop of DMF; (iv) anhydrous THF, TEA, *n*-butyllithium

Scheme 8. Synthetic route of chlorine containing dihydropyridine substituted quinoline chalcones as potent anticancer agent. Reagents and conditions: (i) Wittig-Hornor reaction; (ii) KOH, 16 h; (iii) anhydrous DCM, pivaloyl chloride, one drop of DMF; (iv) anhydrous THF, TEA, *n*-butyllithium.



Reagents and conditions: (i) $NH_2NH_2{\cdot}HCl$, MeOH, 60 °C, 3 h; (ii) HCl, CH_2Cl_2, -2 °C, 13 h; (iii) 2-amino-4,6-dichloropyrimidine-5-carbaldehyde, TEA, CH_2Cl_2, −2 °C, 13 h.

Scheme 9. Synthetic route of pyrazolopyrimidin derivatives as potent anticancer agents. Reagents and conditions: (i) $NH_2NH_2{\cdot}HCl$, MeOH, 60 °C, 3 h; (ii) HCl, CH_2Cl_2, -2 °C, 13 h; (iii) 2-amino-4,6-dichloropyrimidine-5-carbaldehyde, TEA, CH_2Cl_2, −2 °C, 13 h.

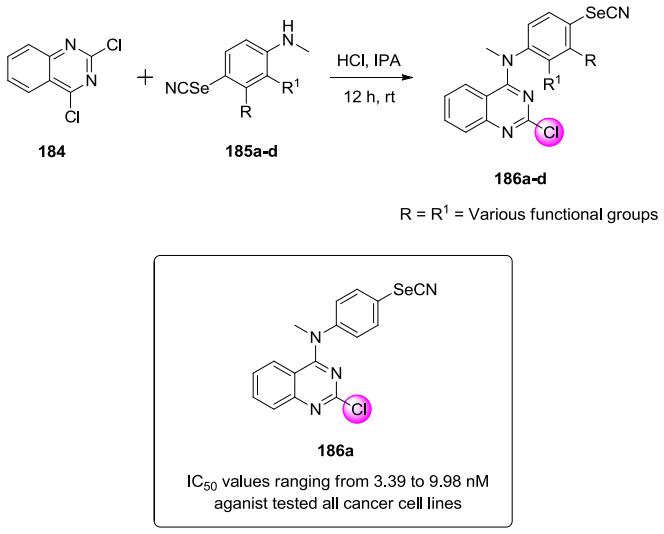


Reagent and Conditions: (i) Triethyl amine, amino propanol, 120-130 °C for 6 h (ii) triethylamine, methane sulfonyl chloride, THF, RT, 4 h (iii) amino component, NaH, DMF reflux at 65 °C, 12 h

Scheme 10. Synthetic route of potent anticancer agents. Reagent and Conditions: (i) Triethyl amine, amino propanol, 120–130 °C for 6 h (ii) triethylamine, methane sulfonyl chloride, THF, RT, 4 h (iii) amino component, NaH, DMF reflux at 65 °C, 12 h.

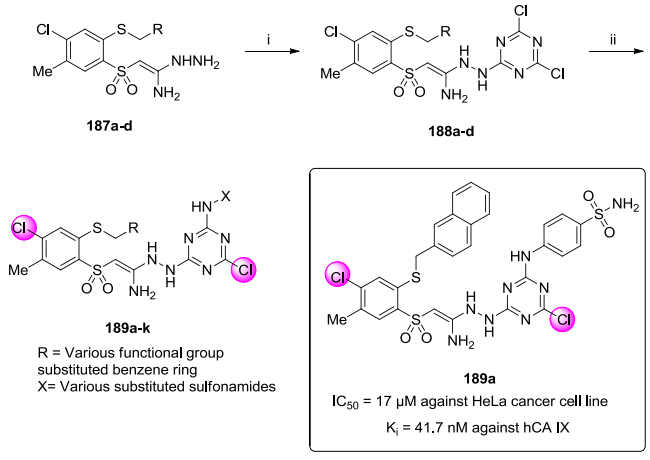
amine in triethyl amine yielded the 3-((7-chloroquinoline-4-yl) amino)propane-ol (**181**) according to the previous reported method [34]. Compound **181** was reacted with sulfonyl chloride in the presence of base under the optimal reaction condition to yield mesylate (**182**) in high yield. The intermediate **182** was treated with various substituted amino components utilizing sodium hydride as the base to afford the final *N*-alkylated 4-aminoquinoline derivatives (**183a-n**) in moderate to good yields. All the synthesized compounds were evaluated for their *in vitro* anti-breast cancer activity. Among them, compound **183a** was found to be the most potent analogues against tested two cancer cell lines MDA- MB221 ($GI_{50} = 6.33$ μM) and MCF-7 ($GI_{50} = 4.99$ μM). The bio assays result suggests that, compound **183a** analogues could serve as potent anticancer agent for the development of a new group of effective cancer chemotherapeutics [35].

Baijiao et al. have reported a simple protocol for the synthesis of quinoline containing hybrids and evaluated for their *in vitro* anticancer activity against different cancer cell lines. Initially, starting material dichloroquinazoline (**184**) was reacted with substituted selenium containing analogues (**185a-d**) in the presence of hydrogen chloride in isopropanol to afford the target compounds **186a-d** in good yields (Scheme 11). Among them, compound **186a** was found to be the most potent anticancer agent against all tested cell lines with IC_{50} values ranging from 3.39 to 9.98 nM [36].



Scheme 11. Synthetic route of chloro containing quinoline hybrids as potent anticancer agents.

Zolnowska and co-workers have reported a well-designed synthetic approach towards the synthesis of functionalized guanidine containing derivatives (**189a-d**) and screened for their anticancer activity. The synthetic route was outlined in Scheme 12. Initially, intermediate compounds 2-(2-arylmethylthio-4-chloro-5-methylbenzenesulfonyl)-1-(4,6-dichloro-1,3,5-triazin-2-ylamino) guanidine derivatives **188a-d** were synthesized from the reaction of appropriate aminoguanidine (**187a-d**) with 2,4,6-trichloro-1,3,5-triazine in the presence of triethylamine under the optimal reaction conditions. Then intermediates **187a-d** were treated with various substituted amines in the presence of DIPEA as base and argon atmosphere under reflux conditions for 3–11 h to yield corresponding guanidine substituted hybrids **189a-k** in good to moderate yields. Compound **189a** displayed excellent inhibitory potency against hCA IX with Ki values of 41.7 nM and showed prominent cytotoxic effect with IC_{50} of 17 μM against HeLa cancer cell line [37]. The SAR represented that the presence of two chlorine



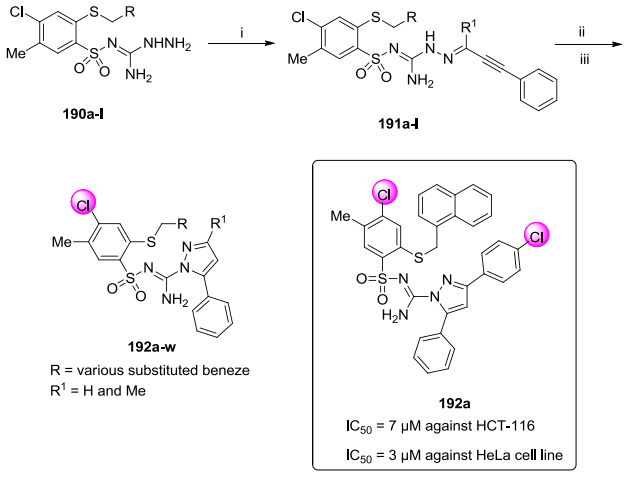
Reagents and conditions: (i) 2,4,6-trichloro-1,3,5-triazine, TEA, anhydrous THF, 1 h at 0 °C, 2 h, rt (ii) X-NH_2, DIPEA, 80 °C, argon atmosphere, 3-11 h.

Scheme 12. Synthetic route of chlorine containing drugs as potent anticancer agents. Reagents and conditions: (i) 2,4,6-trichloro-1,3,5-triazine, TEA, anhydrous THF, 1 h at 0 °C, 2 h, rt (ii) X-NH_2, DIPEA, 80 °C, argon atmosphere, 3–11 h.

electron-withdrawing groups at aromatic rings highly enhanced the anticancer activity. On the other hand, the presence of sulfonyl and sulfonamide groups also increases the anticancer activity of compound **189a**.

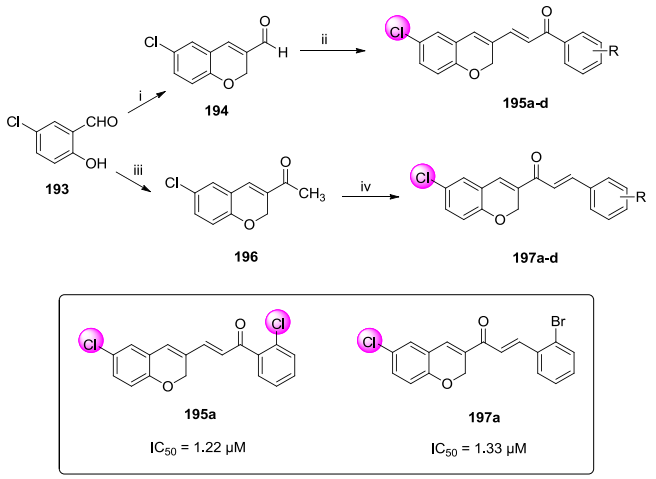
Pogorzelska et al. have evaluated their synthesized compounds for anticancer activity and found effective compounds. The syntheses of new series of target compounds **192a-w** was showed in Scheme 13. The starting materials **190a-l** were reacted with phenylpropiolaldehyde diethyl acetal in the presence of PTSA in ethanol under reflux conditions to yield 2-(2-alkylthiobenzenesulfonyl)-3-(phenylprop-2-ynylideneamino)guanidines **191a-l** in moderate to good yields. All the synthesized compounds **191a-l** underwent CuI mediated electrophilic cyclizations of α, β-alkynic hydrazones, unfortunately, this step did not provided the desired derivatives but led to copper complexes with pyrazole moiety. In another way, treatment of compounds **191a-i** with 20% PTSA under the optimal reaction conditions afforded the final compounds **192a-w**. Compounds **192a-w** were studied for their *in vitro* cytotoxic activity against MTT assays including three human cancer cell lines such as MCF-7, HCT-116 and HeLa cell lines. Compound **192a** was found to be an excellent anticancer agent with IC_{50} value of 7 μM against HCT-116 and IC_{50} value of 3 μM against HeLa cell lines [38].

Nazarian and co-workers reported the synthesis of a series of novel antileishmanial activity compounds. Firstly, 5-chloro-2-hydroxybenzaldehyde **193** was reacted with acrolein in the presence of the base potassium carbonate in dioxane under reflux conditions to obtain intermediate compound chromene-3-carbaldehyde **194**. Claisen-Schmidt condensation of compound **194** with various acetophenones in ethanolic solution of NaOH afforded 3-(6-chloro-2H-chromen-3-yl)propen-1-ones **195a–d** (Scheme 14). In another way, same starting material 5-chloro-2-hydroxybenzaldehyde **193** was reacted with methyl vinyl ketone in the presence of potassium carbonate base in dioxane under reflux conditions to afford 1-(6-chloro-2*H*-chromen-3-yl)ethanone **196**. Then, Claisen-Schmidt condensation of compound **196** with different aldehydes in ethanolic solution of NaOH yielded the corresponding 1-(6-chloro-2*H*-chromen-3-yl)propen-1-ones **197a**–d (Scheme 14). The target compounds were evaluated for their



Reagents and conditions: (i) phenylpropiolaldehyde diethyl acetal (1 eq.) or 4-phenylbut-3yn-2-one (1 eq.), PTSA (0.1 eq.), EtOH, reflux, 2-20 h, (ii) CuI, Et_3N, MeCN, 82 °C, 1-4 h, (iii) 20% PTSA/MeCN, 1 h.

Scheme 13. Potent anticancer agents. Reagents and conditions: (i) phenylpropiolaldehyde diethyl acetal (1 eq.) or 4-phenylbut-3yn-2-one (1 eq.), PTSA (0.1 eq.), EtOH, reflux, 2–20 h, (ii) CuI, Et_3N, MeCN, 82 °C, 1–4 h, (iii) 20% PTSA/MeCN, 1 h.



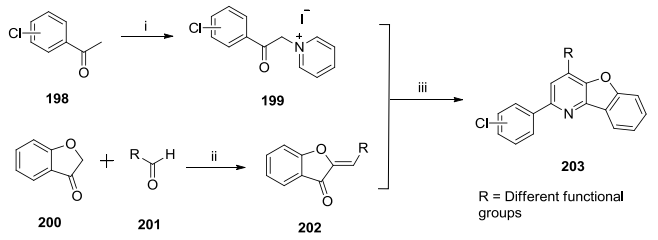
Reagents and conditions: (i) acrolein, 1,4-dioxane, K_2CO_3, reflux (ii) appropriate acetophenone, NaOH, EtOH (iii) methyl vinyl ketone, 1,4-dioxane, K_2CO_3, reflux (iv) appropriate aldehyde, NaOH, EtOH.

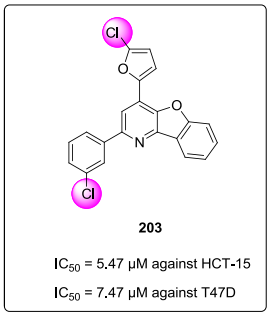
Scheme 14. Synthetic route of chlorine containing chalcones analogues as potent antileishmanial activity. Reagents and conditions: (i) acrolein, 1,4-dioxane, K_2CO_3, reflux (ii) appropriate acetophenone, NaOH, EtOH (iii) methyl vinyl ketone, 1,4-dioxane, K_2CO_3, reflux (iv) appropriate aldehyde, NaOH, EtOH.

antileishmanial activity against the promastigote form of *Leishmania* major using MTT assay. Compounds **195a** ($IC_{50} = 1.22$ μM) and **197a** ($IC_{50} = 1.33$ μM) were showed excellent antileishmanial activity. Compound **195a** was considered as a promising lead for the development of an effective agent for chemotherapy of leishmaniasis and other protozoan infections [39].

Magar and co-workers synthesized a series of novel benzofuran substituted hybrids and screened for their *in vitro* anti-proliferative activity. Usually the target compound **203** was synthesized in three simple steps. In the first step, three different chlorine-substituted pyridinium iodide salts (**199**) were synthesized in good yields by the heating of corresponding aryl methyl ketones (**198**) in the presence of iodine and pyridine at 140 °C for 3 h. In the second step, Al_2O_3 catalyzed condensation reaction was applied to prepare six aryl benzofuran-3(2*H*)-ones **202** by condensing benzofuran-3(2*H*)-one (**200**) with aryl aldehydes **201** in methylene chloride for 3 h at room temperature. Finally, a modified Kröhnke pyridine synthetic method [40] was used to synthesize the target compounds **203**. A mixture of aryl benzofuran-3(2*H*)-ones **202**, pyridinium iodide salts (**199**) and NH_4OAc in glacial acetic acid was heated at 100 °C for 12–24 h to afford compound **203** (Scheme 15) in considerable yields. All the synthesized compounds were evaluated for *in vitro* topoisomerase I and II inhibition and anti-proliferative activity. Compound **203** exhibited more potent anti-proliferative activity than the positive control etoposide against HCT15 ($IC_{50} = 5.47$ μM) and T47D ($IC_{50} = 7.47$ μM) cell line. The SAR results suggested that, the chlorinated compounds showed better anti-proliferative activity than those of corresponding non-chlorinated compounds. The chlorination at the 2-phenyl ring is important to inhibit the topo I and II activity. These results provided useful information for the development of benzofuro[3,2-*b*]pyridine derivatives as a novel class of topoisomerase-targeted anticancer agents [41].

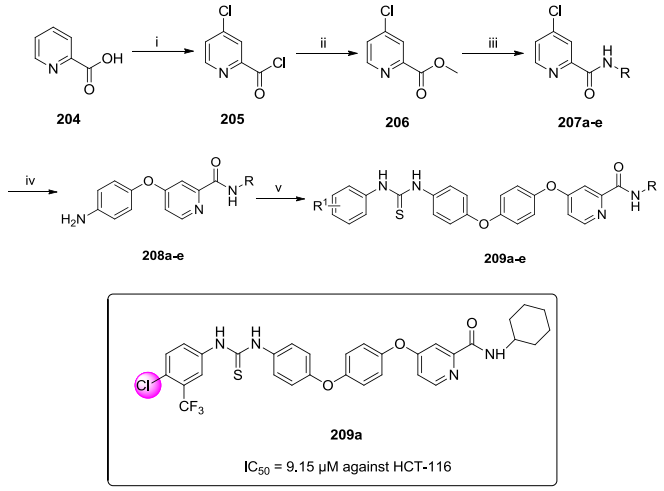
Synthesis of new class of antiproliferative agent was carried out by Yao et al. The synthetic route was lengthy and included five steps started from 2-picolinic acid **204** (Scheme 16). Compound **204** was reacted with $SOCl_2$ under reflux condition at 72 °C for 14 h to produce 4-chloropicolinoyl chloride **205** followed by the addition of





Reagents and conditions: (i) iodine, pyridine, 140 °C, 3 h, 76.7–93.0% yield; (ii) Al_2O_3, CH_2Cl_2, rt, 3 h, 55–72% yield; (iii) NH_4OAc, glacial acetic acid, 100 °C, 12-24 h, and 16-54%

Scheme 15. Synthetic route of chlorine containing benzofuro[3,2-*b*]pyridine derivatives as potent anti-proliferative drugs. Reagents and conditions: (i) iodine, pyridine, 140 °C, 3 h, 76.7–93.0% yield; (ii) Al_2O_3, CH_2Cl_2, rt, 3 h, 55–72% yield; (iii) NH_4OAc, glacial acetic acid, 100 °C, 12–24 h, and 16–54%.



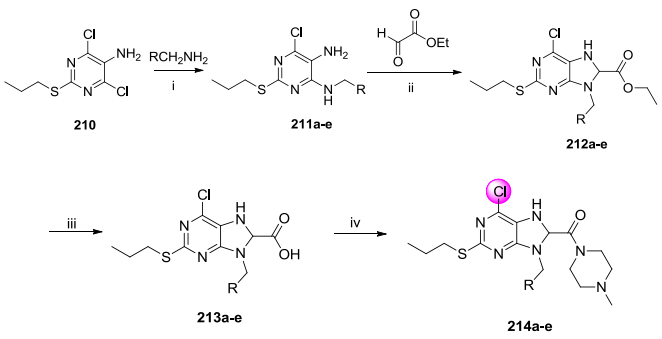
Reagents and conditions: (i) $SOCl_2$, reflux, 72 °C, 14 hr, (ii) CH_3OH, rt, 1 hr; (iii) RNH_2, CH_3OH/THF, 2 °C, 3 h; (iv) 4-aminophenol, DMF, KOBu-*t*, 1 hr; (v) substituted isocyanates, DCM, 0-5 °C, 2 hr then 18 hr at rt.

Scheme 16. Synthetic route of thiourea substituted derivatives as potent anti-proliferative agents. Reagents and conditions: (i) $SOCl_2$, reflux, 72 °C, 14 h, (ii) CH_3OH, rt, 1 h; (iii) RNH_2, CH_3OH/THF, 2 °C, 3 h; (iv) 4-aminophenol, DMF, KOBu-*t*, 1 h; (v) substituted isocyanates, DCM, 0–5 °C, 2 h then 18 h at rt.

methanol at room temperature for 1 h to generate methyl 4-chloropicolinate **206**. Consequently, compound **206** was reacted with various substituted amines in the presence of CH_3OH/THF at 2 °C for 3 h to yield **207a-e**. Then, they were treated with 4-aminophenol to provide corresponding diaromatic ethers **208a-e** in considerable yields. Finally, compounds **208a-e** were treated with substituted diaromatic ethers **208a-e** in DCM to afford the final targeted thiourea (**209a-e**) derivatives in considerable yields (Scheme 16). All the newly synthesized compounds were evaluated for their *in vitro* antiproliferative activities against HCT116 and MDA-MB-231 cell lines. Compound **209a** was found to be the most potent antiproliferative agent with IC_{50} value of 9.15 μM against HCT-116 cell line [42].

Zhao et al. have performed the synthesis of anti-proliferative compounds and tested their activity against four human cancer cell lines such as A549, MGC803, PC-3 and TE-1. The intermediates **211a-e** were prepared by following the earlier reported procedure [43]. Then, the prepared intermediates **211a-e** were treated with ethyl glyoxalate in EtOH under reflux condition for 2 h and led to the 6-chloro-2-(propylthio)-8,9-dihydro-7*H*-purine-8-carboxylate **212a-e** in moderate yields, and then intermediates **212a-e** were hydrolyzed into carboxyl in AcOH/H_2O to yield **213a-e**. Finally, compounds **213a-e** were coupled with various substituted amines using coupling reagent EDCI/HOBt in dichloromethane at room temperature to afford final target compounds **214a-e** (Scheme 17). Compound **214a** showed excellent anti-proliferative activity with IC_{50} values of 2.80 μM against A549 and 303.03 μM against GES-1, respectively. The SAR revealed that the presence of piperazine group highly enhanced the anti-proliferative activity, which suggested that the piperazine substitution was played an important role to enhance the anti-proliferative activity. The compound **214a**, with a methyl substitution on the piperazine group, was found to be the most potent anti-proliferative agent in the series [44].

Luo and co-workers developed a series of novel chlorine containing compounds with enhanced *in vitro* anti-tumour activity. Initially, commercially available 2-amino-4-chlorobenzoic acid **215** was condensed with formamide at 140–145 °C for 4.5 h to obtain intermediate **216**, and then treated with $SOCl_2$ in the presence of DMF under reflux conditions to produce intermediate **217**. In addition, commercially available salicylaldehyde **218** was reacted with acetone in the presence of sodium hydride at room temperature to afford intermediate **219**. Compounds **217** and **219** were



Reagents and conditions: (i) DMF, DIPEA, 100 °C, 12h, (ii) EtOH, 80 °C, (iii) AcOH/H_2O, 80 °C, (iv) 1-methylpiperazine, EDCI/HOBt, CH_2Cl_2.

Scheme 17. Synthetic route of potent chlorine containing anti-proliferative agents. Reagents and conditions: (i) DMF, DIPEA, 100 °C, 12 h, (ii) EtOH, 80 °C, (iii) AcOH/H_2O, 80 °C, (iv) 1-methylpiperazine, EDCI/HOBt, CH_2Cl_2.

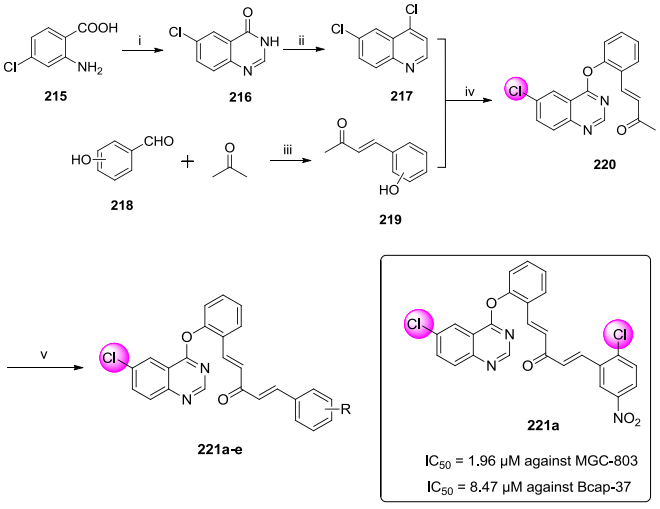
reacted with K_2CO_3 in acetonitrile at 30–40 °C for 3.5 h to yield intermediates **220**. Compound **220** was reacted with substituted aldehydes in the presence of anhydrous alcohol in acetone at room temperature to provide the final target compounds **221a-e** in good yields (Scheme 18). Compound **221a** was found to be the most potent antitumor agent with IC_{50} value of 1.96 μM against MGC-803 and 8.47 μM against Bcap-37 cell lines. Compound **221a** could be considered as useful templates for the future development of more potent antitumor agents [45].

2.3. Synthesis of chlorine containing anti-inflammatory agents

Inflammation demote to localised physical conditions causing swellness, redness, heat with pain, which are mediated by the release of proinflammatory mediators like bradykinin and cytosine to increase the prostaglandin synthesis rate [46,47]. Non-steroidal anti-inflammatory drugs (NSAIDs), which existing in two isomeric forms, namely, constitutive form (COX-1) and an inducible form (COX-2), inhibit cyclooxygenases (COX) and further inhibiting the biosynthesis of prostaglandins (PGs) [48,49]. The role of COX-1 enzyme is to maintain the gastric integrity and kidney functioning whereas COX-2 may cause inflammation and pain [50,51].

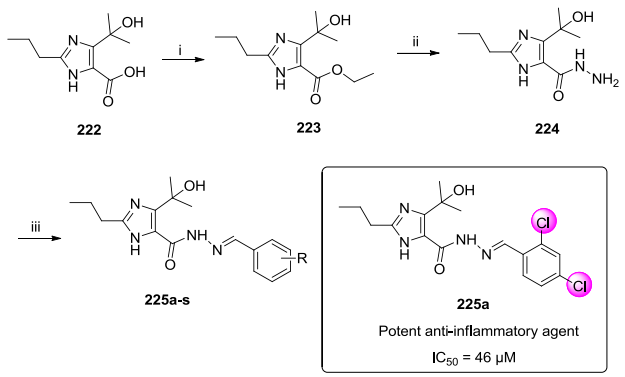
Shantharam and co-workers have developed new series of imidazole hydrazones as potent anti-inflammatory agents. The synthesis of imidazole based hydrazones **225a-s** wer performed in a manner outlined in Scheme 19. Starting material 4-(2-hydroxypropan-2-yl)-2-propyl-1*H*-imidazole-5-carboxylic acid **222** was converted into ethylester using TMS-Cl in ethanol at room temperature followed by the addition of excess hydrazine hydrate afforded the corresponding imidazole hydrazide **224**. Compound **224** was treated with various substituted aldehydes in ethanol at 80 °C for 8–10 h to yield final imidazole-hydrazones **225a-s** in good yields. Compound **225a** was found to be the most potent anti-inflammatory agent with IC_{50} value of 46 μM. The SAR revealed that the presence of electron withdrawing (-Cl) groups on the phenyl ring highly enhanced the anti-inflammatory activity [52].

Continuation of their interest in drug development program, the research group of Rakesh identified the novel quinazolinone-hydrazones as potent *in vitro* anti-inflammatory activity. The quinazolinone starting materials **226** were methylated using TMS-Cl in methanol at room temperature followed by the addition of excess hydrazine hydrate afforded the corresponding quinazolinone hydrazides **228**. The quinazolinone-hydrazones **229a-t** were obtained by the reaction of **228** with different aromatic aldehydes in the presence of catalytic amount of glacial acetic acid (Scheme 20). Compounds **229a** (IC_{50} = 84 μM/mL) and **229b** (IC_{50} = 67 μM/mL) showed excellent anti-inflammatory activities with lower IC_{50} values than that of the standard compound aspirin (IC_{50} = 166 μM/mL). The SAR revealed that the presence of electron withdrawing (-Cl) groups on the phenyl ring highly enhanced the anti-inflammatory activity and the length of quinozolinone alkyl chain also played a major role to increases the activity. The presence of EDGs (OH and OMe) on the phenyl ring diminishes the anti-inflammatory activity [53].



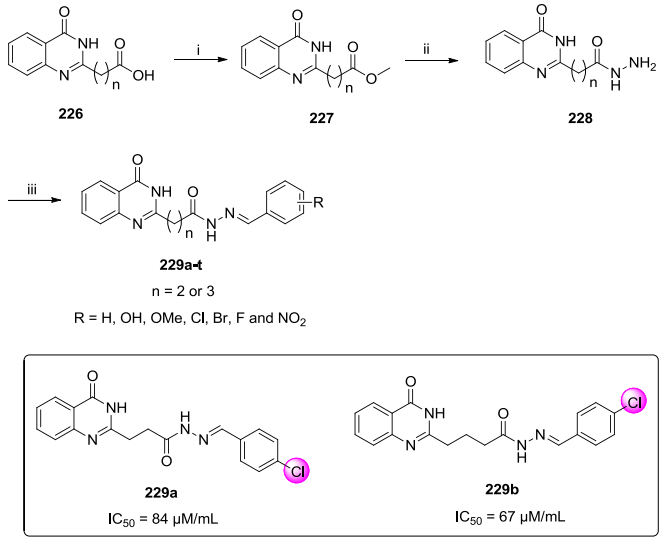
Reagents and conditions: (i) formamide, 140-145 °C, (ii) $SOCl_2$, DMF, reflux, (iii) NaOH, H_2O, rt (iv) CH_3CN, K_2CO_3, 30-40 °C, (v) R-CHO, EtOH, NaOH.

Scheme 18. Synthetic route of potent chlorine containing anti-proliferative agents. Reagents and conditions: (i) formamide, 140–145 °C, (ii) $SOCl_2$, DMF, reflux, (iii) NaOH, H_2O, rt (iv) CH_3CN, K_2CO_3, 30–40 °C, (v) R-CHO, EtOH, NaOH.



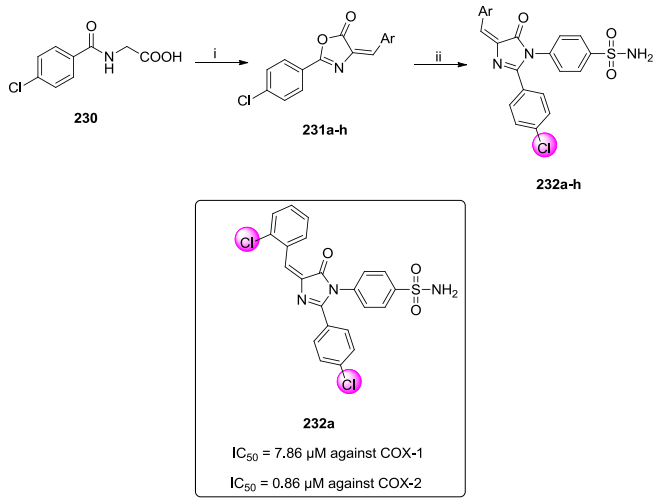
Reagents and conditions: (i) TMS-Cl, MeOH, rt, 2-3 hr, (ii) $NH_2NH_2.H_2O$, EtOH, reflux, 78-80 °C, (iii) Ar-CHO, EtOH, reflux, 80 °C, 8-10 hr

Scheme 19. Synthetic route of imidazole-hydrazones as potent anti-inflammatory agents. Reagents and conditions: (i) TMS-Cl, MeOH, rt, 2–3 h, (ii) $NH_2NH_2.H_2O$, EtOH, reflux, 78–80 °C, (iii) Ar-CHO, EtOH, reflux, 80 °C, 8–10 h.



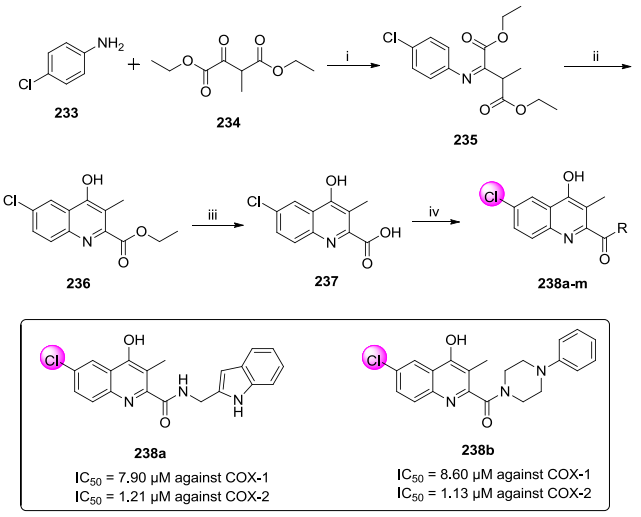
Reagents and conditions: (i) TMS-Cl, MeOH, rt, 4 h, (ii) $NH_2NH_2.H_2O$, EtOH, reflux, 16 h, (iii) EtOH, CH_3COOH, reflux, 7-8 h

Scheme 20. Synthetic route of quinazolinone-hydrazones as potent anti-inflammatory agents. Reagents and conditions: (i) TMS-Cl, MeOH, rt, 4 h, (ii) $NH_2NH_2.H_2O$, EtOH, reflux, 16 h, (iii) EtOH, CH_3COOH, reflux, 7–8 h.



Reagents and conditions: (i) appropriate Ar-CHO, CH_3COONa, acetic anhydride, 100 °C, 6 h, (b) $H_2NC_6H_4SO_2NH_2$, CH_3COONa, glacial acetic acid, reflux, 24 h

Scheme 21. Synthesis of chlorine containing imidazole hybrids as potent anti-inflammatory agents. Reagents and conditions: (i) appropriate Ar-CHO, CH_3COONa, acetic anhydride, 100 °C, 6 h, (b) $H_2NC_6H_4SO_2NH_2$, CH_3COONa, glacial acetic acid, reflux, 24 h.



Reagents and reaction conditions: (i) acetic acid, ethanol, reflux, 48 h; (ii) PPA, 120 °C, 2 h; (iii) 5% NaOH, ethanol, 80 °C, 4 h; (iv) appropriate amine, BOP, DIPEA, DCM, overnight, rt.

Scheme 22. Synthesis of the chlorine containing quinoline-2-carboxamides hybrids as potent anti-inflammatory agents. Reagents and reaction conditions: (i) acetic acid, ethanol, reflux, 48 h; (ii) PPA, 120 °C, 2 h; (iii) 5% NaOH, ethanol, 80 °C, 4 h; (iv) appropriate amine, BOP, DIPEA, DCM, overnight, rt.

Abdellatif et al. have developed a novel class of imidazoles compounds and screened for their *in vitro* anti-inflammatory activity. Compound *p*-chlorobenzoylglycine **230** was synthesized by heating the mixture of glycine and 4-chlorobenzoyl chloride in sodium hydroxide solution (10%) as previously reported method [54]. Cyclocondensation of compounds **231a-h** with substituted aldehydes in the presence of catalytic amount of sodium acetate in acetic anhydride under the optimal reaction conditions yielded **231a-h** in good yield [54]. Then, compounds **231a-h** were treated with sulfanilamide in glacial acetic acid to afford the compounds **232a-h** in good yields (Scheme 21). Among all the synthesized compounds, compound **232a** was found to be excellent anti-inflammatory activities with IC_{50} of 7.86 μM against COX-1 and IC_{50} of 0.86 μM against COX-2 which was more potent than that of the standard Celecoxib in the series [55].

Abdelrahman and colleagues have reported a set of thirteen quinoline-2-carboxamide derivatives from *p*-chloroaniline **233**. Firstly, condensation of *p*-chloroaniline **233** with diethyl oxalpropionate **234** afforded the corresponding imine **235**, which cyclized in polyphosphoric acid to yielded quinoline-2-carboxylic acid ethyl ester **236** in excellent yield. The quinoline-2-carboxylate **236** was hydrolyzed into its carboxylic acid **237** under basic conditions, which then coupled with substituted amine using BOP in the presence of DIPEA to yield quinoline-2-carboxamides **238a-m** (Scheme 22**)**. All the developed hybrids were evaluated for their *in vitro* anti-inflammatory activities. Compounds **238a** (IC_{50} = 7.9 μM against COX-1 and IC_{50} = 1.21 μM against COX-2) and **238b** (IC_{50} = 8.6 μM against COX-1 and IC_{50} = 1.13 μM against COX-2) showed excellent anti-inflammatory activity compared to the reference drug Celecoxib. The docking study explained the results obtained from the *in vitro* COXs assays based on the structural features and their binding patterns inside the active sites. Obviously, the two active hits **238a** and **238b** adopted similar binding patterns and interactions to that of the co-crystallized bromocelecoxib, S-58 ligand where the benzimidazole and phenyl piperazine moieties in **238a** and **238b**, respectively assumed the same position of sulfonamide moiety of S-58 within the additional side pocket of COX-2 in Fig. 2 [56].

A new series of eighteen benzo[*d*]imidazole-hydrazones were synthesized by Kumar et al. using commercially available compound **239** as starting material**.** Compound **239** was esterified by using con. H_2SO_4 in ethanol under reflux conditions to obtain compound **240** in good yield [57]. Subsequently, compound **240** was treated with propylamine and TEA to afford compound **241**. Compound **242** was prepared from nitro reductive cyclization of **241** with 2,4-dichlorobenzaldehyde using sodium dithionite in DMSO as solvent at 90 °C. The one-pot reaction produced the compound **242** within 3 h in an excellent yield (94%). The ester group was then treated with hydrazine hydrate in ethanol medium under reflux condition for 6 h to provide hydrazide **243**. Finally, the target hydrazones **244a-r** were obtained by condensation of **243** with various substituted aldehydes in ethanol with catalytic amount of glacial acetic acid (Scheme 23). All the prepared analogues were screened for their *in vitro* anti-inflammatory activity. Compound **244a** showed excellent anti-inflammatory activity with 71.97% inhibition compared to the reference drug indomethacin (69.34% inhibition). The SAR results revealed that, the presence of EWDs (Cl, Br and NO_2) on the phenyl ring increased the anti-inflammatory activity and the presence of EDGs (OH and OCH_3) on phenyl ring reduced the anti-inflammatory activity [58].

2.4. Synthesis of chlorine bearing anti-tuberculosis drugs

Tuberculosis is a highly infectious chronic deadly disease caused by *Mycobacterium tuberculosis* (MTB). This disease threatens the human life by affecting lungs primarily (pulmonary TB) distant from other vital organs. Drug-resistant TB (DR-TB), multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB) and totally drug resistant TB (TDR) emerging nowadays are completely resistant for the action of presently available standard drugs [59]. The infection of TB is so common that it has caused around 1.4 million deaths and 10.4 million clinical cases all over globe as reported in 2015 [60,61]. However the treatment of TB with drugs such as Isoniazid (INH), Ethambutol (EMB0, Rifampicin (RIF) and Pyrazinamide (PZA) is proved to be highly effective.

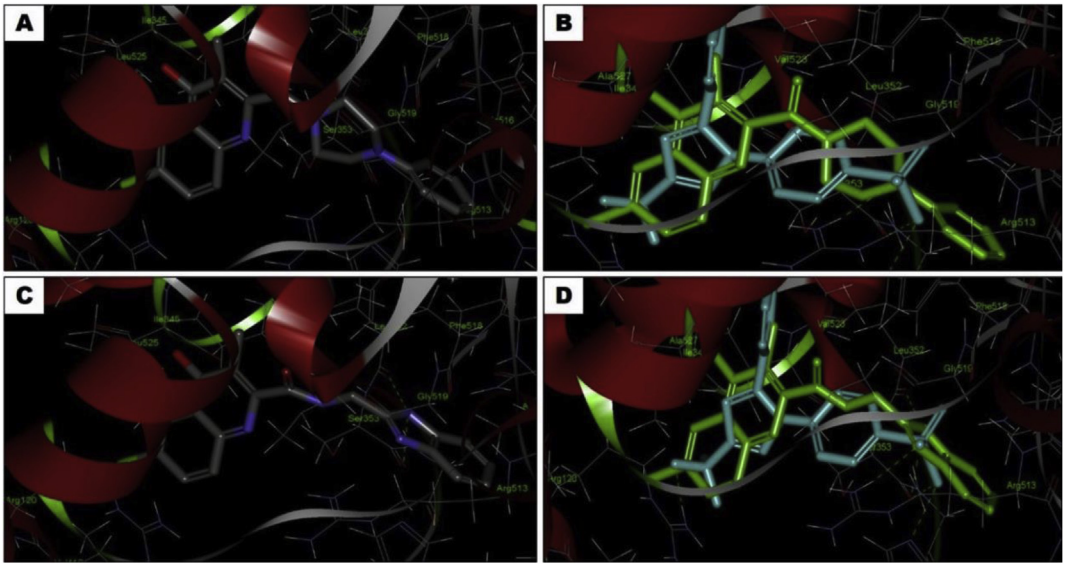
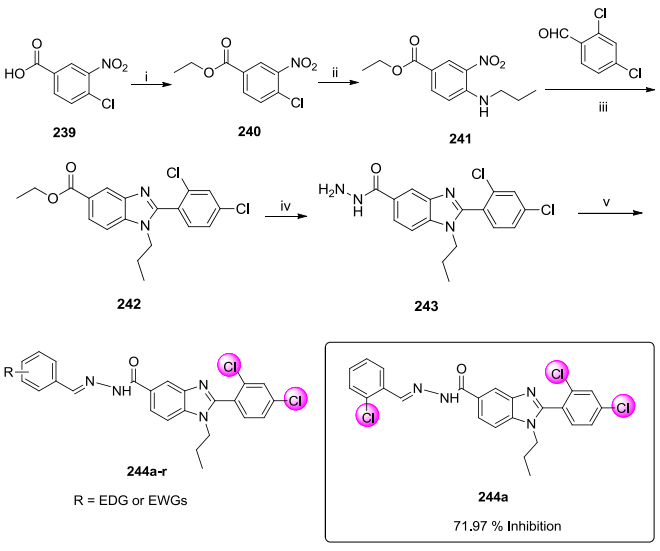


Fig. 2. (A) Docking and binding pattern of compound **238b** into COX-2 active site (PDB code: 1CX2). (B) The superimposition of the docked pose of **238b** (red) and the co-crystallized S-58 (cyan) within active site of COX-2. (C) Docking and binding pattern of compound **238a** into the same COX-2 binding pocket. (D) The superimposition of the docked pose of **238a** (red) and the co-crystallized S-58 (cyan) within active site of COX-2. Dashed green lines represent hydrogen bonds. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



Reagents and conditions: (i) ethanol, con. H_2SO_4, reflux; (ii) propylamine TEA, THF, rt; (iii) $Na_2S_2O_4$, DMSO, 90 °C, 3 h; (iv) hydrazine hydrate, ethanol, 78-80 °C, reflux, 8 h; (v) Ar-CHO, ethanol, cat. glacial acetic acid, reflux, 10 h.

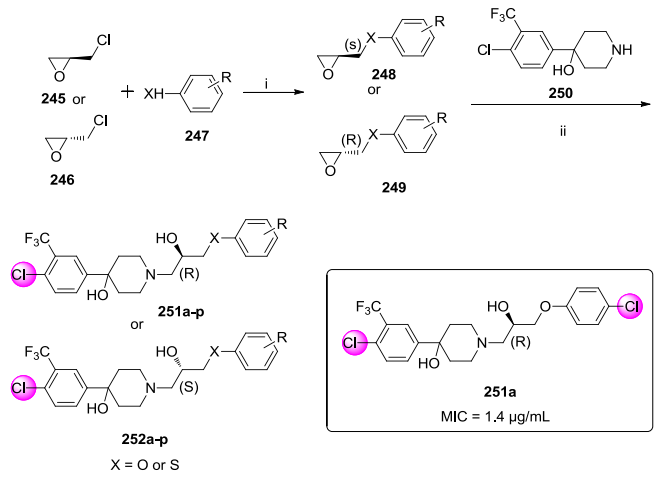
Scheme 23. Synthetic route of chlorine containing benz[*d*]imidazole hybrids as potent anti-inflammatory agents. Reagents and conditions: (i) ethanol, con. H_2SO_4, reflux; (ii) propylamine TEA, THF, rt; (iii) $Na_2S_2O_4$, DMSO, 90 °C, 3 h; (iv) hydrazine hydrate, ethanol, 78–80 °C, reflux, 8 h; (v) Ar-CHO, ethanol, cat. glacial acetic acid, reflux, 10 h.

Discovery of Rifampicin (RIF) helped in developing handful of anti-TB drug compounds to the humans. However, there is still a number of derivatives awaiting to be explored to stop the activity of bacteria and further spreading of TB [62,63].

Sun et al. have developed a new series of sixteen chiral piperidinol derivatives and screened for their *in vitro* anti-tuberculosis activity. The synthesis of the chiral piperidinol compounds **251a-p** or **252a-p** were first performed by reacting optically active epoxide intermediate (S)-(+)-epichlorohydrin (**245**) or (R)-(−)-epichlorohydrin (**246**) with a substituted phenol or thiophenol (**247**) in acetonitrile under reflux condition in the presence of cesium carbonate to afford chiral epoxide derivative **248** or **249** [64,65]. Subsequently, the crude product **248** or **249** was reacted with 4-[4-chloro-3-(trifluoromethyl)-phenyl]-4-piperidinol (**250**) in ethanol under reflux condition to afford alcohol diols **251a-p** or **252a-p** in moderate yields (Scheme 24). Compound **251a** was found to be potent anti-tuberculosis activity with MIC values of 1.4 μg/mL, which could be attributed to the presence of electron-withdrawing groups (CF_3 and Cl) [66].

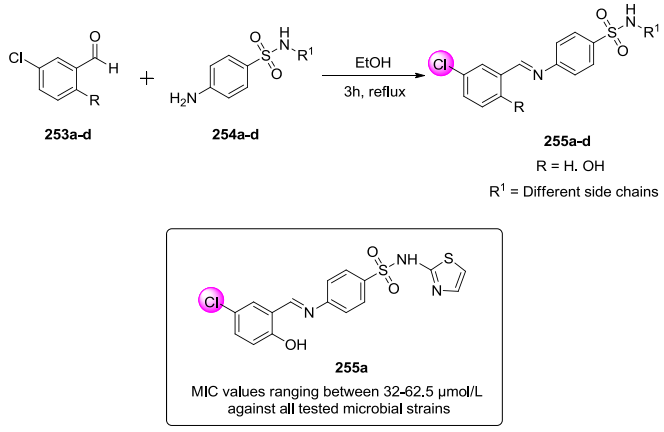
In 2012, Kratky and co-workers have developed a novel class of sulfonamides as potent antimycobacterial activity against *M. tuberculosis* 331/88, *M. avium* (330/88) and two strains of *M. kansasii* (235/80 and 6509/96). The target compounds of sulfonamide derivatives were synthesized in a simple and single step. Sulfonamide **254a-d** and substituted aldehydes **253a-d** reacted in ethanol under reflux conditions for 3 h and stirred at room temperature for another 12 h to yield final compounds **255a-d** at 4 °C in good yields (Scheme 25). Compound **255a** was found to be the most potent antimycobacterial activity against *M. tuberculosis* 331/88, *M. avium* (330/88) and two strains of *M. kansasii* (235/80 and 6509/96) with MIC values ranging between 32 and 62.5 μmol/L [67]. The SAR predicted that the presence of electron-donating group (OH) on the phenyl ring highly enhanced the antimycobacterial activity. Furthermore, the introduction of electron-withdrawing chloro group to the same phenyl ring increases the activity.

Shah and co-workers have developed a new series of active anti-tuberculosis agents in one pot synthesis. The final target compounds *N*-arylamino biquinoline derivatives **259a-x** were synthesized from the reaction of 2-chloro-3-formyl quinolines **256**, malononitrile **257** with appropriate enhydrazinoketones **258** in absolute ethanol in the presence of base piperidine under optimal reaction conditions (Scheme 26). All the prepared hybrids were evaluated for their *in vitro* antituberculosis activity against *M. tuberculosis* H37Rv. Among them, compound **259a** exhibited the most potent anti-tuberculosis inhibition (87%) against *M. tuberculosis* H37Rv [68].

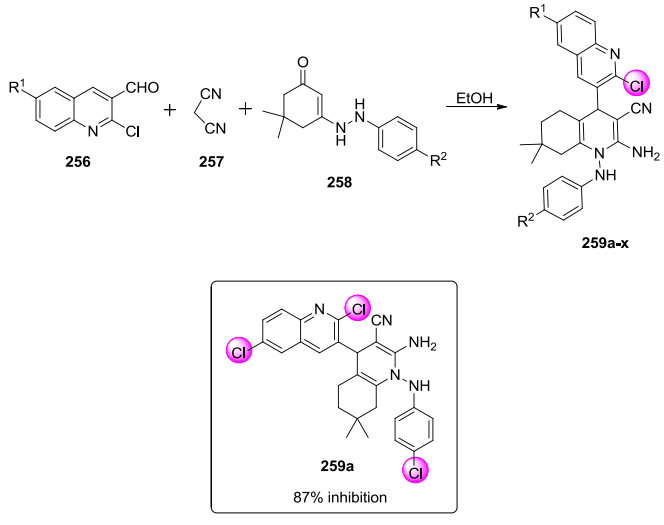


Reagents and conditions: (i) CS_2CO_3, MeCN, reflux, overnight, (ii) EtOH, reflux, overnight

Scheme 24. Synthesis of chlorine containing piperidinol derivatives as potent anti-tuberculosis agents. Reagents and conditions: (i) CS_2CO_3, MeCN, reflux, overnight, (ii) EtOH, reflux, overnight.



Scheme 25. Synthetic route to potent anti-tuberculosis agents.



Scheme 26. Synthetic route to *N*-arylamino biquinoline derivatives as potent anti-tuberculosis agents.

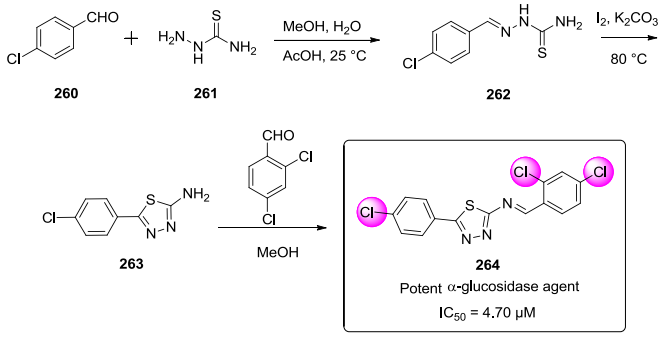
2.5. Synthesis of chlorine containing α-glucosidase agents

Diabetes is one of the insistent diseases rising in the world. According to the estimated data obtained in 2010, around 285 million peoples were suffered from diabetes all over the world and it may increase to 439 million by 2030 [69,70]. Blood glucose changing due to the insulin resistance is regarded as the feature of being diabetic in 95% of the cases [71] which give raise to several problems like high blood pressure, heart problem, kidney failure, stroke and blindness [72]. Consequently, the inhibition of α-glucosidase (EC. 3.2.1.20), a key carbohydrate hydrolyzing enzyme, could serve as an effective methodology in both preventing and treating diabetes through controlling the postprandial glucose level and suppressing postprandial hyperglycemia [73]. α-Glucosidase specifically performs the hydrolysis of α-glucopyranoside bond, resulting in the production of α -D-glucose from the non-reducing end of the sugar [74]. Several α-glucosidase inhibitors like acarbose, voglibose, and miglitol, have appeared in clinic for the treatment of type II diabetes mellitus [75], however, number and intensity of side effects call for the development of potent, structurally diverse, safe and efficacious drugs for the effective treatment of diabetes mellitus.

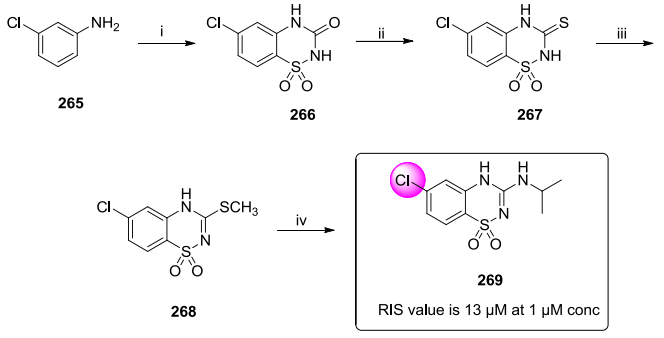
Very recently, Javid et al. have developed the synthesis and SAR study of a series of novel thiosemicarbazide compounds. The targeted thiosemicarbazide compounds were synthesized in simple and three steps. First, equimolar amount of commercially available *p*-chlorobenzaldehyde **260** was treated with thiosemicarbazide **261** in methanol in the presence of catalytic amount of HCl under reflux condition for 3–4 h to yield compound **262**. Then compound **262** was cyclized in the presence of iodine and potassium carbonate in 1,4-dioxane to afford compound **263.** Next, compound **263** was reacted with dichloro benzaldehyde in methanol in the presence of catalytic amount of conc. HCl to yield final compound **264** in good yield (Scheme 27). Compound **264** was found to be excellent α-glucosidase inhibitory agent with IC_{50} value of 4.70 μM. The presence of electron withdrawing group (Cl) on the phenyl ring highly enhanced the α-glucosidase activity [76].

In 2010, Pirotte et al. have synthesized a series of new 6-chloro-substituted-3-alkylamino/cycloalkylamino-4H-1,2,4-benzothiadiazine 1,1-dioxides analogues and tested for their *in vitro* α-glucosidase activity. The starting material aniline **265** was reacted with chlorosulfonyl isocyanate under the optimal reaction conditions to yield 6-chloro-substituted 3-oxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide **266**. Subsequent thionation of the oxo derivatives **266** with phosphorus pentasulfide in pyridine led to the corresponding compound **267**. In the next step, compound **268** was prepared from the reaction of thioxo compound **267** with methyl iodide in the presence of sodium hydrogenocarbonate. Finally, compound **268** was treated with isopropyl amine under optimal reaction conditions to obtain final product 269 [77] (Scheme 28). The compound **269** was found to be the most potent glucose-induced insulin secretion with RIS value of 13 μM per 1 μM concentration. The position of the chlorine atom on the benzene ring strongly affected the activity on insulin-secreting cells. Taken as a whole, the rank order of potency of 3-isopropylamino-substituted compounds on pancreatic β-cells was found to be 6-chloro = 6,7-dichloro > 7-chloro > 8-chloro > 5-chloro [78].

Taha et al. have synthesized novel imidazole-pyridine hybrids and screened for their *in vitro* biological activities. These compounds were prepared from commercially available starting materials 5-chloropyridine-2,3-diamine **270**. Compound **270** was reacted with substituted aldehydes **271** in the presence of $Na_2S_2O_5$ with DMF as solvent under reflux conditions to afford desired products **272a-z** in high yields (Scheme 29). All the newly

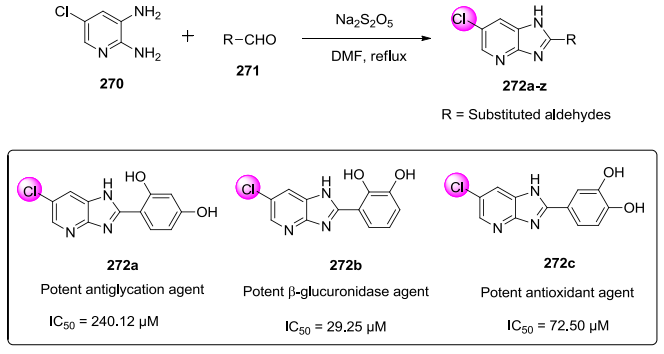


Scheme 27. Synthesis of chlorine containing drugs as potent α-glucosidase activity.



Reagents and conditions: (i) (a) $ClSO_2NCO$, CH_3NO_2; (b) $AlCl_3$; (ii) P_2S_5, pyridine; (iii) CH_3I, $NaHCO_3$, CH_3OH/H_2O; (iv) R_3NH_2

Scheme 28. Synthesis of chlorine containing drugs as potent α-glucosidase activity. Reagents and conditions: (i) (a) $ClSO_2NCO$, CH_3NO_2; (b) $AlCl_3$; (ii) P_2S_5, pyridine; (iii) CH_3I, $NaHCO_3$, CH_3OH/H_2O; (iv) R_3NH_2.



Scheme 29. Synthesis of chlorine containing drugs as potent α-glucosidase activity.

synthesized derivatives were tested for their *in vitro* biological activities such as antioxidant, antiglyacation and β-glucuronidase activities. Among them, compound **272a** ($IC_{50} = 240.12$ μM) was found to be the most potent antiglyacation agent, compound **272b** ($IC_{50} = 29.25$ μM) showed excellent β-glucuronidase activities and compound **272c** ($IC_{50} = 72.50$ μM) exhibited promising antioxidant activity [79].

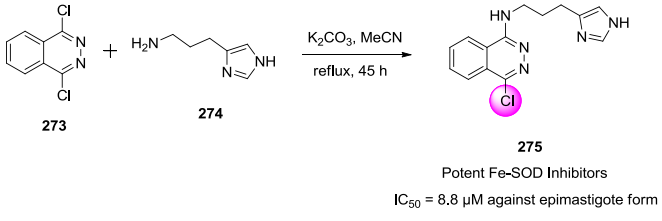
2.6. Synthesis of chlorine derived anti-malarial agents

Malaria refers to parasitic infection which spreads worldwide and caused serious problems in the tropical and subtropical parts of Asia, Central and South America, Africa and Middle East [80,81]. A parasitic class called *Plasmodium* which carried by the female Anopheles mosquito is the cause of this disease which get entered into human bloodstream. The treatment and management of this disease is irrationally high not only because of medication but also due to low production [82]. The complexities in controlling malaria lies in growing resistance of malaria parasite to most of the anti-malarial drugs are used [83].

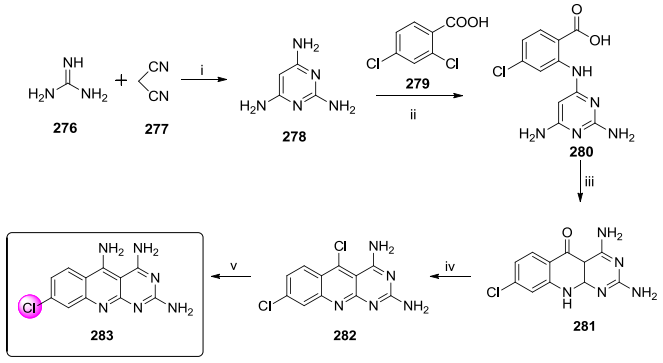
A series of phthalazine containing imidazole derivatives with different substitution pattern have been synthesized and evaluated for their *in vitro* anti-malarial activity extra and intracellular forms of *T. cruzi*. The starting material 1,4-dichlorophthalazine **273** treated with 3-(imidazole-1-yl)propylamine **274** in the presence of K_2CO_3 under reflux conditions to provide compound **275** in 48% yield (Scheme 30). Compound **275** was found to be most active *in vitro* against extra and intracellular forms of *T. cruzi* (IC_{50} value is 8.8 μM against epimastigote form) and less toxic against Vero cells which was better than the standard drug benznidazole. Furthermore, the study of antiparasitical activity of compound **275** was at a higher level for developing a new drug in future [84].

In 2005, Joshi et al. have designed, synthesized and evaluated a series of compounds for their antimalarial activity. Starting material guanidine nitrate **276** reacted with malononitrile **277** in the presence of sodium alkoxide in dry ethanol or methanol under optimal reaction conditions to yield 2,4,6-triaminopyrimidine **278**. Compound **278** was condensed with 2,4-dichlorobenzoic acid **279** in the presence of activated copper bronze powder at 180–190 °C to yield *N*-(2,4-diamino-6-pyrimidino)-4-chloroanthranilic acid **280** which further cyclized using concentrated sulfuric acid, yielded 5-oxo-(10*H*)-2,4-diamino-8-chloropyrimido-[4,5-*b*]quinoline **281**. Compound **281** was reacted with phosphorous oxychloride to obtain 2,4-diamino-5,8-dichloropyrimido-[4,5-*b*]quinoline **282**, which stirred with liquid ammonia at room temperature to yield 2,4,5-triamino-8-chloropyrimido-[4,5-*b*]quinoline **283** (Scheme 31). The synthesized compounds were screened using Rane's test for blood schizonticidal activity in mice infected by *P. berghei*. Based on the results, three compounds possessed antimalarial activity comparable to chloroquine and compound **283** was most active one [85].

A library of novel triazines substituted hybrids have been developed by Kumar et al. and were evaluated for *in vitro* anti-malarial activity against *P. falciparum*. Compound 4,7-dichloroquinoline **282** was stirred with excess of 2-aminoethanol in n-butanol under optimal reaction conditions to give the 2-(7-chloro-quinolin-4-ylamino)-ethanol **283** in moderate to good yield [86]. Chemoselective *o*-mesylation was synthesized in pyridine at 0 °C for 5 h to yield themethanesulfonic acid 2-(7-chloro-quinolin-4-ylamino)-ethyl ester **284** [87]. Compound **284** was subjected to nucleophilic substitution with trisubstituted triazines to yield the corresponding targeted compounds **285a-s** under microwave condition (Scheme 32). Compound **285a** displayed more than 99% suppression activity after four days against *in-vitro* model of *P. falciparum* and showed high 99.11% suppression against chloroquine resistant strain N-67 of *P. yoelii* in an *in vivo* assay [88].

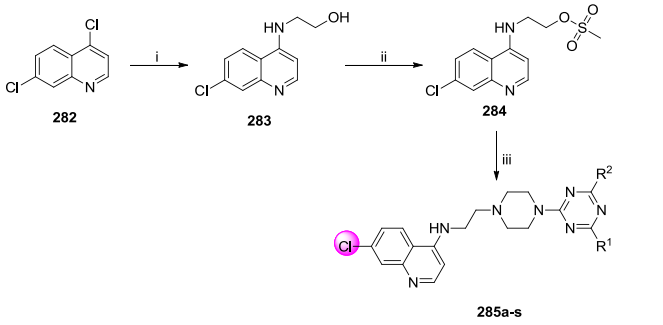


Scheme 30. Synthetic route of chlorine containing potent anti-malarial agent.



Reagents and conditions: (i) sodium alkoxide, reflux, 6h, (ii) activated Cu bronze powder, 180-190 °C, 12h (iii) Con. H_2SO_4, 100 °C, 8h, (iv) $POCl_3$, 135-140 °C, (v) liq. NH_3, rt, 1hr.

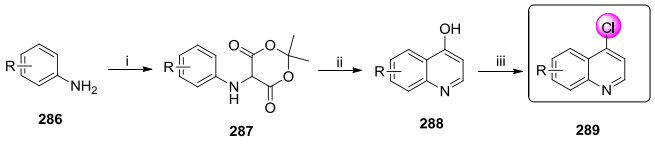
Scheme 31. Synthetic route to potent anti-malarial agents. Reagents and conditions: (i) sodium alkoxide, reflux, 6 h, (ii) activated Cu bronze powder, 180–190 °C, 12 h (iii) Con. H_2SO_4, 100 °C, 8 h, (iv) $POCl_3$, 135–140 °C, (v) liq. NH_3, rt, 1hr.



Reagents and conditions: (i) 1-amino ethanol, n-butanol, 90 °C, 8 hr, (ii) methanesulfonyl chloride, pyridine, 0 °C, 3hr, (iii) tri-substituted triazines, MW, NMP, 30 sec.

Scheme 32. Synthetic route of triazine substituted hybrids as potent anti-malarial agents. Reagents and conditions: (i) 1-amino ethanol, n-butanol, 90 °C, 8 h, (ii) methanesulfonyl chloride, pyridine, 0 °C, 3hr, (iii) tri-substituted triazines, MW, NMP, 30 s.

A new series of anti-malarial active compounds has been developed by Madrid et al. [89]. A simple two-step synthesis method was used to prepare ring substituted 4-chloroquinolines derivatives **289** allowing analysis of the effect of ring substitutions on inhibition of growth of chloroquine sensitive and resistant strains of *P. falciparum*. The first step in the sequence was the condensation of substituted aniline **286** with Meldrum's acid and trimethylorthoformate to give eneamine **287** intermediates, which then sealed into a glass reaction tube with a small volume of phenyl ether as solvent and subjected to microwave irradiation for 5 min at 300 °C (Scheme 33). The synthesized compounds were evaluated for their growth inhibition activity against *P. falciparum* with the help of fluorescent-active cell sorting (FACS) assay. For *in vitro* activity, two strains i.e. drug-sensitive and a drug-resistant were employed. Form this study it was found that substitutions with small electron withdrawing groups were found most active for anti-malarial activity.



Reagents and conditions: (i) Meldrum's acid, $CH(OCH_3)_3$, DMF, reflux, 2hr, (ii) diphenylether, 300 °C, 300 W, 5min, (iii) $POCl_3$, reflux, 3hr

Scheme 33. Synthesis of chloroquinolines as potent anti-malarial agents. Reagents and conditions: (i) Meldrum's acid, $CH(OCH_3)_3$, DMF, reflux, 2hr, (ii) diphenylether, 300 °C, 300 W, 5min, (iii) $POCl_3$, reflux, 3hr.

2.7. Chlorine containing drugs as miscellaneous applications

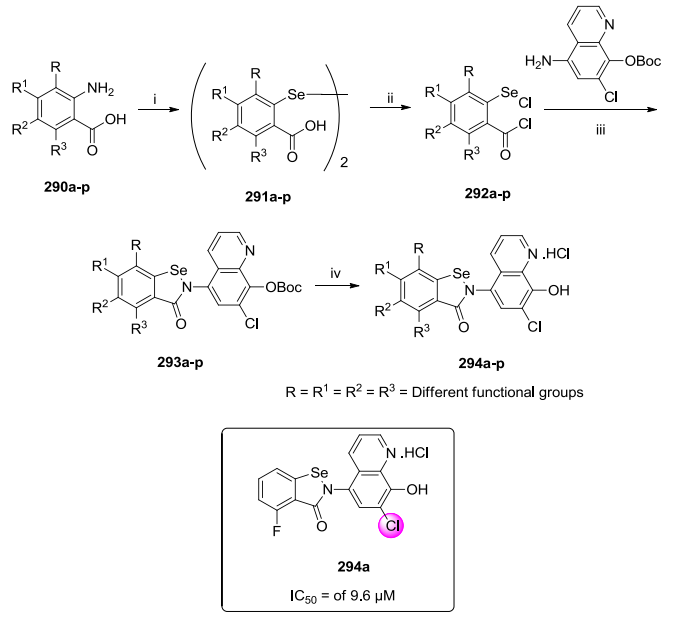
Alzheimer's disease (AD) is neurodegenerative disorder featured with cognitive dysfunction and memory lapse which accounts for the major dementia cases. According to the present estimation, about 45 million people are going through this disease worldwide and it may reach up to 131 million by 2050 if the condition left untreated [90–92]. Though actual etiology for the AD progression is not known yet, a number of pathophysiology factors are believed to be responsible for the progression of this disease. Deficits of acetylcholine (Ach), inflammation, β-amyloid (Aβ) deposits, oxidative stress, dyshomeostasis of biometals, tau-protein aggregation are considered to be such pathophysiological factors [93–95]. Unfortunately the medicines for the cure of AD and its progression have not been developed yet. But certain medicines were approved and prescribed for the AD patients for the temporary relief [96,97].

Wang et al. have synthesized a new series of selenium containing hydrochloride derivatives and tested for their *in vitro* multitarget activity against Alzheimer's disease. Firstly, Na_2Se_2 reacted with the corresponding benzenediazonium salts, which were prepared from commercially available substituted 2-amino benzoic acids **290a-p** and HNO_2 to yield 2,2-diselenobisbenzoic acids **291a-p**. Subsequently, $SOCl_2$ reacted under reflux conditions to obtain **292a-p**, which then reacted with corresponding chloro substituted amines in anhydrous CH_2Cl_2 to afford final target compounds **293a-p**. In final step, the Boc group was removed from compounds **293a-p** using HCl gas to yield de-protected hydrochloride compounds **294a-p** (Scheme 34). Compound **294a** showed excellent Alzheimer's disease inhibition activities against tested all multitargeted enzymes. Mainly, compound **294a** was found to be the most potent A$\beta_{1\text{-}42}$ aggregation agent with IC_{50} value of 9.6 μM [98].

Viruses are infectious agents affecting the life forms. They are responsible for various dangerous diseases like human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV and HCV, respectively), severe acute respiratory syndrome (SARS), corona viruses (Middle east respiratory Syndrome, MERS; influenza (seasonal, pandemic), viral haemorrhagic fevers (Ebola), dengue, and chikungunya etc. These diseases have caused adverse impact on human health by leading to unexpected illnesses and deaths and troubling day-to-day normal life activities. Viruses are the major cause for the emergence of newer pandemics e.g. H1N1 influenza, Ebola, and Zika virus etc. threatening the public health [99,100].

Likewise, more than 60 antiviral drugs of diverse chemical classes have been approved by the FDA, mainly for the treatment of HIV, the hepatitis B and C, herpes and influenza A and B viruses and still many molecules are in various stages of clinical trials. But there is still a pressing need for the development of new drugs acting through several mechanisms and combat the viral resistance as viruses [101]. However it is always challenging for the medicinal chemists to develop newer drugs focus on the unique biological features of viruses and treat the emerging viral disease in one or the other way without harming the host cells [102].

In 2012, Regina and co-workers have designed and synthesized a series of novel imidazole derivatives in a simple and single step.

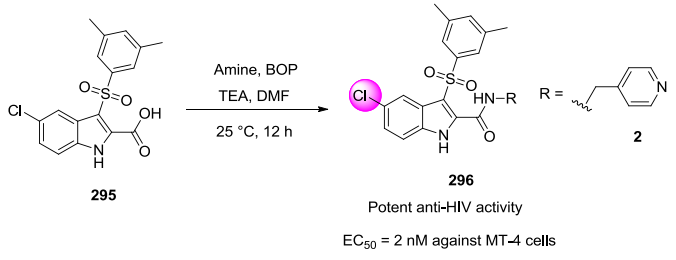


Reagents and conditions: (i) H_2O, $NaNO_2$, HCl, 0-5 °C, 30 min, Na_2Se_2, 50 °C; (ii) $SOCl_2$, reflux; (iii) anhydrous CH_2Cl_2, triethylamine, rt; (iv) CH_2Cl_2, HCl (g), 0-5 °C.

Scheme 34. Synthesis route of potent Alzheimer's agents. Reagents and conditions: (i) H_2O, $NaNO_2$, HCl, 0–5 °C, 30 min, Na_2Se_2, 50 °C; (ii) $SOCl_2$, reflux; (iii) anhydrous CH_2Cl_2, triethylamine, rt; (iv) CH_2Cl_2, HCl (g), 0–5 °C.

All synthesized derivatives were evaluated for their *in vitro* anti-HIV activity against MT-4 cells. Initially, carboxylic group free imidazole **295** was reacted with various substituted amines in the presence of BOP and TEA in DMF at room temperature to yield compound **296** (Scheme 35). Compound **296** exhibited the most potent anti-HIV activity against MT-4 cells with IC_{50} values of 2 nM. Compound **296** emerged as a useful lead compound for the development of new therapeutic tools for EFV-based HIV-1 therapies which showed the L100I and K103 N mutations [103]. The SAR revealed that the presence of pyridine group at R position highly enhanced the activity. Moreover, the electron-withdrawing chloro group was also played a crucial role in increasing anti-HIV activity.

Boland and co-workers have synthesized a novel series of potent candidate of PDE4 inhibitors in six steps. Starting from the commercially available 3,4-dihydroxybenzaldehyde **297**. Difluoromethylation of **297** in DMSO using sodium chlorodifluoroacetate as a source of difluorocarbene provided the compound **298**. Alkylation of the remaining hydroxyl group of **298** was performed with alkyl dibromides to yield intermediates **299**. In the next step, the aldehyde compound was oxidized into the corresponding benzoic acids **300**, using sodium chlorite (Lindgren oxidation) in combination with sulfamic acid as chlorine dioxide scavenger.

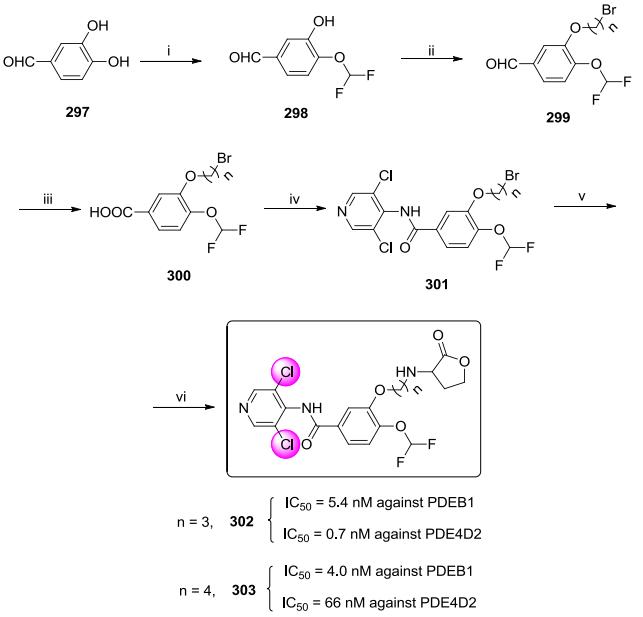


Scheme 35. Synthesis of imidazole analogues as potent anti-HIV agents.

Compound **300** coupled with 3,5-dichloropyridin-4-amine to provide intermediates **301**. Further, compound **301** underwent nucleophilic substitution with 3-amino-sulfanyldihydrofuranone to afford final compound **302** (Scheme 36). The final synthesized compounds were screened for their PDE4 inhibition activity against two PDEB1 and PDE4D2. Compounds **302** (IC_{50} = 5.4 nM against PDEB1 and 0.7 nM against PDE4D2) and **303** (IC_{50} = 4.0 nM against PDEB1 and 66 nM against PDE4D2) showed excellent PDE4 inhibition activity compared to standard drug Rolipram (IC_{50} = 52 nM against PDEB1 and 130 nM against PDE4D2) [104].

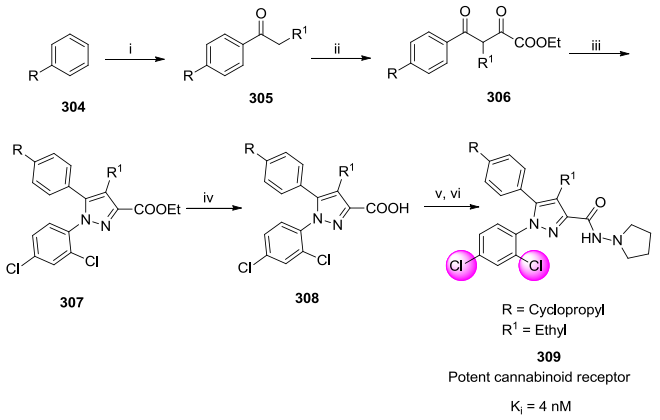
A series of novel cannabinoid type 1 receptor antagonists were synthesized by Szabo et al. In the beginning, cycloalkyl-benzenes **304** reacted with the acyl-chloride in trichloroethylene under the optimal reaction conditions to provide phenones **305**. Claisen condensation of **305** with imidazole-1-yl-oxo-acetic acid ethyl ester was reacted under optimal reaction condition at −78 °C to yield diketone esters **306** in good yields. The synthesis of acids **308** involved basic hydrolysis of the corresponding esters **307**, which in turn were prepared by condensing diketone esters **306** with suitably substituted phenyl hydrazines. The intermediates **308** were then converted into their acid chlorides by using thionyl chloride in refluxing toluene and these intermediates were reacted with commercially available 1-aminopyrrolidine in dichloromethane at room temperature to afford compounds **309** (Scheme 37). Compound **309** was found to be the most potent cannabinoid Type 1 receptor antagonist with K_i values of 4 nM. The SAR studies suggest that, the pyrazole substituents and the presence of chloro groups on the phenyl ring and pyrrolidine ring enhanced the activity of these novel CB1 antagonists [105].

Lan et al. have reported a series of aminoalkoxy pyrimidine



Reagents and conditions: (i) $ClF_2CCOONa$, NaOH, DMF, H_2O, 120 °C, 2 h; (ii) $Br(CH_2)_nBr$, K_2CO_3, ACN, reflux, 4 h; (iii) H_2NSO_3H, $NaClO_2$, AcOH, H_2O, 10 °C, 30 min; (iv) (1) $SOCl_2$, toluene, 90 °C, 1.5 h; (2) 3,5-dichloro-4-aminopyridine 60% NaH, THF, 10 °C, 1 h; (v) 2-oxo-3-amino-oxolane, K_2CO_3, ACN, reflux, 1.5 h.

Scheme 36. Synthetic route of chlorine containing hybrids as potent PDE4 inhibitors. Reagents and conditions: (i) $ClF_2CCOONa$, NaOH, DMF, H_2O, 120 °C, 2 h; (ii) $Br(CH_2)_nBr$, K_2CO_3, ACN, reflux, 4 h; (iii) H_2NSO_3H, $NaClO_2$, AcOH, H_2O, 10 °C, 30 min; (iv) (1) $SOCl_2$, toluene, 90 °C, 1.5 h; (2) 3,5-dichloro-4-aminopyridine 60% NaH, THF, 10 °C, 1 h; (v) 2-oxo-3-amino-oxolane, K_2CO_3, ACN, reflux, 1.5 h.



Reagents and conditions: (i) R^1CH_2COCl, $AlCl_3$, trichloroethylene, -50 °C; (ii) LiHMDS, THF, Imidazol-1-yl-oxo-acetic acid ethyl ester, -78 °C, 1 N HCl; (iii) 2,4-dichlorophenylhydrazine hydrochloride, EtOH, reflux; (iv) 2.5N KOH, MeOH, reflux; (v) $(COCl)_2$, DMF, CH_2Cl_2 rt; (vi) 1-aminopyrrolidine, CH_2Cl_2, rt.

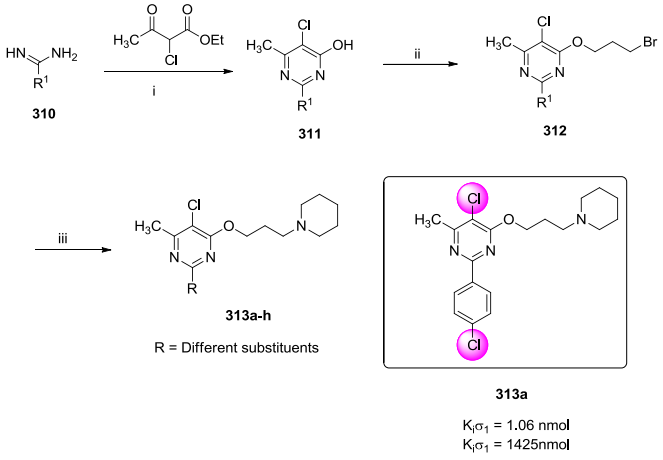
Scheme 37. Synthetic route of pyrrolidine containing hybrids as potent cannabinoid Type 1 receptor antagonists. Reagents and conditions: (i) R^1CH_2COCl, $AlCl_3$, trichloroethylene, −50 °C; (ii) LiHMDS, THF, Imidazole-1-yl-oxo-acetic acid ethyl ester, −78 °C, 1 N HCl; (iii) 2,4-dichlorophenylhydrazine hydrochloride, EtOH, reflux; (iv) 2.5 N KOH, MeOH, reflux; (v) $(COCl)_2$, DMF, CH_2Cl_2 rt; (vi) 1-aminopyrrolidine, CH_2Cl_2, rt.

derivatives as potent neuropathic pain agents. The targeted compounds were synthesized in three steps from starting material aryl- or alkyl-amidine **310.** Compound **310** was reacted with ethyl 2-chloro-3-oxobutanoate under optimal reaction conditions to yield intermediate **311**, and then compound **311** was treated with $Br(CH_2)_3Br$ under reflux conditions to provide compound **312**. Compound 1,3-dibromopropane **312** was reacted with piperidine in the presence of Cs_2CO_2 in acetonitrile to afford aminoalkoxy pyrimidine derivatives **313a-h** (Scheme 38). Compound **313a** was found to be the most potent *in vitro* neuropathic pain agents with $K_i\sigma_1$ of 1.06 nmol and $K_i\sigma_2$ of 1425 nmol. Moreover, compound **313a** exhibited good safety, acceptable pharmacokinetic properties and good selective profile to some specific targets. Thus, compound **313a** may facilitate the development of a novel class drugs for the treatment of neuropathic pain. Further studies of compound **313a** and evaluation of these series of derivatives are currently underway in their laboratory and will be reported in due course [106].

In 2016, Cao and co-workers have designed and synthesized a new series of pyridazinone substituted analogues and evaluated for their *in vitro* antineuropathic pain activity. Starting material phenylhydrazine hydrochloride **314** was reacted with maleic anhydride **315** in the presence of conc. HCl at reflux conditions to obtain cyclization product **316**. Then, compound **316** alkylated with 1,3-dibromopropane to yield **317**, and then reacted with the piperidine to afford the final compounds **318** in moderate yields (Scheme 39). Compound **318** showed potent σ_1 receptor affinity ($K_i\sigma_1 = 1.4$ nM) and excellent selectivity over not only σ_2 receptor (1366-fold). These profiles suggested that compound **318** may be a novel class of candidate drugs for treatment of neuropathic pain [107].

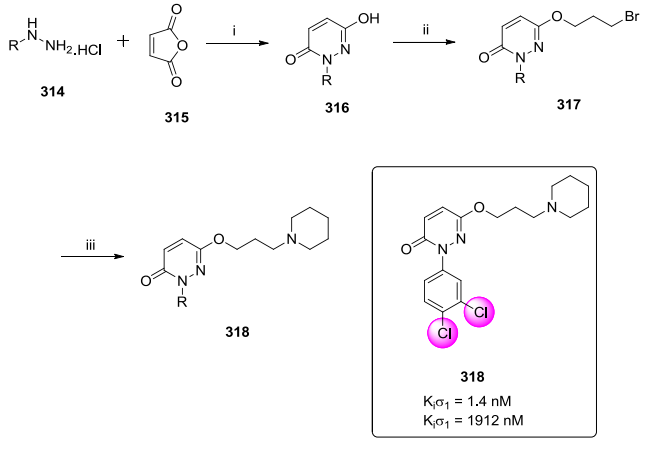
In 2007, Nencka and co-workers have developed a series of novel substituted-6-chlorouracils analogues as potent inhibitory agent against recombinant human TP expressed in V79 Chinese hamster cells. Commercially available 4-chloro-2,6-dimethoxypyrimidine **319** underwent direct *ortho*-lithiation with butyllithium at −78 °C to afford intermediate compound **320**. Then compound **320** was reacted with acetone at −78 °C until the temperature reached to room temperature to afford **321**. In the final step, compound **321** was treated with con. HCl in dioxane under reflux conditions to obtain target compound **322** in good yield (Scheme 40). The most effective inhibitor is compound **322**, which inhibited the enzyme expression in V79 cells competitively with K_i of 0.20 μM and the enzyme purified from placenta with *K*i of 0.29 μM. In this manner, this study changes the traditional view on uracil-based TP inhibitors and provides a novel lead for further research [108].

Recently, Tzvetkov and co-workers have reported indole substituted analogues as potent monoamine oxidase B inhibitors. The targeted compounds were synthesized in single step from commercially available indole carboxylic acid **323.** Compound **323** was coupled with dichloro amine **324** using coupling reagent EDC.HCl in methanol at room temperature to give compound **325** in good yield (Scheme 41. Compound **325** was screened for its



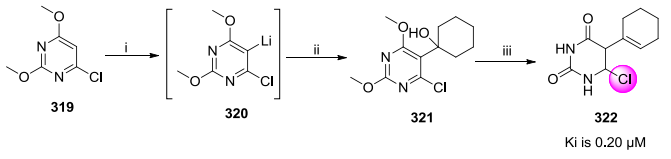
Reagents and conditions: (i) *t*-BuOK, MeOH, reflux; (ii) $Br(CH_2)_3Br$, K_2CO_3, acetone, reflux; (III) piperidine, Cs_2CO_3, acetonitrile, reflux.

Scheme 38. Synthetic route for aminoalkoxy pyrimidine derivatives as potent neuropathic pain agents. Reagents and conditions: (i) *t*-BuOK, MeOH, reflux; (ii) $Br(CH_2)_3Br$, K_2CO_3, acetone, reflux; (III) piperidine, Cs_2CO_3, acetonitrile, reflux.



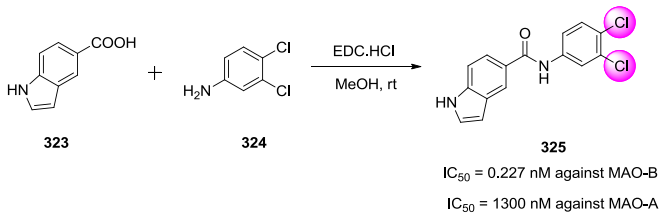
Reagents and conditions: (i) H_2O, conc. HCl, reflux; (ii) $Br(CH_2)_3Br$, K_2CO_3, acetone, reflux; (iii) piperidine, K_2CO_3, KI, acetonitrile, reflux.

Scheme 39. Synthetic route for chlorine containing pyridazinone substituted analogues as potent antineuropathic pain agents. Reagents and conditions: (i) H_2O, conc. HCl, reflux; (ii) $Br(CH_2)_3Br$, K_2CO_3, acetone, reflux; (iii) piperidine, K_2CO_3, KI, acetonitrile, reflux.

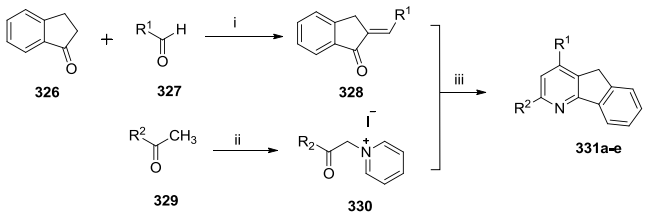


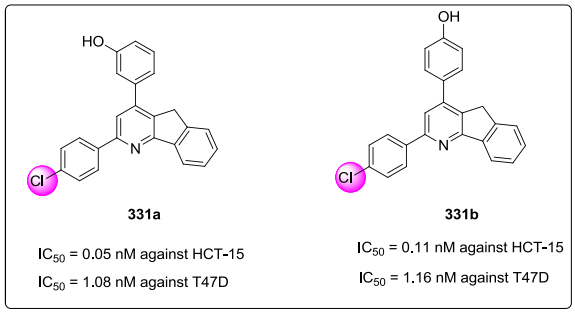
Reagents and Conditions: (i) *n*-BuLi, THF, -78 °C; (ii) ketone, -78 °C to rt; (iii) concd HCl, dioxane, reflux.

Scheme 40. Synthesis of substituted-6-chlorouracils analogues as potent inhibitory activity. Reagents and Conditions: (i) *n*-BuLi, THF, −78 °C; (ii) ketone, −78 °C to rt; (iii) concd HCl, dioxane, reflux.



Scheme 41. Synthesis of chlorine containing indole analogues as potent monoamine oxidase B inhibitors.





Reagents and conditions (i) aq. NaOH (5%), EtOH, 1-12 h, room temperature; (ii) pyridine, iodine, 3 h, 140 °C, (iii) NH_4OAc, methanol or glacial acetic acid, 24-36 h, 100 °C

Scheme 42. Synthesis of chlorine containing hybrids as potent topoisomerase inhibitor. Reagents and conditions (i) aq. NaOH (5%), EtOH, 1–12 h, room temperature; (ii) pyridine, iodine, 3 h, 140 °C, (iii) NH_4OAc, methanol or glacial acetic acid, 24–36 h, 100 °C.

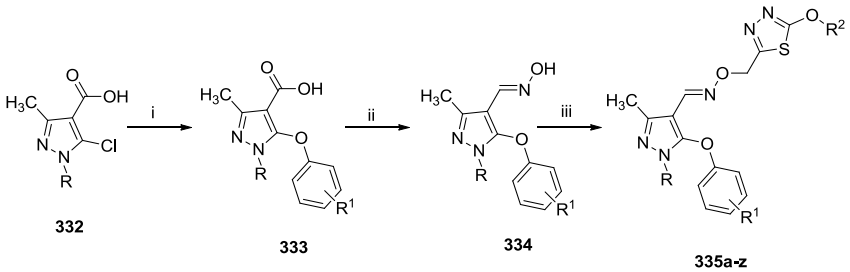
monoamine oxidase B inhibition activity and showed potent activity with IC_{50} values of 0.227 nM against human MAO-B and 1300 nM against human MAO-A enzymes. Future efforts will be directed toward further improving the compounds' drug-like properties with regard to water-solubility, bioavailability, metabolism, and toxicity and to evaluate the new MAO-B inhibitors in relevant animal models [109].

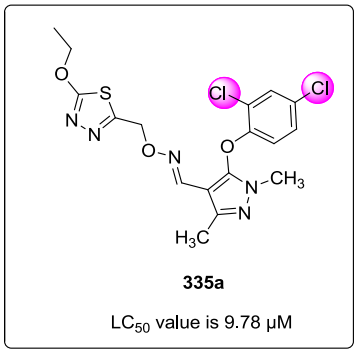
Very recently, Kadayat and co-workers developed 2,4-diphenyl-5*H*-indeno[1,2-*b*]pyridines as potent topoisomerase inhibitor. In the first step, 1-indanone **326** was condensed with aryl aldehydes **327** to prepare indanone intermediates **328** in the presence of 5% aqueous NaOH in ethanol using Claisen-Schmidt condensation reaction [110]. Then, six pyridinium iodide salts **330** were synthesized by refluxing acetophenones **329** with iodine in pyridine. Finally, using modified Kröhnke synthesis [111], indanone intermediates **328** and pyridinium iodide salts **330** were reacted in the presence of dry ammonium acetate in methanol or acetic acid to yield compounds **331a-e** in the moderate yields (Scheme 42). All the synthesized eighteen new chlorinated compounds were assessed for topoisomerase inhibitory activity and cytotoxicity against HCT15, T47D, and HeLa cancer cell lines. Among them, compounds **331a** ($IC_{50} = 0.05$ nM against HCT-15 and $IC_{50} = 1.08$ nM against T47D cell lines) and **331b** ($IC_{50} = 0.11$ nM against HCT-15 and $IC_{50} = 1.16$ nM against T47D cell lines) showed the most potent topoisomerase activity which is better than the reference drugs. All of the chlorinated compounds displayed significant cytotoxic effect, revealing potent anticancer activity against T47D breast cancer cells [112].

Synthesis of new class of acaricidal and insecticidal agents was carried out by Kadayat and co-workers. The synthetic route was medium length and included three chemical steps. In the first step, 5-chloropyrazole-4-carbaldehyde **332** was reacted with substituted phenols in the presence of KOH under the optimal reaction conditions to obtain intermediate compound **333** [113]. Further, the compound **333** was reacted with hydroxylamine hydrochloride in methanol or ethanol medium to yield compound 5-aryloxy pyrazole oximes **334** in good yields. The treatment of intermediate **334** with 2-chloromethyl-5-alkoxy-1,3,4-thiadiazole in acetonitrile medium using potassium carbonate as alkali produced corresponding pyrazole oximes containing a substituted 1,3,4-thiadiazole moiety **335a-z** (Scheme 43). All the newly synthesized compounds were evaluated for their *in vitro* acaricidal and insecticidal activities. Compound **335a** showed the most potent insecticidal activities against *P. xylostella* with LC_{50} value of 9.78 μM which was better than the control compound Pyridalyl ($LC_{50} = 17.40$ μM) [114].

Very recently, Taha and co-workers have developed a novel class of indole derivatives as potent α-amylase inhibition agent. The synthetic route was very simple and it included only two steps. In the first step, indole ethyl ester **336** was converted into indole-hydrazide **337** using hydrazine hydrate in ethanol under reflux condition for 6 h. The indole hydrazide **337** was reacted with various aromatic isothiocyanate in chloroform and stirred for 3 h to yield final target indole derived products **338a-s** in good yields (Scheme 44). All the synthesized compounds were tested for their α-amylase inhibitory activity. Compounds **338a** and **338b** displayed the most potent α-amylase inhibitory activity with IC_{50} values of 2.10 μM and 2.03 μM respectively. The SAR revealed that the presence of electron withdrawing groups (Cl and F) on the phenyl ring highly enhanced the α-amylase activity. Compounds having substituents on *para*-position are more active than their *ortho* and *meta* counterpart [115].

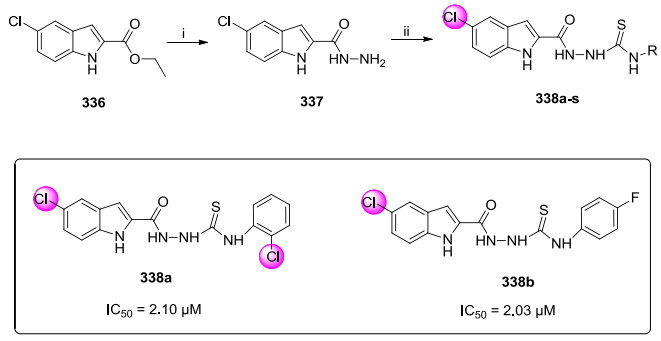
Chourey and co-workers have designed and synthesized a novel eicosatetraenoic acid as potent OXE receptor agent. Chloro substituted indole analog **339** was reacted with (R)-methyl 5-chloro-3-methyl-5-oxopentanoate under optimal reaction conditions to obtain intermediate **340** in very good yield. Then methyl ester group of intermediate **340** was converted into free carboxylic acid group using $LiOH \cdot H_2O$ in THF/H_2O (4:1) at room temperature to obtain final compound **341** in good yield (Scheme 45). The synthesized compound was found to be the most potent OXE receptor with IC_{50} value of 120 pM. These new highly potent OXER antagonists may provide a novel strategy for the treatment of eosinophilic disorders like asthma. The SAR revealed that the addition of a phenyl group at the end of the hexyl side chain of the





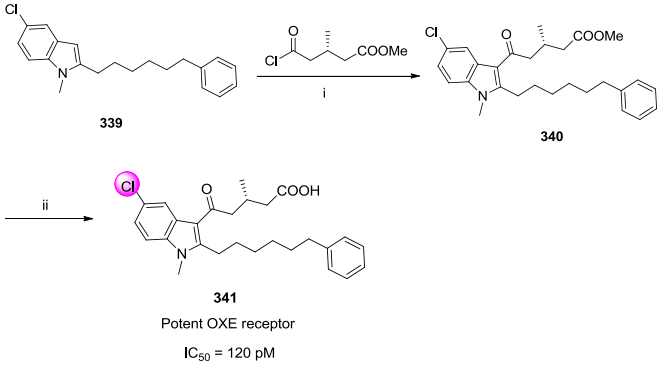
Reagents and conditions: (i) substituted phenols, KOH, DMF or DMSO, 45 °C, 2 h, 110 °C, 6-22 h; (ii) $NH_2OH.HCl$, KOH, CH_3OH or CH_3CH_2OH, reflux, 5-20 h; (iii) substituted 2-chloromethyl-5-alkoxy-1,3,4-thiadiazole, K_2CO_3, CH_3CN, reflux, 8-17 h.

Scheme 43. Synthesis of thiadiazole containing pyrazole oxime derivatives as potent acaricidal and insecticidal agents. Reagents and conditions: (i) substituted phenols, KOH, DMF or DMSO, 45 °C, 2 h, 110 °C, 6–22 h; (ii) $NH_2OH.HCl$, KOH, CH_3OH or CH_3CH_2OH, reflux, 5–20 h; (iii) substituted 2-chloromethyl-5-alkoxy-1,3,4-thiadiazole, K_2CO_3, CH_3CN, reflux, 8–17 h.



Reagents and condition: (i) NH_2-NH_2, ethanol, reflux, 6 h; (ii) arylisothiocyanatee $CHCl_3$, stir.

Scheme 44. Synthesis of chlorine containing indole derivatives as potent α-amylase inhibitory agents. Reagents and condition: (i) NH_2-NH_2, ethanol, reflux, 6 h; (ii) arylisothiocyanatee $CHCl_3$, stir.

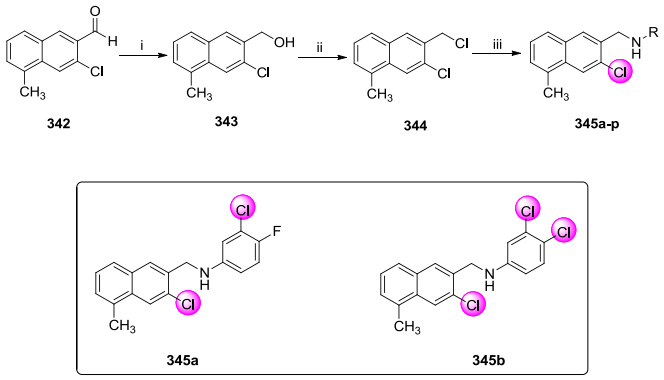


Reagents and conditions: (i) Me_2AlCl, CH_2Cl_2, rt, 3 h, 93%; (b) $LiOH·H_2O$, THF/H_2O (4:1), MeOH, rt, 16 h, 95%.

Scheme 45. Synthesis of eicosatetraenoic acid as potent OXE receptor agent. Reagents and conditions: (i) Me_2AlCl, CH_2Cl_2, rt, 3 h, 93%; (b) $LiOH·H_2O$, THF/H_2O (4:1), MeOH, rt, 16 h, 95%.

OXE-R antagonist **S-230** contribute to dramatic increasement in both *in vitro* potency and half-life in the circulatory system when administered orally to monkeys [116].

In 2011, Kumar et al. have designed and synthesized a novel series of quinolinyl amines and screened for their *in vitro* antidepressant activity. The intermediate product 2-chloro-3-(chloromethyl)-8-methylquinoline **344** was prepared in two steps from 2-chloro-3-formyl-8-methylquinoline **342** via its reduction with $NaBH_4$ followed by chlorination with $SOCl_2$. The quinolinyl amines **345a-p** were prepared by nucleophilic substitution reaction of **344** with various amines in absolute ethanol in the presence of base triethylamine (Scheme 46). Compounds **345a** and **345b** showed promising antidepressant activities. The preliminary SAR of quinolinyl amines suggested that compound with electron



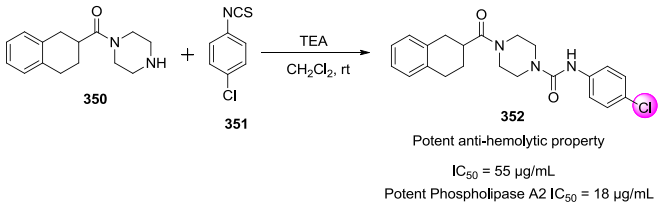
Reagent and conditions: (i) $NaBH_4$, methanol, stirring rt; (ii) $SOCl_2$, dry benzene, 80 °C, reflux. (iii) Various amine, ethanol, TEA, reflux.

Scheme 46. Synthesis of chlorine containing quinolinyl amines as potent antidepressant agent. Reagent and conditions: (i) $NaBH_4$, methanol, stirring rt; (ii) $SOCl_2$, dry benzene, 80 °C, reflux. (iii) Various amine, ethanol, TEA, reflux.

withdrawing groups (F and Cl) showed good antidepressant activity [117].

In 2010, Bouloc and co-workers have developed pyrazine substituted hybrids and tested their *in vitro* Aurora kinase inhibitory activity. The starting material 6,8-Dibromoimidazo[1,2-*a*]pyrazine **346** was chlorinated at the C-3 position in the presence of NCS under the optimal reaction conditions to afford intermediate compound **347.** Then, intermediate **374** underwent aromatic nucleophilic substitution at the C-8 position to provide compound **348** followed by a chemoselective Suzuki cross-coupling at C-6 position to afford final compound **349** (Scheme 47). Compound **349** was found to be the most potent aurora inhibitory agent with IC_{50} of 0.190 ± 0.138 μM [118].

In 2018, Karthik and co-workers have developed piperazine-1-carbothioamide chitosan silver nanoparticles (P1C-Tit*CAgNPs) as potent anti-hemolytic agents. The starting materials **350** and *p*-chloro isocyanates **351** were reacted with the base TEA in dichloromethane under room temperature to obtain compound (*N*-(4-chlorophenyl)-4-(2,3dihydrobenzoic[*b*]1,4]dioxine-2-carbonyl) piperazine-1carbothioamide **352** in good yield (Scheme 48). The final compound **352** was converted to silver nanoparticles (P1C-

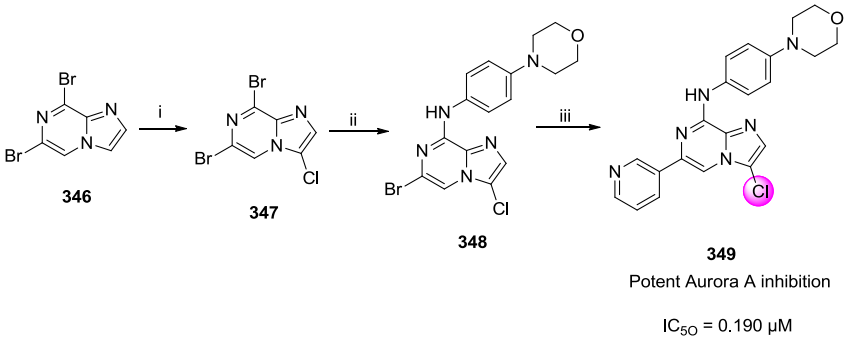


Scheme 48. Synthesis of chlorine containing piperazine-1-carbothioamide chitosan silver nanoparticles (P1C-Tit*CAgNPs) as potent anti-hemolytic agents.

Tit*CAgNPs) and the final silver coated nanoparticles were evaluated for their *in vitro* anti-inflammatory activity. Compound **352** showed potent anti-hemolytic activity with IC_{50} value of 55 μg/mL. Compound **352** also showed potent phospholipase A2 (PLA2) enzyme inhibitory activity with IC_{50} value of 18 μg/mL, which was much better than the reference drug Diclofenac (70 μg/mL) [119].

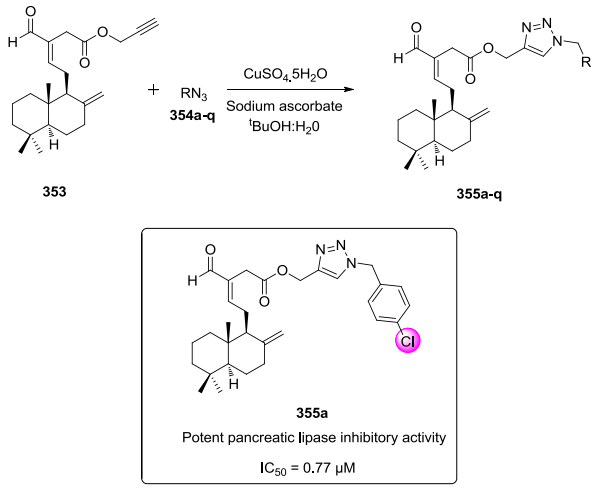
Very recently, Jalaja et al. have prepared triazoles derived natural products as potent pancreatic lipase inhibitors. The starting material propargylated labdane **353** was reacted with various substituted benzyl and phenacyl azides **354a-q** at room temperature to provide 1,2,3-triazole appended labdane derivatives **355a-q** in good to excellent yields (Scheme 49). All the synthesized natural product derived labdane appended triazoles were evaluated for their pancreatic lipase inhibitor activity. Among them, compound **355a** was found to be the most potent pancreatic lipase inhibitor agents with IC_{50} value of 0.77 μM, which was much better than the reference drug Orlistat ($IC_{50} = 0.8 \pm 0.03$ μM) [120].

In 2018, Hangeland and co-workers synthesized potent lipase inhibitors from starting material Ethyl 1-ethyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate **356** [121,122]. Compound **356** was first *o*-methylated with trimethylsilyldiazomethane in the presence of DIPEA [123], followed by saponification of the ester. The free carboxylic acid **357** was coupled with amines using the corresponding acid chloride which was generated from oxalyl chloride. The resulting amides were demethylated with boron trichloride to yield final products **358a-d** in moderate yields (Scheme 50). All the produced analogues were screened as a small set of nonselective lipase inhibitors against endothelial lipase (EL) to identify a potent and reversible inhibitor. Compound **358a** (EL_{HDL} $IC_{50} = 218$ nM) showed good inhibitory activity against the tested endothelial lipase [124].

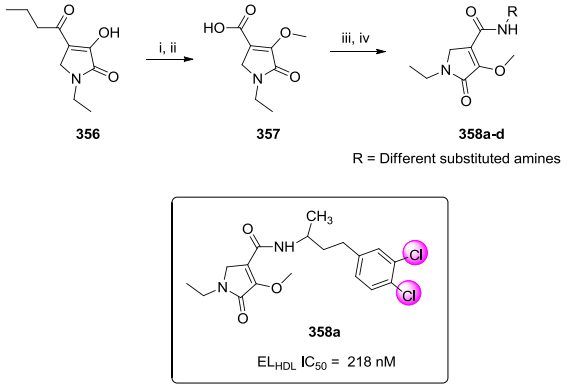


Reagents and conditions: (i) NCS, CH_3CN/DCE (3:1), reflux, (ii) 4-(4-morpholino)aniline, DIPEA, Dioxane, 180 °C, reflux, (iii) 3-pyridylboronic acid, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, CH_3CN, 150 °C, 30min.

Scheme 47. Synthesis of pyrazine substituted hybrids as potent Aurora kinase A inhibitory agent. Reagents and conditions: (i) NCS, CH_3CN/DCE (3:1), reflux, (ii) 4-(4-morpholino) aniline, DIPEA, Dioxane, 180 °C, reflux, (iii) 3-pyridylboronic acid, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, CH_3CN, 150 °C, 30min.



Scheme 49. Synthesis of triazoles derived natural products as potent pancreatic lipase inhibitors.



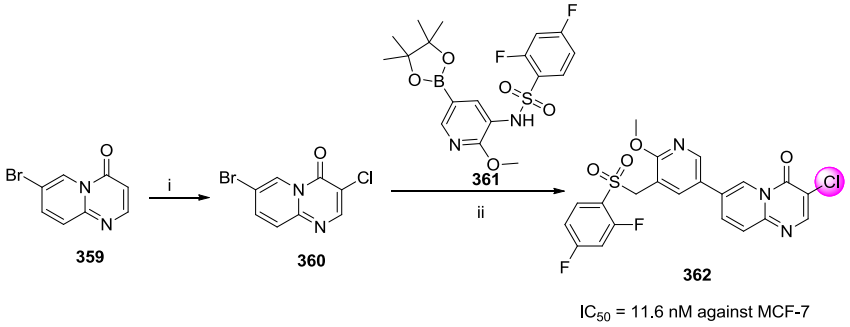
Reagents and conditions: (i) $TMSCH_2N_2$, DIPEA, Et_2O, rt, 48 h; (ii) NaOH, MeOH/H_2O (1:1), 70 °C, 1 h; (iii) oxalyl chloride, CH_2Cl_2, DMF(cat), (iv) R^3-NH_2, DIPEA, CH_2Cl_2, rt, 3 h; BCl_3, CH_2Cl_2, rt, 5 h.

Scheme 50. Synthesis of chlorine containing hybrids as potent lipase inhibitors. Reagents and conditions: (i) $TMSCH_2N_2$, DIPEA, Et_2O, rt, 48 h; (ii) NaOH, MeOH/H_2O (1:1), 70 °C, 1 h; (iii) oxalyl chloride, CH_2Cl_2, DMF(cat), (iv) R^3-NH_2, DIPEA, CH_2Cl_2, rt, 3 h; BCl_3, CH_2Cl_2, rt, 5 h.

A novel class of pyridopyrimidinones derivatives have been synthesized by Yu et al. and evaluated the enzyme activity against PI3K and mTOR. In addition, reaction of 7-bromo-4H-pyrido[1,2-*a*] pyrimidin-4-one **359** with NCS under the optimal reaction conditions provided intermediate **360**. Subsequently, chlorine-substituted **360** reacted with pyridineboronic acid pinacol ester **361** to afford final product **362** (Scheme 51). Compound **362** was evaluated as a novel class of efficacious dual PI3K/mTOR inhibitors. Compound **362** showed good enzyme activity against PI3K and mTOR (IC_{50} (PI3kα/mTOR) = 3.4/4.7 nM) and potent suppression of Akt and p70s6k phosphorylation in cellular assays. Furthermore, compound **362** also demonstrated significant *in vivo* efficacy in a PC-3M tumour xenograft model [125].

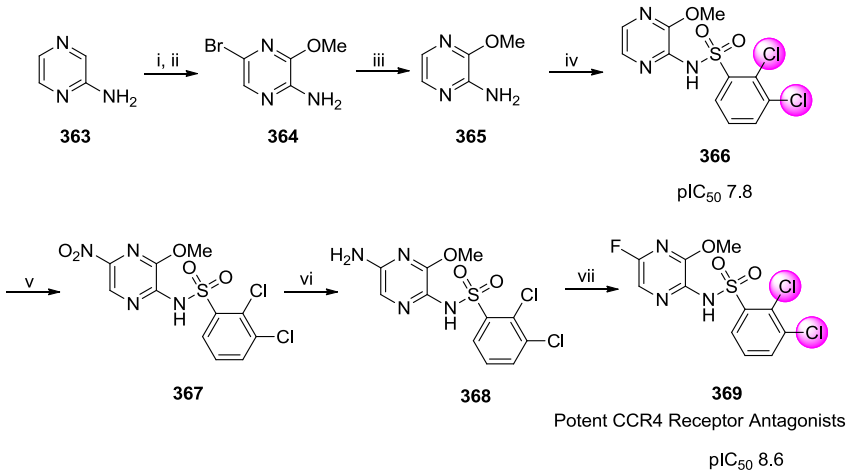
A novel class of sulfonamide derivatives have been synthesized by Kindon et al. and evaluated as CCR4 receptor antagonists. The syntheses of target compounds was lengthy and it includes six chemical steps starting from 2-aminopyrazine **363**. Commercially available 2-aminopyrazine **363** was diboration by selective displacement of the bromine in the 3-position with sodium methoxide to obtain 2-amino-5-bromo-3-methoxypyrazine **364**. The bromine at 5-position was then removed by hydrogenation and coupling of the 2,3-dichlorophenylsulphonyl chloride with 2-amino-3-methoxypyrazine **365** to yield **366**. A highly selective 5-position nitration of **366** followed by reduction of the nitro group **367** gave an amino-pyrazine **368** which was diazotized in the presence of hydrofluoric acid to give **369** in good yield (Scheme 52). The synthesized final compound and intermediates were screened for their CCR4 receptor inhibition activity. Compounds **366** (pIC_{50} 7.8) and **369** (pIC_{50} 8.6) were showed good potency against Human CCR4 receptor [126].

At last, very recently, Filipski and co-workers have developed potent Sodium-Phosphate Cotransporter NaPi2a (SLC34A1) inhibitors. Pyrrole derivative **370** [127] were reacted with enol tosylate **371** [128] to form **372** and then DBU was used to effect pyridine ring cyclization to give azaindole **373**. Conversion of 7-hydroxyazindole **373** to the corresponding 7-chloroazaindole **374** was accomplished using phosphorus oxychloride. N-Chlorosuccinimide chlorination of the 3-position yielded **374** and S_NAr with (S)-morpholin-2-ylmethanol **375** provided the desired **376** (Scheme 53. The compound **376** was screened for their Sodium-Phosphate Cotransporter NaPi2a (SLC34A1) inhibitor activity and compound **376** (NaPi2a IC_{50} = 380 nM) was found to be good NaPi2a inhibitor. Compound **376** (PF-06869206) was the first orally bioavailable selective NaPi2a inhibitor and represented a pharmacological tool to probe the functional effects of selective NaPi2a inhibition *in vivo* [129].



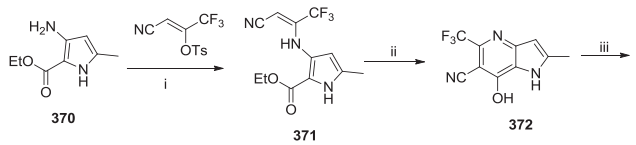
Reagents and conditions: (i) NSC, DMF, rt, (ii) 3, $Pd(dppf)_2Cl_2$, K_2CO_3, dioxane/H_2O, 100 °C

Scheme 51. Synthetic route of chlorine containing pyridopyrimidinones derivatives as potent enzyme activity agents. Reagents and conditions: (i) NSC, DMF, rt, (ii) 3, $Pd(dppf)_2Cl_2$, K_2CO_3, dioxane/H_2O, 100 °C.



Reagents and conditions: (i) Br_2, dichloromethane, 2,6-lutidine; (ii) NaOMe, MeOH, reflux (iii) H_2, Pd/C, ethanol, rt (iv) $ArSO_2Cl$, KOtBu, 0-25°C, THF, (v) HNO_3, AcOH, 70-85 °C, (vi) H_2, Pd/C, AcOH, 60 °C, (vii) HBF_4, CH_3CN, 0-5 °C, $NaNO_2$ or HF/pyridine/$NaNO_2$

Scheme 52. Synthesis of sulfonamides derivatives as potent CCR4 receptor antagonists. Reagents and conditions: (i) Br_2, dichloromethane, 2,6-lutidine; (ii) NaOMe, MeOH, reflux (iii) H_2, Pd/C, ethanol, rt (iv) $ArSO_2Cl$, KOtBu, 0–25 °C, THF, (v) HNO_3, AcOH, 70–85 °C, (vi) H_2, Pd/C, AcOH, 60 °C, (vii) HBF_4, CH_3CN, 0–5 °C, $NaNO_2$ or HF/pyridine/$NaNO_2$.



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Reagents and conditions: (i) *i*-Pr_2NEt, CH_3CN, -10 to -5 °C, 87%; (ii) DBU, CH_3CN, 90 °C, 70%; (iii) $POCl_3$, CH_3CN, 60 °C, 90%; (iv) NCS, DMF, 30 °C, 76%; (v) i-Pr_2NEt, CH_3CN, 80 °C, 86%

Scheme 53. Synthesis of chlorine containing hybrids as potent NaPi2a (SLC34A1) inhibitors. Reagents and conditions: (i) *i*-Pr_2NEt, CH_3CN, −10 to −5 °C, 87%; (ii) DBU, CH_3CN, 90 °C, 70%; (iii) $POCl_3$, CH_3CN, 60 °C, 90%; (iv) NCS, DMF, 30 °C, 76%; (v) i-Pr_2NEt, CH_3CN, 80 °C, 86%.

3. Conclusion

Chlorine based drugs in medicinal chemistry is an attractive and useful to study the exact frequency, drug target, distribution, and diverse biological application ways in U.S. FDA approved pharmaceuticals. Additionally, we hope that the synthetic organic chemistry researchers could improve the ways to synthesize potent chlorine-based drugs as well as underrepresented and non-existent drugs. In this review, we mainly focused on the synthesis of chlorinated drugs, chlorinated drugs as a function of approval date, disease condition, chlorine attachment and structure-activity relationship. We believe that this review article will be useful for inspiring the structural design and developments of less toxic and powerful chlorine-based drugs against the numerous death-causing diseases.

Acknowledgements

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