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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.

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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 (CCl2), and none of the approved drugs has trisubstituted (CCl3) groups. This interesting research gap suggests that, chlorine will further advance the pharmaceuticals in the future [1]. To improve the quality and success 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, hetero-aromatic 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 ≫ Br > I) [8–10].

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 1

| Therapeutic category                  | Sales in billions |
|--------------------------------------|------------------|
| Cardiovascular disease               | $4.7             |
| Central nervous system               | $4.9             |
| Alimentary-metabolism                | $26.5            |
| Respiratory                          | $19.4            |
| Anti-infective                       | $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**       |
**Table 2**
List out the FDA approved chlorine containing drugs in market (1949–2012).

| SLNo | Drug Name       | Structure                      | Diseases                                | Approved Year |
|------|-----------------|--------------------------------|-----------------------------------------|---------------|
| 1    | Chloromycetin   | ![Structure](image1)            | AIN/DER/GUS/SEN                         | 1949          |
| 2    | pHisoHex        | ![Structure](image2)            | Dermatological                          | 1949          |
| 3    | Tace            | ![Structure](image3)            | Genito-Urinary and Sex hormone          | 1950          |
| 4    | Chloro-Trimeton | ![Structure](image4)            | NES/RES                                 | 1950          |
| 5    | Clonidine       | ![Structure](image5)            | NER/CAR/SEN                              | 1950          |
| 6    | Ethchlorvynol   | ![Structure](image6)            | Nervous System                           | 1950          |
| 7    | Phenoxybenzamine| ![Structure](image7)            | Cardiovascular                           | 1953          |
| 8    | Nesacaine       | ![Structure](image8)            | Nervous System                           | 1955          |
| 9    | Ambenonium      | ![Structure](image9)            | Nervous System                           | 1956          |
| 10   | Halothane       | ![Structure](image10)           | Nervous System                           | 1956          |
| 11   | Atarax          | ![Structure](image11)           | Nervous System                           | 1956          |
| 12   | Compazine       | ![Structure](image12)           | Nervous System                           | 1956          |
| 13   | Leukeran        | ![Structure](image13)           | Oncological                              | 1957          |

(continued on next page)
| SL No | Drug Name | Structure | Diseases                               | Approved Year |
|-------|-----------|-----------|----------------------------------------|---------------|
| 14    | Diuril    | ![](diagram1.png) | Cardiovascular                        | 1957          |
| 15    | Thorazine | ![](diagram2.png) | Nervous System                         | 1957          |
| 16    | Trilafon  | ![](diagram3.png) | Nervous System                         | 1957          |
| 17    | Diabinese | ![](diagram4.png) | Alimentary tract and metabolism        | 1958          |
| 18    | Chlorprothixene | ![](diagram5.png) | Nervous System                         | 1958          |
| 19    | Parafon   | ![](diagram6.png) | Musculo-skeletal                       | 1958          |
| 20    | Cytoxan   | ![](diagram7.png) | Oncological                            | 1959          |
| 21    | Hydrochlorothiazide | ![](diagram8.png) | CAR/END                                | 1959          |
| 22    | Librium   | ![](diagram9.png) | Nervous System                         | 1960          |
| 23    | Trancopal | ![](diagram10.png) | Musculo-skeletal                       | 1960          |
| 24    | Clomifene | ![](diagram11.png) | Genito-Urinary and Sex hormone         | 1960          |
| 25    | Clomipramine | ![](diagram12.png) | NER/END                                | 1960          |
| 26    | Methoxyflurane | ![](diagram13.png) | Nervous System                         | 1960          |
| 27    | Enduron   | ![](diagram14.png) | Cardiovascular                         | 1960          |
| 28    | Daranide  | ![](diagram15.png) | Sensory organ                          | 1960          |
| SL.No | Drug Name | Structure | Diseases       | Approved Year |
|-------|-----------|-----------|----------------|---------------|
| 29    | Grisactin | ![Grisactin](image) | Dermatological | 1962          |
| 30    | Valium    | ![Valium](image) | Nervous System | 1963          |
| 31    | Alkeran   | ![Alkeran](image) | Oncological    | 1964          |
| 32    | Maolate   | ![Maolate](image) | Dermatological | 1965          |
| 33    | Serax     | ![Serax](image) | Nervous System | 1965          |
| 34    | Enflurane | ![Enflurane](image) | Nervous System | 1966          |
| 35    | Lasix     | ![Lasix](image) | Cardiovascular | 1966          |
| 36    | Atromid-S | ![Atromid-S](image) | CAR            | 1967          |
| 37    | Haldol    | ![Haldol](image) | Nervous System | 1967          |
| 38    | Pathocil  | ![Pathocil](image) | Anti-infective | 1968          |
| 39    | Cleocin   | ![Cleocin](image) | AIN/DER/GUS   | 1970          |
| 40    | Floxapen  | ![Floxapen](image) | Anti-infective | 1970          |
| S.No | Drug Name | Structure | Diseases                     | Approved Year |
|------|-----------|-----------|------------------------------|---------------|
| 41   | Dalmane   | ![Structure Image](image1) | Nervous System               | 1970          |
| 42   | Ketalas   | ![Structure Image](image2) | Nervous System               | 1970          |
| 43   | Lysodren  | ![Structure Image](image3) | Oncological                  | 1970          |
| 44   | Tranxene  | ![Structure Image](image4) | Nervous System               | 1972          |
| 45   | Hyperstat | ![Structure Image](image5) | Cardiovascular               | 1973          |
| 46   | Sanorex   | ![Structure Image](image6) | Alimentary tract and Metabolism | 1973         |
| 47   | Closapen  | ![Structure Image](image7) | Anti-infective               | 1974          |
| 48   | Monistat 7| ![Structure Image](image8) | AIN/ALM/DER/GUS              | 1974          |
| 49   | Klonopin  | ![Structure Image](image9) | Nervous system               | 1975          |
| 50   | Lotrimin  | ![Structure Image](image10) | AIN/ALM/DER/GUS              | 1975          |
| 51   | Loxitane  | ![Structure Image](image11) | Nervous system               | 1975          |
| 52   | CeeNU     | ![Structure Image](image12) | Oncological                  | 1976          |
| SLNo | Drug Name | Structure | Diseases                     | Approved Year |
|------|-----------|-----------|------------------------------|---------------|
| 53   | Imodium   | ![Imodium Structure](image) | Alimentary tract and Metabolism | 1976          |
| 54   | Lioresal  | ![Lioresal Structure](image) | Musculo-skeletal             | 1977          |
| 55   | BiCNU     | ![BiCNU Structure](image)   | Oncological                  | 1977          |
| 56   | Tavist    | ![Tavist Structure](image)  | RES/NER                      | 1977          |
| 57   | Cloderm   | ![Cloderm Structure](image) | Dermatological               | 1977          |
| 58   | Ativan    | ![Ativan Structure](image)  | Nervous system               | 1977          |
| 59   | Buclizine | ![Buclizine Structure](image) | Respiratory System         | 1979          |
| 60   | Ceclor    | ![Ceclor Structure](image)  | Anti-infective               | 1979          |
| 61   | Forane    | ![Forane Structure](image)  | Nervous system               | 1979          |
| 62   | Reglan    | ![Reglan Structure](image)  | Alimentary tract and Metabolism | 1979         |
| 63   | Adinazolam| ![Adinazolam Structure](image) | Nervous system             | 1980          |
| 64   | Asendin   | ![Asendin Structure](image) | Nervous system               | 1980          |
| 65   | Halotex   | ![Halotex Structure](image) | Dermatological              | 1980          |
| SLNo | Drug Name | Structure | Diseases          | Approved Year |
|------|-----------|-----------|-------------------|---------------|
| 66   | Meclomen  | ![Structure](image1.png) | Musculo-skeletal   | 1980          |
| 67   | Domperidone | ![Structure](image2.png) | ALT/Met           | 1980          |
| 68   | Xanax     | ![Structure](image3.png) | Nervous system    | 1981          |
| 69   | Midamor   | ![Structure](image4.png) | Cardiovascular    | 1981          |
| 70   | Emeyt     | ![Structure](image5.png) | Oncological       | 1981          |
| 71   | Paxipam   | ![Structure](image6.png) | Nervous system    | 1981          |
| 72   | Nizoral   | ![Structure](image7.png) | AIN/DER/GUS       | 1981          |
| 73   | Restoril  | ![Structure](image8.png) | Nervous system    | 1981          |
| 74   | Spectazole| ![Structure](image9.png) | DER/GUS           | 1982          |
| 75   | Halcion   | ![Structure](image10.png) | Nervous system    | 1982          |
| 76   | Lozol     | ![Structure](image11.png) | Cardiovascular    | 1983          |
| Sl.No | Drug Name | Structure | Diseases                      | Approved Year |
|-------|-----------|-----------|-------------------------------|---------------|
| 77    | TZ-3      | ![TZ-3 Structure](image-url) | DER/GUS                      | 1983          |
| 78    | Wellbutrin | ![Wellbutrin Structure](image-url) | Nervous system               | 1985          |
| 79    | Femstat   | ![Femstat Structure](image-url) | Genito-Urinary and Sex hormone | 1985          |
| 80    | Versed    | ![Versed Structure](image-url) | Nervous system               | 1985          |
| 81    | Progabide | ![Progabide Structure](image-url) | Nervous system               | 1985          |
| 82    | Lamprene  | ![Lamprene Structure](image-url) | Anti-infective               | 1986          |
| 83    | Tenex     | ![Tenex Structure](image-url) | Cardiovascular               | 1986          |
| 84    | Trazodone | ![Trazodone Structure](image-url) | NER/END                      | 1986          |
| 85    | Zopiclone | ![Zopiclone Structure](image-url) | Nervous system               | 1986          |
| 86    | Lopidine  | ![Lopidine Structure](image-url) | Sensory organ                | 1987          |
| 87    | Mykrox    | ![Mykrox Structure](image-url) | Cardiovascular               | 1987          |

(continued on next page)
| 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          |
| Sl.No | Drug Name | Structure | Diseases                          | Approved Year |
|-------|-----------|-----------|-----------------------------------|---------------|
| 101   | Propulsid | ![Propulsid](image1) | Alimentary tract and Metabolism   | 1993          |
| 102   | Leustatin | ![Leustatin](image2) | Oncological                       | 1993          |
| 103   | Lipidil   | ![Lipidil](image3)   | CAR/END                           | 1993          |
| 104   | Claritin  | ![Claritin](image4)  | Respiratory system                | 1993          |
| 105   | Lamictal  | ![Lamictal](image5)   | Nervous system                     | 1994          |
| 106   | Zyrtec    | ![Zyrtec](image6)    | Respiratory system                | 1995          |
| 107   | Cozaar    | ![Cozaar](image7)    | Cardiovascular                    | 1995          |
| 108   | Astelin   | ![Astelin](image8)   | RES/SEN                           | 1996          |
| 109   | Zanaflex  | ![Zanaflex](image9)  | Musculo-skeletal                  | 1996          |
| 110   | Agrylin   | ![Agrylin](image10)  | BBO/ONC                           | 1997          |
| 111   | Plavix    | ![Plavix](image11)   | BBO/END/CAR                       | 1997          |
| 112   | Corlopam  | ![Corlopam](image12) | Cardiovascular                    | 1997          |
| SLNo | 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            |               |
| SL.No | Drug Name       | Structure | Diseases         | Approved Year |
|-------|----------------|-----------|------------------|---------------|
| 123   | Ertaczo        | ![Ertaczo](image) | Dermatological   | 2003          |
| 124   | Clolar         | ![Clolar](image) | Oncological      | 2004          |
| 125   | Lunesta        | ![Lunesta](image) | Nervous system   | 2004          |
| 126   | Nexavar        | ![Nexavar](image) | Oncological      | 2005          |
| 127   | Sprycel        | ![Sprycel](image) | Oncological      | 2006          |
| 128   | Fenofibrac acid| ![Fenofibrac acid](image) | Cardiovascular    | 2007          |
| 129   | Xyzal          | ![Xyzal](image) | DER/RES          | 2007          |
| 130   | Cleviprex      | ![Cleviprex](image) | Cardiovascular  | 2008          |
| 131   | Saphris        | ![Saphris](image) | Nervous system   | 2009          |
| 132   | Bepreve        | ![Bepreve](image) | Sensory organ    | 2009          |
| 133   | Zipsor         | ![Zipsor](image) | Nervous system   | 2009          |

(continued on next page)
Mujumdar and co-workers synthesized a novel class of sulfamate-containing natural products and screened for their \textit{in vitro} antibacterial properties. Title compound \ref{compound_143} was synthesized according to the literature reported as shown in Scheme 1. Commercially available 2-chloroadenosine \ref{compound_140} was reacted with tosylic acid under the optimal reaction condition to afford 2',3'-O-isopropylidene protected adenosine precursors \ref{compound_141}, which then reacted with chlorosulfonyl amine in the presence of DBU as base to obtain the corresponding 5'-O-sulfamoyl adenosine \ref{compound_142} in moderate to good yields. The protecting group of compound \ref{compound_142} was removed by using a mixture solution of TFA and water (v/v = 4:2) to afford the target compound \ref{compound_143}. In \textit{in vitro} antimicrobial activity evaluation showed that the compound \ref{compound_143} possessed highest antibacterial activity with a MIC of 5 \(\mu\)M against \textit{E. coli} \cite{13}. The structure-activity relationship (SAR) revealed that the presence of chlorine atom highly enhanced the antibacterial properties of compound \ref{compound_143}. In addition, the presences of sulfonamide group also most favour to increases the antibacterial activity of potent compound \ref{compound_143}. The compound \ref{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 \textit{in vitro} antimicrobial activity. Substituted thiophenols (\ref{compound_144a-d}) were reacted with KOH and ethanol in the presence of water at 60 °C to yield the compounds \ref{compound_145a-d}. Compounds \ref{compound_145a-d} were reacted with \(\beta\)-chloropropionic acid and then cyclized in the presence of concentrated H\(_2\)SO\(_4\) to afford thiochroman-4-ones \ref{compound_146a-d} via intra-molecular Friedel-Crafts reaction. Later, compounds \ref{compound_146a-d} were treated under Vilsmeier-Haack conditions to produce the key intermediates of \ref{compound_147a-d}. Then, compounds \ref{compound_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 \ref{compound_148a-d} (Scheme 2) \cite{14}. All the synthesized compounds were tested for \textit{in vitro} antifungal activities against different fungal strains. Based on the \textit{in vitro} antimicrobial results, two compounds (\ref{compound_148a} and \ref{compound_148b}) were showed an excellent antifungal activities against \textit{C. albicans} (MICs = 0.5–8 \(\mu\)g/mL) and \textit{C. neoformans} (MIC = 0.25–1 \(\mu\)g/mL) respectively \cite{15}.

Karthikeyan et al. synthesized the novel chlorine containing potent antimicrobial compounds \ref{compound_154a-f}. From the beginning, starting material \ref{compound_149} was reacted with various substituted aldehydes (\ref{compound_150a-f}) in the presence of ethanol and Aq. KOH under reflux conditions to yield 1,3-diaryl-2-propen-1-ones (\ref{compound_151a-f}) in good yields. Then, compounds \ref{compound_151a-f} underwent bromination in chloroform to give bromo substituted compounds \ref{compound_152a-f}. Chalcone dibromides (\ref{compound_152a-f}) further treated with aryloxy acid hydrazides (\ref{compound_153a-f}) in the presence of triethylamine in absolute ethanol to furnish 1-aryloxy-3-aryl-5-hydroxy-5-aryl pyrazolines (\ref{compound_154a-f}, Scheme 3) in good yields. Compounds \ref{compound_154a} (zone of inhibition was 22 mm against \textit{P. aeruginosa}) and \ref{compound_154b} (zone of inhibition was 21 mm against \textit{P. aeruginosa}) turned out to be the most potent antibacterial agents. Compounds \ref{compound_154a} (zone of inhibition was 21 mm against \textit{A. fumigatus}) and \ref{compound_154b} (zone of inhibition was 20 mm against \textit{P. marneffei}) turned out to be the most potent antifungal agents \cite{16}.

Very recently, Zha and co-workers synthesized benzol[d]thiazole-hydrazones and tested for their \textit{in vitro} antimicrobial activities. The synthetic route was depicted in Scheme 4\(<$/b>\). The intermediate 7-methylbenzo[d]thiazol-2-amine (\ref{compound_156}) was synthesized according to the literature of reported method \cite{17,18}. Then,
**Scheme 1.** Synthesis of chlorine containing sulfamate-containing natural products as potent antibacterial agent.

Reagents and conditions: (i) $p$-TsOH, acetone, rt, 4hr; (ii) $\text{Cl}_2\text{SO}_2\text{NH}_2$, DBU, DCM, rt.

**Scheme 2.** Synthesis of potent chlorine containing thiochromenes as antifungal agents. Reagents and conditions: (i) KOH, H$_2$O, EtOH, 60 °C; (ii) $\beta$-chloropropionic acid, 30% K$_2$CO$_3$ aqueous solution, reflux; (iii) H$_2$SO$_4$; (iv) POCl$_3$, DMF, 50 °C, (v) NaBH(OAc)$_3$, amine, DCE, N$_2$, rt.

Reagents and conditions: (i) KOH, H$_2$O, EtOH, 60 °C; (ii) $\beta$-chloropropionic acid, 30% K$_2$CO$_3$ aqueous solution, reflux; (iii) H$_2$SO$_4$; (iv) POCl$_3$, DMF, 50 °C, (v) NaBH(OAc)$_3$, amine, DCE, N$_2$, rt.
compound 156 was converted into hydrazides 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, NO2 and F) on the phenyl ring increased the antifungal properties and the presence of electron donating groups (EDGs) (OH and OCH3) 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 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

![Scheme 3. Synthesis of chlorine containing pyrazoline analogues as potent antimicrobial agents. Reagents and conditions: (i) EtOH, aq. KOH, (ii) Br2, CHCl3, (iii) EtOH, Et3N.](image)

Reagents and conditions: (i) EtOH, aq. KOH, (ii) Br2, CHCl3, (iii) EtOH, Et3N.

![Scheme 4. Synthesis of benzo[d]thiazole-hydrazones as potent antifungal agent. Reagents and conditions: (i) NH4SCN, Br2, glacial acetic acid, NH3, (ii) hydrazine hydrate, Con. HCl, ethylene glycol, 3–4 h, rt, (iii) R-CHO, catalytic amount of acetic acid, EtOH, reflux, 8–10 h.](image)

Con. HCl, ethylene glycol, 3-4 h, rt, (iii) R-CHO, catalytic amount of acetic acid, EtOH, reflux, 8–10 h.
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 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.
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 acyl chloride 174. Without isolation, compound 174 directly treated with 6-chloro-5,6-dihydropyridin-2(1H)-one, base and n-butyllithium to afford compound 175 in good yields (Scheme 8). Compound 175 showed excellent anticancer activity against HT-29 (IC50 = 0.92 μM), HCT-8 (IC50 = 1.79 μM) and HCT-116 (IC50 = 0.47 μM) 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-dichloropyrimidine-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 IC50 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
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-MB-221 (GI50 = 6.33 μM) and MCF-7 (GI50 = 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].

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 the base to afford the final N-alkylated 4-aminoquinoline 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 IC50 of 17 μM against HeLa cancer cell line [37]. The SAR represented that the presence of two chlorine...
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 198a.

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-1 were reacted with phenylpropionaldehyde diethyl acetal in the presence of PTSA in ethanol under reflux conditions to yield 2-(2-alkylthiobenzenesulfonyl)-3-(phenylprop-2-ynylideneamino)guanidines 191a-i in moderate to good yields. All the synthesized compounds 191a-i underwent CuI mediated electrophilic cyclizations of α, β-alkynyl 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 IC50 value of 7 µM against HCT-116 and IC50 value of 3 µM against HeLa cell lines. The SAR results suggested that, the chlorinated compounds showed better anti-proliferative activity than those of corresponding non-chlorinated compounds. On the other hand, the presence of sulfonyl and sulfonamide groups also increases the anticancer activity of compounds 198a. 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-1 were reacted with phenylpropionaldehyde diethyl acetal in the presence of PTSA in ethanol under reflux conditions to yield 2-(2-alkylthiobenzenesulfonyl)-3-(phenylprop-2-ynylideneamino)guanidines 191a-i in moderate to good yields. All the synthesized compounds 191a-i underwent CuI mediated electrophilic cyclizations of α, β-alkynyl 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.

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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 afford 1-(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 obtain intermediate compound chromene-3-carbaldehyde 194. Claisen-Schmidt condensation of compound 194 with various acetoephones 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-2H-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-2H-chromen-3-yl)propen-1-ones 197a-d (Scheme 14). The target compounds were evaluated for their antileishmanial activity against the promastigote form of Leishmania major using MTT assay. Compounds 195a (IC50 = 1.22 µM) and 197a (IC50 = 1.33 µM) 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 benzoferon 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, Al2O3 catalyzed condensation reaction was applied to prepare six aryl benzofuran-3(2H)-ones 202 by condensing benzofuran-3(2H)-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(2H)-ones 202, pyridinium iodide salts (199) and NH4OAc 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 (IC50 = 5.47 µM) and T47D (IC50 = 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 benzofero[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 SOCl2 under reflux condition at 72 °C for 14 h to produce 4-chloropicolinol chloride 205 followed by the addition of

Reagents and conditions: (i) phenylpropionaldehyde diethyl acetal (1 eq.) or 4-phenylbut-3-en-2-one (1 eq.), PTSA (0.1 eq.), EtOH, reflux, 2-20 h, (ii) CuI, Et3N, MeCN, 82 °C, 1-4 h, (iii) 20% PTSA/MeCN, 1 h.

Scheme 15. Potent anticancer agents. Reagents and conditions: (i) phenylpropionaldehyde diethyl acetal (1 eq.) or 4-phenylbut-3-en-2-one (1 eq.), PTSA (0.1 eq.), EtOH, reflux, 2-20 h, (ii) CuI, Et3N, MeCN, 82 °C, 1-4 h, (iii) 20% PTSA/MeCN, 1 h.

Reagents and conditions: (i) acrolein, 1,4-dioxane, K2CO3, reflux (ii) appropriate acetoephone, NaOH, EtOH (iii) methyl vinyl ketone, 1,4-dioxane, K2CO3, 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, K2CO3, reflux (ii) appropriate acetoephone, NaOH, EtOH (iii) methyl vinyl ketone, 1,4-dioxane, K2CO3, reflux (iv) appropriate aldehyde, NaOH, EtOH.
methanol at room temperature for 1 h to generate methyl 4-
chloropicolinate. Consequently, compound 206 was reacted
with various substituted amines in the presence of CH₃OH/THF at
RT/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 IC₅₀ 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-7H-purine-8-carboxylate
212a-e in moderate yields, and then intermediates 212a-e were
hydroyzed into carboxyl in AcOH/H₂O 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, 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 contain-
ing compounds with enhanced in vitro anti-tumour activity.
Initially, commercially available 2-amino-4-chlorobenzoic acid
215 was condensed with formamide at 140–145 ºC for 4.5 h to obtain
intermediate 216, and then treated with SOCl₂ in the presence of
DMF under reflux conditions to produce intermediate 217. In
addition, commercially available salicylaldehyde 218 was reacted
with aceton in the presence of sodium hydride at room temper-
ature to afford intermediate 219. Compounds 217 and 219 were

Scheme 15. Synthetic route of chlorine containing benzofuro[3,2-
b]pyridine der-
rivatives as potent anti-proliferative drugs. Reagents and conditions: (i) iodine, pyri-
dine, 140 ºC, 3 h, 76.7–93.0% yield; (ii) Al₂O₃, CH₂Cl₂, rt, 3 h, 55–72% yield; (iii)
NH₄OAc, glacial acetic acid, 100 ºC, 12–24 h, and 16–54%.

Scheme 16. Synthetic route of thiourea substituted derivatives as potent anti-
proliferative agents. Reagents and conditions: (i) SOCl₂, reflux, 72 ºC, 14 hr, (ii)
CH₂OH, rt, 1 hr; (iii) RNH₂, CH₃OH/THF, 2 ºC, 3 h; (iv) 4-aminophenol, DMF, KOBu-t, 1 hr; (v) substituted isocyanates,
DCM, 0–5 ºC, 2 hr then 18 hr at rt.

Scheme 17. Synthetic route of potent chlorine containing anti-proliferative agents.
Reagents and conditions: (i) DMF, DIPEA, 100 ºC, 12 h, (ii) EtOH, 80 ºC, (iii)
AcOH/H₂O, 80 ºC, (iv) 1-methylpiperazine, EDCI/HOBt, CH₂Cl₂.

Reagents and conditions: (i) iodine, pyridine, 140 ºC, 3 h, 76.7–93.0% yield; (ii) Al₂O₃,
CH₂Cl₂, rt, 3 h, 55–72% yield; (iii) NH₄OAc, glacial acetic acid, 100 ºC, 12–24 h, and 16–54%.

Reagents and conditions: (i) SOCl₂, reflux, 72 ºC, 14 hr, (ii) CH₂OH, rt, 1 hr; (iii) RNH₂,
CH₂OH/THF, 2 ºC, 3 h; (iv) 4-aminophenol, DMF, KOBu-t, 1 hr; (v) substituted isocyanates,
DCM, 0–5 ºC, 2 hr then 18 hr at rt.
reacted with K₂CO₃ 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 IC₅₀ 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 localized physical conditions causing swelling, redness, heat with pain, which are mediated by the release of proinflammatory mediators like bradykinin and cytokine 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 was performed in a manner outlined in Scheme 19. Starting material 4-(2-hydroxypropan-2-yl)-2-propyl-1H-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 80–100 °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 IC₅₀ 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 anti-inflammatory agents. 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 (IC₅₀ = 84 μM/mL) and 229b (IC₅₀ = 67 μM/mL) showed excellent anti-inflammatory activities with lower IC₅₀ values than that of the standard compound aspirin (IC₅₀ = 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].
Abdellatif et al. have developed a novel class of imidazoles compounds and screened for their in vitro anti-inflammatory activity. Compound p-chlorobenzenzoylglycine 230 was synthesized by heating the mixture of glycine and 4-chlorobenzoic acid 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 yield [54]. Among all the synthesized compounds, compound 232a was found to be excellent anti-inflammatory activities with IC₅₀ of 7.86 µM against COX-1 and IC₅₀ 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-carboxamides as potent anti-inflammatory agents. Reagents and 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.

A new series of eighteen benzimidazo-hydrzones were synthesized by Kumar et al. using commercially available compound 239 as starting material. Compound 239 was esterified by using con. H₂SO₄ 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 analoges 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 NO₂) on the phenyl ring increased the anti-inflammatory activity and the presence of EDGs (OH and OCH₃) 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 [39]. 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 (EMB), Rifampicin (RIF) and Pyrazinamide (PZA) is proved to be highly effective.
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 mg/mL, which could be attributed to the presence of electron-withdrawing groups (CF3 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 μg/mL [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 enhydrizinoketones 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].

![Fig. 2. (A) Docking and binding pattern of compound 238b into COX-2 active site (PDB code: 1CG2). (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.)](image)
2.5. Synthesis of chlorine containing \(\alpha\)-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 \(\alpha\)-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]. \(\alpha\)-Glucosidase specifically performs the hydrolysis of \(\alpha\)-glycopyranside bond, resulting in the production of \(\alpha\)-glucose from the non-reducing end of the sugar [74]. Several \(\alpha\)-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 2,5-dimethyl-1,3,4-oxadiazole 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 \(\alpha\)-glucosidase inhibitory agent with IC_{50} value of 4.70 \(\mu\)M. The presence of electron withdrawing group (Cl) on the phenyl ring highly enhanced the \(\alpha\)-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 \textit{in vitro} \(\alpha\)-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-2H-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 hydrosulfite. 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 \(\mu\)M per 1 \(\mu\)M 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 \(\beta\)-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 \textit{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 \(\text{Na}_{2}\text{S}_{2}\text{O}_{5}\) with DMF as solvent under reflux conditions to afford desired products 272a-z in high yields (Scheme 29). All the newly...
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 irrational 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 antimalarial 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$_2$CO$_3$ 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°C for 5 h to yield methanesulfonic acid 2-(7-chloro-5-oxo-(10H)-2,4-diamino-8-chloropyrimido-[4,5-b]quinoline 280. 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-chloroquinolin-4-yamino)-ethanol 283 in moderate to good yield [86]. Chemoselective o-mesylation was synthesized in pyridine at 0°C for 5 h to yield chemically unstable acid 2-(7-chloroquinolin-4-yamino)-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].

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 synthesized derivatives were tested for their *in vitro* biological activities such as antioxidant, antialgyacation and β-glucuronidase activities. Among them, compound 272a (IC$_{50}$ = 240.12 μM) was found to be the most potent antialgyacation 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].

![Scheme 27](image)

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

![Scheme 28](image)

**Scheme 28.** Synthesis of chlorine containing drugs as potent α-glucosidase activity. Reagents and conditions: (i) (a) CISO$_2$NCO, CH$_3$NO$_2$; (b) AlCl$_3$; (ii) P$_2$S$_5$, pyridine; (iii) CH$_3$I, NaHCO$_3$, CH$_3$OH/H$_2$O; (iv) R$_3$NH$_2$.

![Scheme 29](image)

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

![Scheme 30](image)

**Scheme 30.** Synthetic route of chlorine containing potent anti-malarial agent.
methanesulfonyl chloride, pyridine, 0
Con. H2SO4, 100°C, 5 min at 300
phenyl ether as solvent and subjected to microwave irradiation for
which then sealed into a glass reaction tube with a small volume of
and trimethylorthoformate to give enamine
the condensation of substituted aniline
stitutions on inhibition of growth of chloroquine sensitive and
derivatives
method was used to prepare ring substituted 4-chloroquinolines
with the help of
evaluated for their growth inhibition activity against
2.7. Chlorine containing drugs as miscellaneous applications
Alzheimer’s disease (AD) is a neurodegenerative disorder
worst way without harming the host cells [102].
Viruses are infectious agents affecting the life forms. They are
responsible for various dangerous diseases like human immuno-
deficiency virus (HIV), hepatitis B and C viruses (HBV and HCV,
respectively), severe acute respiratory syndrome (SARS), corona
viruses (Middle east respiratory Syndrome, MERS; in
chikungunya etc. These diseases have caused adverse impact on
personal, pandemic), viral haemorrhagic fevers (Ebola), dengue, and
infection, about 45 million people are going through this disease
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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 IC50 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. Dirfluoromethylation 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. Compound 300 coupled with 3,5-dichloropyridin-4-amine to provide intermediates 301. Further, compound 301 underwent nucleophilic substitution with 3-amino-sulfanylhydrofurane 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 (IC50 = 5.4 nM against PDEB1 and 0.7 nM against PDE4D2) and 303 (IC50 = 4.0 nM against PDEB1 and 66 nM against PDE4D2) showed excellent PDE4 inhibition activity compared to standard drug Rolipram (IC50 = 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. Cisien 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-aminoypyrylolidine 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 Kᵢ 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) H₂O, NaNO₂, HCl, 0-5 °C, 30 min, Na₂Se₂, 50 °C; (ii) SOCl₂, reflux; (iii) anhydrous CH₂Cl₂, triethylamine, rt; (iv) CH₂Cl₂, HCl (g), 0-5 °C.

Scheme 34. Synthesis route of potent Alzheimer’s agents. Reagents and conditions: (i) H₂O, NaNO₂, HCl, 0-5 °C, 30 min, Na₂Se₂, 50 °C; (ii) SOCl₂, reflux; (iii) anhydrous CH₂Cl₂, triethylamine, rt; (iv) CH₂Cl₂, HCl (g), 0-5 °C.

Scheme 35. Synthesis of imidazole analogues as potent anti-HIV agents.
derivatives as potent neuropathic pain agents. The targeted compounds were synthesized in three steps from starting material 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(CH2)3Br under reflux conditions to provide compound 312. Compound 1,3-dibromopropane 312 was reacted with piperidine in the presence of Cs2CO3 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 Kᵢ of 1.06 nmol and Kᵢ 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 phe-
nylhydrazine 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 σ₁ receptor affinity (Kᵢ = 1.4 nM) and excellent selectivity over not only σ₂ 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 conc. 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 Kᵢ of 0.20 μM and the enzyme purified from placenta with Kᵢ 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) R'-CH₂COCl, AlCl₃, 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) 2.5N KOH, MeOH, reflux; (v) (COCl)₂, DMF, CH₂Cl₂ rt; (vi) 1-aminopyrrolidine, CH₂Cl₂, rt.

Scheme 37. Synthetic route of pyrrolidine containing hybrids as potent cannabinoid Type 1 receptor antagonists. Reagents and conditions: (i) R 1CH₂COCl, AlCl₃, 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) 2.5N KOH, MeOH, reflux; (v) (COCl)₂, DMF, CH₂Cl₂ rt; (vi) 1-aminopyrrolidine, CH₂Cl₂, rt.
monooamine oxidase B inhibition activity and showed potent activity with IC50 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 to evaluate the new MAO-B inhibitors in relevant animal models [109].

Very recently, Kadayat and co-workers developed 2,4-diphenyl-5H-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 acetylphenones 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-e (IC50 = 0.05 nM against HCT-15 and IC50 = 1.08 nM against T47D cell lines) and 331b (IC50 = 0.11 nM against HCT-15 and IC50 = 1.16 nM against T47D cell lines) showed the most potent topoisomerase activity which is better than the control drug Pyridalyl (IC50 = 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 IC50 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 OXER 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. H2O in THF/H2O (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 OXER receptor with IC50 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 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 LC50 value of 9.78 μM which was better than the control compound Pyridalyl (LC50 = 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 42). 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 IC50 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 OXER 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. H2O in THF/H2O (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 OXER receptor with IC50 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 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 LC50 value of 9.78 μM which was better than the control compound Pyridalyl (LC50 = 17.40 μM) [114].

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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 NaBH₄ followed by chlorination with SOCl₂. 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

Reagents and conditions: (i) substituted phenols, KOH, DMF or DMSO, 45 °C, 2 h, 110 °C, 6-22 h; (ii) NH₂OH.HCl, KOH, CH₃OH or CH₃CH₂OH, reflux, 5-20 h; (iii) substituted 2-chloromethyl-5-alkoxy-1,3,4-thiadiazole, K₂CO₃, CH₃CN, 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, DM or DMSO, 45 °C, 2 h, 110 °C, 6-22 h; (ii) NH₂OH.HCl, KOH, CH₃OH or CH₃CH₂OH, reflux, 5-20 h; (iii) substituted 2-chloromethyl-5-alkoxy-1,3,4-thiadiazole, K₂CO₃, CH₃CN, reflux, 8-17 h.

Scheme 44. Synthesis of chlorine containing indole derivatives as potent a-amylase inhibitory agents. Reagents and condition: (i) NH₂-NH₂, ethanol, reflux, 6 h; (ii) arylisothiocyanate CHCl₃, stir.

Scheme 45. Synthesis of eicosatetraenoic acid as potent OXE receptor agent. Reagents and conditions: (i) Me₂AlCl, CH₂Cl₂, rt, 3 h, 93%; (b) LiOH·H₂O, THF/H₂O (4:1), MeOH, rt, 16 h, 95%.

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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 347 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 IC50 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-(2,3-dihydrobenzo[1,4]dioxine-2-carbonyl) piperazine-1-carbothioamide 352 in good yield (Scheme 48). The final compound 352 was converted to silver nanoparticles (P1C-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 IC50 value of 55 μg/mL. Compound 352 also showed potent phospholipase A2 (PLA2) enzyme inhibitory activity with IC50 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 IC50 value of 0.77 μM, which was much better than the reference drug Orlistat (IC50 = 0.8 ± 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 IC50 = 218 nM) showed good inhibitory activity against the tested endothelial lipase [124].

Reagents and conditions: (i) NaBH4, methanol, stirring rt; (ii) SOCl2, 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) NaBH4, methanol, stirring rt; (ii) SOCl2, dry benzene, 80 °C, reflux. (iii) Various amine, ethanol, TEA, reflux.

Scheme 47. Synthesis of pyrazine substituted hybrids as potent Aurora kinase A inhibitory agent. Reagents and conditions: (i) NCS, CH3CN/DCE (3:1), reflux, (ii) 4-(4-morpholino)aniline, DIPEA, Dioxane, 180 °C, reflux, (iii) 3-pyridylboronic acid, Pd(PPh3)2Cl2, Na2CO3, CH3CN, 150 °C, 30min.

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

Scheme 49. Synthesis of chlorine containing piperazine-1-carbothioamide chitosan silver nanoparticles (P1C-Tit*CAgNPs) as potent anti-hemolytic agents.
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 (IC50 (PI3k/a/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 (pIC50 7.8) and 369 (pIC50 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<sub>N</sub>N<sub>S</sub><sub>Ar</sub> 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 IC50 = 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].

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

**Scheme 50.** Synthesis of chlorine containing hybrids as potent lipase inhibitors. Reagents and conditions: (i) TMSCH<sub>2</sub>N<sub>2</sub>, DIPEA, Et<sub>2</sub>O, rt, 48 h; (ii) NaOH, MeOH/H<sub>2</sub>O (1:1), 70 °C, 1 h; (iii) oxalyl chloride, CH<sub>2</sub>Cl<sub>2</sub>, DMF(cat), (iv) R<sup>3</sup>-NH<sub>2</sub>, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 3 h; BCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 5 h.

**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)<sub>2</sub>Cl<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, dioxane/H<sub>2</sub>O, 100 °C.
Reagents and conditions: (i) Br₂, dichloromethane, 2,6-lutidine; (ii) NaOMe, MeOH, reflux (iii) H₂, Pd/C, ethanol, rt (iv) ArSO₂Cl, KO⁻Bu, 0–25 °C, THF, (v) HNO₃, AcOH, 70–85 °C, (vi) H₂, Pd/C, AcOH, 60 °C, (vii) IBF₅, CH₃CN, 0–5 °C, NaN₂O₃ or HBF₄/pyridine/NaNO₂.

Scheme 52. Synthesis of sulfonamides derivatives as potent CCR4 receptor antagonists. Reagents and conditions: (i) Br₂, dichloromethane, 2,6-lutidine; (ii) NaOMe, MeOH, reflux (iii) H₂, Pd/C, ethanol, rt (iv) ArSO₂Cl, KO⁻Bu, 0–25 °C, THF, (v) HNO₃, AcOH, 70–85 °C, (vi) H₂, Pd/C, AcOH, 60 °C, (vii) IBF₅, CH₃CN, 0–5 °C, NaN₂O₃ or HBF₄/pyridine/NaNO₂.

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 nonexistent 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.

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