Chapter-IV

Synthesis and biological evaluation of pyrano[2,3-d]pyrimidine tagged triazolo derivatives.
Introduction:

Heterocycles, an important class of organic compounds, constitute more than 70% of promising bioactive and drug molecules presently available in literature. Among these widespread heterocyclic compounds, oxygen heterocycles occupy a distinct position because of their wide natural abundance and broad biological as well as pharmaceutical significance. In these particular classes of O-heterocycles, “chromene” heterocyclic scaffolds represent a “privileged” structural motif well distributed in natural products with a broad spectrum of potent biological activities. Six-membered heterocyclic compounds containing oxygen such as pyrans constitute an important class of biologically active natural and synthetic products, playing a fundamental role in bioorganic chemistry.

A pyran or oxine is a six-membered heterocyclic compound, there are two isomers of pyran that differ by the location of the double bonds. In 2H-pyran, the saturated carbon is at position 2, whereas in 4H-pyran, the saturated carbon is at position 4.

![2H-pyran](image1) ![4H-pyran](image2)

2H-Pyran-2-ones and their fused derivatives are well-represented structural units of a variety of natural products\(^1\), their synthetic analogs and many other compounds not having natural counterparts, but nevertheless in many cases exhibiting important biological activity. Furthermore, due to their multifunctional character they display a plethora of potential applications in organic synthesis\(^2\). For example, a recent report by Lee et al.,\(^3\) shows a promising in vitro anticancer activity for 6-substituted-4-amino-2H-pyran-2-ones (APO) representing a simplified version of the tanshinlactones (1), which were shown to be even more potent against the ER+ human breast cancer cell lines than the tamoxifen citrate. In 2009 Cardellina II and co-workers isolated\(^4\) (R)-rugulactone (3) from the plant Cryptocarya rugulosa, possessing 5,6-dihydropyran-2-one skeleton and inhibiting nuclear factor B activation pathway that is active in many types of cancers. (R)-Rugulactone and both epimers of its 4-hydroxy analog have been recently prepared via a stereoselective synthesis by employing proline-catalyzed aminooxylatation, Sharpless epoxidation and Mitsunobu reaction as chirality introducing steps\(^5\). 3,4,6-Triaryl-2H-pyran-2-ones and their analogs exhibited high in vitro ability to
inhibit the cyclooxygenase isozymes COX-1 and COX-2. This inhibition is important when treating inflammatory diseases such as rheumatoid arthritis and osteoarthritis. Development of selective COX-2 inhibitors has furthermore brought significant advances in the treatment of colon, breast and prostate cancers.

L. Hua and Wu with co-workers have recently reported promising cytotoxicity against human non-small-cell lung carcinoma cell lines of various polyene derivatives (the best two cases having IC₅₀ values of 0.6 and 0.01 μM. All of the compounds synthesized and investigated were of the gymnoconjugatin, auxarconjugatin and isorumbrin classes (of the general structure) and all posses a tetraene chain containing a substituted pyrrole ring on one end, with the other end of the chain attached to the position 6 of a substituted 2H-pyran-2-one ring (4).

In recent years, 4H-pyrans and its derivatives have attracted strong interest due to their useful biological and pharmacological properties. Furthermore, substituted 4H-pyrans also constitute a structural unit of a series of natural products. Specifically, 4H-benzo[b]pyrans and their derivatives are of considerable interest due to their pharmacological activities, such as spasmolytic, diuretic, anticoagulant, anticancer and anti-anaphylactic activity. In addition, they have been used as cognitive enhancers for the treatment of neurodegenerative diseases, including Huntington’s disease, Alzheimer’s disease, amyotrophic lateral sclerosis, AIDS-associated dementia, and Down’s syndrome, as well as for the treatment of schizophrenia and myoclonus. 4H-Pyrans also constitute building blocks of a series of natural products. A number of 2-amino-4H-pyrans are useful as photoactive materials, pigments, and potential biodegradable agrochemicals.
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Considering the importance of these compounds, many methods have been reported for the synthesis of tetrahydro-4H-benzo[b]pyran derivatives\textsuperscript{16-23}.

An efficient synthesis of tetrahydrobenzo[b]pyran derivatives (5) has been achieved by Fotouhi and co-workers\textsuperscript{24} using an electrogenerated base of the anion of malononitrile in a one pot, three component condensation of an aromatic aldehyde, an active methylene compound and dimedone. The reaction was carried out at room temperature in acetonitrile with the use of a sacrificial magnesium anode in a singlecompartment cell. Electrosynthesis at a constant current of malononitrile, aryl aldehydes and dimedone proceeded in an undivided cell containing a Pt electrode as cathode and a sacrificial magnesium strip as anode to avoid electrochemical side reactions.

\[
\text{ArCHO} + \begin{array}{c}
\text{CN} \\
\text{CN}
\end{array} + \begin{array}{c}
\text{O} \\
\text{O}
\end{array} \xrightarrow{\text{Electrolysis}} \begin{array}{c}
\text{O} \\
\text{Ar} \\
\text{CN} \\
\text{O}
\end{array} \quad \text{(5)}
\]

Khurana et al.\textsuperscript{16} have been reported 1,8-diazabicycloundec-7-ene (DBU) catalyzed one pot synthesis of tetrahydro-4H-chromenes, tetrahydro[b]pyrans, pyrano[d]pyrimidines and 4H-pyran (6,7) from aldehydes, active methylene compounds e.g. malononitrile/ethyl cyanocacete and activated C–H acids such as dimedone, cyclohexane-1,3-dione, cyclopentane-1,3-dione, 1,3-dimethylbarbituric acid and ethyl acetoacetate in water under reflux.

\[
\text{ArCHO} + \begin{array}{c}
\text{CN} \\
\text{CN}
\end{array} + \begin{array}{c}
\text{O} \\
\text{O}
\end{array} \xrightarrow{\text{DBU}} \begin{array}{c}
\text{O} \\
\text{Ar} \\
\text{R}^1 \\
\text{NH}_2
\end{array} \quad \text{(6)}
\]

\[
\text{ArCHO} + \begin{array}{c}
\text{CN} \\
\text{CN}
\end{array} + \begin{array}{c}
\text{O} \\
\text{O}
\end{array} \xrightarrow{\text{DBU}} \begin{array}{c}
\text{O} \\
\text{Ar} \\
\text{R}^1 \\
\text{NH}_2
\end{array} \quad \text{(7)}
\]

Islami et al.\textsuperscript{17} have developed an efficient method for the synthesis of 4Hbenzo[b]pyrans (8) by heating the mixture of an appropriate aldehyde, malononitrile and dimedone in the presence of \(\text{Ce(SO}_4\text{)}_2\cdot\text{H}_2\text{O}\) (2.5 mol\%) as a catalyst at 45 °C in a mixture of water: ethanol (1:1).

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Pore et al.,\textsuperscript{18} have been synthesized tetrahydrobenzo[b]pyrans (9) achieved by three component condensation of aldehydes, 1,3-diketones and malononitrile using potassium phosphate in 20\% ethanol, basic ionic liquid N,N-dimethylaminoethylbenzyldimethyl ammonium chloride under solvent free conditions, and with cerium (III) chloride in ethanol under reflux\textsuperscript{19}.  

Recently, the natural products of cyclopenta[b]pyran with potential biological activity have been reported\textsuperscript{25,26}. 7-Allylidene-5-hydroxy-7,7\&-dihydrocyclopenta[b]pyran-6(2H)-one (10) was isolated from the Ascidian diplosoma. Therefore, it is believed that these variations in the basic structure like (11) may contribute to the bioactivity and provide new compound libraries for biomedical screening.

Yao et al.,\textsuperscript{27} have been reported a rapid and facile synthesis of cyclopenta[b]pyran derivatives namely, 2-amino-5-oxo-4-aryl-4,5,6,7-tetrahydrocyclopenta[b]pyran-3-carbonitriles and ethyl 2-amino-4-aryl-5-oxo-4,5,6,7-tetrahydrocyclopenta[b]pyran-3-carboxylates (12) recently under solvent free conditions by triturating a mixture of the three components at 85 °C.
Seeliger and co-workers\textsuperscript{28} have been reported the formation of
dihydropyrano[2,3-c]pyrimidines in the reactions of arylidene malononitrile with 1,3-
dimethylbarbituric and thiobarbituric acids upon protonation. Dihydropyrano[2,3-
d]pyrimidines reacted further with cyclohexanone under these conditions via a
Friedlander reaction to give pyrano[2,3-b]quinolines (13).

Shaabani et al.,\textsuperscript{29} have been reported a one pot, three component condensation
reaction in water using an activated C-H acid, an aldehyde and alkyl nitriles to afford the
 corresponding pyran annulated heterocyclic systems in water under reflux in good yields.
Reaction of 4-hydroxycoumarin, 4-hydroxy-6-methylpyrone, 1,3-dimethylbarbituric
acid, 1,3-dimethyl-6-aminouracil or dimedone with p-substituted benzaldehydes and
alkyalkyl nitriles gave a variety of pyran annulated heterocyclic compounds (14).
A novel three component one pot synthesis of pyrano[2,3-d]pyrimidines (15) using microwave heating in the solid state has also been reported from cyclocondensation of barbituric acids, aryl aldehydes and alkyl nitriles in the absence or presence of triethylamine by Devi and co-workers\textsuperscript{30}.

\[
\begin{align*}
\text{R} & \equiv \text{Me, H} \\
\text{O} & \equiv \text{N} \\
\text{O} & \equiv \text{N} \\
\text{N} & \equiv \text{R} \\
\text{ArCHO} & + \text{R}^1\text{CN} \rightarrow \text{R}^1=\text{CN,COOEt} \\
\end{align*}
\]

Penta-substituted 4H-pyran

Polyfunctionalized 4H-pyran are versatile synthons because of the inherent reactivity of the pyran ring\textsuperscript{31}. Polyfunctionalized 4H-pyran are biologically interesting compounds which possess various pharmacological activities\textsuperscript{32}, e.g. antiallergic\textsuperscript{33} and antitumor activities\textsuperscript{34}. 4H-Pyran are also useful intermediates for the synthesis of various compounds, such as pyranopyridine derivatives\textsuperscript{35}, polyazanaphthlenes\textsuperscript{36}, pyrano[2,3-d]pyrazoles\textsuperscript{37}, pyrano[2,3-c]pyrimidines\textsuperscript{38} and pyridin-2-ones\textsuperscript{39}, with potential biological activities. Moreover, 4H-pyran can also be transformed into corresponding pyridines related to important DHP type calcium antagonists\textsuperscript{40}.

Peng et al.,\textsuperscript{41} have been reported a clean and efficient method for the synthesis of 4H-pyran derivatives (16) by one pot condensation of aromatic aldehydes, malononitriles, and dicarbonyl compounds, using tetramethylguanidine in [bmim][BF4] ionic liquid as a recyclable catalytic system.

\[
\begin{align*}
\text{ArCHO} & + \text{CN} + \text{R} \rightarrow \text{R}=\text{OEt, Me} \\
\end{align*}
\]

Martin and co-workers\textsuperscript{42} have been reported one-pot synthesis of pyrano[2,3-b] pyridines (17) from malononitrile and 2-arylidene-1,3-diketones which are easily accessible through a Knoevenagel condensation of aromatic aldehydes and pentane-2,4-dione.
A one pot three component reaction of aromatic aldehydes, malononitrile and ethylacetoacetate using Cu(II) oxymetasilicate as the reusable catalyst to give 4H-functionalized pyrans (18) has been reported by Heravi et al.,43 The condensation can also be achieved by using basic Mg/La mixed oxide catalyst.

Fang et al.,44 have been prepared a recyclable temperature dependent phase separation catalytic system comprising of PEG1000 based functional dicationic acidic ionic liquid and ethylene glycol monomethyl ether to prepare polyfunctionalized 4H-pyrans (19) via one pot three component condensation. The products were separated from the catalyst system by liquid/liquid phase separation at room temperature.

Multicomponent one-pot synthesis of tetrahydrobenzo[b]pyrans (20) using 10 mol% of tetrabutylammonium fluoride (TBAF) as catalyst in aqueous medium under reflux condition was reported by Gao et al.,45 A diverse range of chromene scaffolds were synthesized by the act of Knoevenagel condensation of aldehydes with malononitrile followed by reaction of the intermediate formed with the C-H activated acid (dimedone) and cyclization. In their study they also compared the efficacy of other halide salts such as TBACl, TBABr, TBAI, KF, CsF, NH4F, H2SiF6, HF–pyridine.
Khurana et al., have been synthesized dihydropyrano[3,2-c]chromenes (21) via threecomponent reaction using 4-hydroxy coumarin as the C-H activated acid. Substituted aryl aldehydes, malononitrile and CH-activated acid reacted in one-pot in the presence of 10 mol% tetrabutylammonium bromide (TBAB) either in water to achieve the chromene derivatives in good yields. They also extended their protocol for the synthesis of biscoumarin derivatives (22).

Shaabani et al., have been reported a room-temperature based synthesis of benzo[g]- and dihydropyrano[2,3-g]chromene derivatives (23) via one-pot multicomponent reaction of aldehyde, malononitrile with 2-hydroxynaphthalene-1,4-dione or 2,5-di hydroxycyclohexa-2,5-diene-1,4-dione in the presence of a catalytic amount of Et$_3$N in CH$_3$CN. The products were isolated by simple filtration from the reaction mixture. Both electron-donating and electron-withdrawing groups on the aldehyde counterpart provided good results.
Magedov et al., have been synthesized the same 4H-pyrano-[2,3-b]naphthoquinone (24) via multicomponent protocol using Et$_3$N in EtOH at reflux condition and the synthesized compounds displayed low micromolar antiproliferative activity and induced apoptosis in human cancer cells.

Moafi et al., prepared 2-amino-4-cyano-4Hchromenes (25) via three-component reaction between salicylaldehydes, active methylene compounds (malononitrile or cyanoacetamide) with TMSCN in the presence of 15 mol% LiClO$_4$ as catalyst in ethanolic medium at room temperature. The first step involves Knoevenagel condensation between salicylaldehydes and malononitrile followed by cyclization (Pinner reaction) to generate iminochromenes. In the presence of catalyst, TMSCN made a Michael-type attack on the 4- position of the iminochromenes to provide the 4-cyano chromene derivatives. The mechanism was verified from the two-step synthesis. Substitution on the salicylaldehydes provided diverse libraries of chromene derivatives. Interestingly, they extended their protocol for the synthesis of 2-(chromenopyrimidin-2-yl)phenols (26). Under the same reaction condition when prepared iminochromenes, salicylaldehydes and secondary amines reacted in 1:1:1 mol ratio the product was new chromeno[2,3-d]pyrimidine scaffolds.
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\[
\begin{align*}
\text{CHO} & \quad + \quad X - \text{CN} + \quad \text{TMSCN} \\
\text{R} & = \text{-H,-Cl,-Br,-NO}_2,\text{-OH,-Me,-OMe} \\
\text{X} & = \text{CN, CONH}_2
\end{align*}
\]

\[\text{LiClO}_4 \text{ (15 mol\%)} \quad \text{EtOH \ r.t,} \quad \text{Time: 24h}\]

\[\text{Yield: 83-93\%}\]

\[\text{R}_2: \text{NMe}_2, \text{Piperidine, piperzine, morpholine, pyrrolidine}\]

\[\begin{align*}
\text{CN} & \quad + \quad \text{CHO} + \quad \text{R}_2\text{NH} \\
\text{EtOH \ r.t,} \quad \text{Time: 15h}\end{align*}\]

\[\text{Yield: 76-80\%}\]

Figure 1: Some of the naturally occurring bioactive compounds bearing pyran-annulated scaffolds.
Figure 2: Representative examples of pharmacologically active synthetic 2-amino-3-cyano-4H-pyran.

Substituted 1,2,3-triazoles have biological activities such as antimicrobial\textsuperscript{74}, anti cancer\textsuperscript{75}, anti HIV\textsuperscript{76}, and anti microbial\textsuperscript{77}, alprazolam is used to treat anxiety disorders, and ribavirin is an anti viral drug. These [1,2,3]-triazoles are conveniently synthesized by click reaction. Some important aspects of the click reactions are summarized here. The term “CLICK” refers to a facial, efficient, selective and versatile chemical transformation, which leads to a single product\textsuperscript{78}. Although different chemical reactions e.g. cycloaddition, nucleophilic substitutions addition on carbon-carbon double bonds can be considered to be of the click type, the copper (I)-catalyzed azide alkyne cycloaddition (CuAAC) is generally regarded as the quintessential example of the click chemistry\textsuperscript{79,80}. Hence, the term “click” has been almost exclusively used to denote this reaction in recent literature. The Huisegen 1,3-dipolar cycloaddition between a terminal alkyne and an azide has rapidly become the most popular click reaction to date\textsuperscript{81}.

The formation of triazole via the cycloaddition of azide and acetylene was first reported by Dimorth in the early 1900’s but the generality, scope, and mechanism of these cycloaddition was not fully realized until the 1960’s\textsuperscript{82} the reaction generates a mixture of 1,4- and 1,5-disubstituted triazoles (29,30). Various attempts to control the regioselectivity have been reported without much success until the discovery of the copper (I) catalyzed reaction in 2002, which exclusively yields the 1,4,-disubstituted 1,2,3-triazole\textsuperscript{79,80}.
Synthesis of 1,4 and 1,5-disubstituted 1,2,3-triazoles

In the absence of Cu(I) catalyst, the original 1,3-dipolar Huisgen cycloaddition of azide and terminal alkynes are not regioselective and usually slow. Medal and coworkers reported that the use of catalytic amounts of copper(I), which can bind to terminal alkynes, leads to fast, highly efficient and region selective azide-alkyne cycloaddition at room temperature in organic medium.

Later, Sharpless and Fokin reported that CuAAC can be performed in polar media such as tert-butyl alcohol, ethanol or pure water. These two important reports led to a remarkable renaissance of Huisgen cycloadditions in synthetic chemistry.

Catalyst and solvent used in the click reaction:

The use of copper (I) as a catalyst rejuvenated the Huisgen reaction. The standard catalytic system uses copper (II) salts (e.g., CuSO₄·5H₂O or copper acetate) in the presence of a reducing agent, such as sodium ascorbate or metallic copper, nanocopper, hydrazine and tris (2-carboxy ethyl) phosphine ((TCEP), for the Cu (II) to Cu (I) conversion. They reduce copper (II) to copper (I) in situ maintaining significantly high levels of the catalytic species. A mixture of tert-butanol and water is used as solvent, as under these conditions it is not necessary to use a base to generate the copper acetylide species. Aqueous alcohols (MeOH, EtOH, t-BuOH), TFA, CH₂Cl₂ and DMSO can be used as solvent. When aqueous cannot be used, organic solvents (e.g., THF, toluene, DCM, acetonitrile) in the presence of stoichiometric amount of copper (I) salts (CuI, CuBr(PP₃)₃) and an excess of a base, usually a tertiary amine (e.g., TEA, DIPEA) can be used. For example, copper-in-charcoal is an efficient heterogeneous catalyst for triazole formation. Copper (I) salts (CuI, CuBr) and coordination complexes (such as [Cu(CH₃CN)₄]PF₆,(EtO)₃PCu]₃, [Cu(PP₃)₃]Br can also be
used directly. Copper nanoclusters, which are easily obtained and are air-stable\textsuperscript{95}, and copper/cuprous oxide nanoparticles\textsuperscript{96}, have also shown excellent catalytic activity. Catalytic amounts of Cu(II) and Cu(0), thus further simplifying the experimental procedure. A small piece of copper metal (Wire or turning) is all that is added to the reaction mixture, followed by shaking or stirring for 12-48 hours\textsuperscript{97}.

**Mechanism of the click reaction:**

In general, cycloaddition proceed through a concerted mechanism. However, experimental kinetic data\textsuperscript{98} and molecular modeling\textsuperscript{99} performed on the CuAAC reaction seem to favor a stepwise reaction pathway\textsuperscript{98,100}. It has been calculated that the activation barrier for catalyzed concerted reaction (27.8 kcal/mol vs 26 kcal/mol\textsuperscript{26}). Furthermore, a stepwise-catalyzed CuAAC reaction has an activation barrier 11 kcal/mol lower than a concerted catalyzed reaction\textsuperscript{88}.

Based on experimental\textsuperscript{100} evidence and the fact that Cu (I) can readily insert itself into terminal alkynes as in sonogashira coupling the following steps can be postulated.

1. The step of the reaction involves $\pi$ complexation of Cu(I) dimer to the alkyne.
2. Thereafter, the deprotonation of the terminal hydrogen occurs to form a Cu-Acetylide\textsuperscript{101} (33). The $\pi$ Complexation of copper (I) lowers the pKa of the terminal alkyne by as much as 9.8 pH units, allowing deprotonation to occur in an aqueous solvent without the addition of a base. If a non-basic solvent such as acetonitrile was to be used, then a base, such as 2,6-lutididine or N,N’-diisopropylethylamine (DIPEA), would have to be added\textsuperscript{102}.
3. In the next step, N displaces one of the ligands from the second Cu-acetylide complex to form intermediate (34). In turn, this “Activates” the azide for nucleophilic attack C (5).
4. In the next step due to proximity and electronic factors, N (3) can now easily attack C(4) of the alkyne, leading to a metallocycle (35).
5. To form the respective 1,2,3-triazole (36).
6. Once 36 was formed, the attached Cu dimer immediately complex, and it dissociates upon protonation to reform (36).
7. One final protonation releases the Cu (I) catalyst from the 1,2,3-triazole product (37), to undergo a second catalytic cycle with different substrates.
Some of the main advantages of the click reaction are:

1. The reaction is highly regioselective leading to 1,4-disubstituted 1,2,3-triazoles (anti-isomer), it typically does not require temperature elevation but can be performed over a wide range of temperatures (0-160 °C), in a variety of solvents (including water), and over a wide range of pH values (5-12). It proceeds as much as 10^7 times faster than the unanalyzed version.
2. This reaction can be performed in an aqueous media using readily accessible reagents and without exclusion of atmospheric oxygen.
3. The reaction between alkyne and azide is orthogonal to any functional groups with the reactants.
4. The reaction products are pure and do not require chromatographic purification.
5. The 1,4-disubstituted triazole has high chemical and metabolic stability. The 1,4-disubstituted 1,2,3-triazole is relatively stable, possesses a large dipole moment and the nitrogen atom in positions two and three serve as weak hydrogen bond acceptor improving the solubility of the product in water.
6. It is unaffected by steric factors. “Variously substituted primary, secondary, tertiary and aromatic azides readily participate in this transformation. Tolerance for variation in the acetylene components also excellent”.

**Synthetic applications of click reaction:**

1. Synthesis of inhibitors of HIV-1 protease (40) using click chemistry\textsuperscript{104}.

![Synthesis of inhibitors of HIV-1 protease](image)

2. 1,4-Disubstituted-1,2,3-triazoles (44) are prepared from acetylated Baylis-Hillman adducts (41), terminal alkynes\textsuperscript{103} (42) and sodium azide (43).

![1,4-Disubstituted-1,2,3-triazoles](image)

3. Cu(0) nanosize activated powder and amine hydrochloride salts (45) react with azides (46) to generate 1,2,3-triazoles\textsuperscript{105} (47).

![Cu(0) nanosize activated powder and amine hydrochloride salts](image)

4. The [3+2] cycloaddition of nanoactivated terminal alkynes (48) and terminsilyl aazide (49) proceed smoothly in the presence of Cu(I) catalyst and DMF/MeOH, to give the corresponding N-unsubstituted triazoles\textsuperscript{106} (50).

![The [3+2] cycloaddition of nanoactivated terminal alkynes](image)
5. 1,2,3-triazole-linked β-lactam-bile acid conjugates (51) were synthesized using 1,3-dipolar cycloaddition reaction of azido β-lactam (52) and terminal alkyne (53) of bile acids in the presence of Cu (I) catalyst under microwave irradiation\textsuperscript{107}.

\[
\text{HO}^\ddagger \text{H}^\ddagger \text{R}^\ddagger + \text{H}_3\text{N}^\ddagger \text{O} \xrightarrow{\text{Cu}(0) \text{MW}} \text{HO}^\ddagger \text{H} \text{R}^\ddagger \text{O} \text{Me}
\]

6. Glycosyl triazoles (55) were prepared from propargyl alcohol by using click reaction as shown below by Wilkinson, B.L. Bornaghi\textsuperscript{108}.

\[
\begin{align*}
\text{AcO} & \quad \text{AcO} & \quad \text{AcO} \\
\text{O} & \quad \text{N}_3 & \quad \text{OAc} & \quad \text{OAc} & \quad \text{OH} \\
\text{54} & & & & \quad \text{Cu}(0)
\end{align*}
\]

\[
\text{HO}^\ddagger \text{H} \text{R}^\ddagger \text{O} \xrightarrow{\text{Cu}(0)} \text{HO}^\ddagger \text{H} \text{R}^\ddagger \text{O} \text{N} \text{N}
\]

7. In one pot, acetate protection, bromolysis and subsequent azide generation in the presence of an acetylide yelds the triazole (57)\textsuperscript{88}.

\[
\text{HO} \quad \text{OH} \quad \text{OH} \quad \text{HO} \quad \text{OH}
\]

\[
\text{HO} \quad \text{N}_3 \quad \text{N} \quad \text{R}
\]

8. Azides (59) obtained on epoxide opening react with diethyl acetylene dicarboxylate to give substituted triazoles\textsuperscript{74} (60).

\[
\begin{align*}
\text{O} & \quad \text{N}_3 & \quad \text{N}_3 \\
\text{58} & & & & \quad \text{NaN}_3 \quad \text{NH}_4\text{Cl} \text{H}_2\text{O} \quad \text{Rreflux}2\text{h} \\
\text{59} & & & & \quad \text{EtO}_2\text{C} \quad \text{H}_2\text{O} \quad 70^\circ\text{C} \quad \text{CH}_2\text{OH} > 95\%
\end{align*}
\]

9. Click reaction of triazole synthesis has been reported in solid phase synthetic conditions\textsuperscript{109}.
10. The application of CuAAC to generate fluorogenic compound has been extensively evaluated, since it would be a powerful method to track biomolecules in the cell. Indeed, among the most investigated strategies is the use of coumarin as the fluorescent capacity of coumarins with an electron withdrawing group in position 3 has been exploited. Indeed, fluorescent DNA probes, an indispensable tool in molecular biology, can be generated in this manner. Yet it is also possible to generate fluorogenic probes by reacting non-fluorescent 3-azide coumarins with alkynes, thereby generating in situ probes.

We have reviewed above various methods for the synthesis of tetrahydrobenzopyrans, tetrahydrocyclopentapyrans, pyran annulated heterocycles and penta-substituted 4H-pyran. All these compounds show a variety of biological activities besides other functions. In view of their importance of polyfunctionalised 4H-pyran is an on-going area of interest because of their wide range of applications. These 4H-pyran are isosters of 1, 4-dihydro pyridine with potential pharmacological interest and active synthons that have been extensively used in heterocyclic synthesis. The 4H-pyran are synthesized mainly by three-component coupling reaction of aromatic aldehydes, malononitrile and β-ketones/β-diketones catalyzed by bases like triethylamine, piperidine etc. In view of our interest in the development and synthesis of differently substituted and fused 4H-pyran derivatives from simple available starting materials in shortest reaction time using ammonia as a catalyst. They also extended for the synthesis of pyrano[2,3-d]pyrimidine tagged 1,2,3- triazoles derivatives by click reaction and for their anti microbial activity.
Present work

Among hetero aromatic compounds, 4H-pyrans and its substituted derivatives occupy a unique place in synthetic organic chemistry. 4H-pyrans derivatives constitute highly valuable heterocyclic motifs found in the structure of many natural and synthetic products. Various literatures revealed that, the constant and growing interest in the development of new efficient synthesis of compounds incorporating pyrimidine and triazole moieties has been attracting widespread attention due to their diverse pharmacological properties. By considering these views, in this chapter, we demonstrated an efficient synthesis of pyrano[2,3-d]pyrimidine attach [1,2,3]triazolo derivatives via click chemistry.

1. Synthesis of ethyl 6-amino-4-(4-substitutedphenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate 4a-k.
2. Cyclization of amino, cyano functions of compound 4c into ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 5.
4. Synthesis of target compounds 7a-h from alkyne 6 with various substituted arylazides by Click-chemistry

The reaction carried out is depicted in Scheme IV.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Time (min)</th>
<th>Yield(%)</th>
<th>Mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>C₆H₅</td>
<td>5</td>
<td>92</td>
<td>190-193</td>
</tr>
<tr>
<td>4b</td>
<td>4-FC₆H₄</td>
<td>5</td>
<td>95</td>
<td>190-193</td>
</tr>
<tr>
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<td>4</td>
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<td>10</td>
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<td>190-193</td>
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<td>3,4,5-OMeC₆H₅</td>
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<td>90</td>
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<td>4-CH₃</td>
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<td>95</td>
<td>198-199</td>
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1. Synthesis of ethyl 6-amino-4-(4-substitutedphenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate 4a-j

Compound ethyl 6-amino-4-(4-substitutedphenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate (4) was synthesized via single step process. The solution containing ethyl substituted aldehydes (1), malononitrile (2) and acetoacetate (3) in ammonia as a catalytic was heated to yielded compound 4a-j.

The IR spectra (Fig.4.1.1.) of the compound 4c exhibited peaks at 1711 and 1555 cm⁻¹ corresponding to the stretching frequencies of C=O and C=N groups respectively. Its ¹H-NMR spectra (Fig.4.1.1.1.) exhibited singlets at 4.55 ppm due to one proton of NH₂ and group, quartet at 4.05 ppm due to two protons, triplet at 1.11 ppm of three protons of ester group of pyran nucleus.
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2. Cyclization of amino, cyano functions of compound 1 into ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 5

Ethyl 6-amino-4-(4-chlorodphenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate (4c) was refluxed with acetic anhydrate and poly phosphoric acid to afforded corresponding ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 5.

\[ \text{4c} \xrightarrow{\text{Ac}_2\text{O}, \text{PPA, 3hr, reflux}} \text{5} \]

Proposed mechanism for the synthesis of 4H-pyranopyrimidines.

3. N-Propargylation of the pyrano[2,3-d]pyrimidine-6-carboxylate 3 to afforded pyrano[2,3-d]pyrimidine-6-carboxylate alkyne compounds 6

Formation of alkyne terminated compound 6 was carried out by reacting ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 5 with propargyl bromide and K₂CO₃ in DMF to yielded pyrano[2,3-d]pyrimidine-6-carboxylate alkyne 6.

\[ \text{5} \xrightarrow{\text{K}_2\text{CO}_3, \text{DMF, 2hr, RT}} \text{6} \]

Alkyne 6 was fully characterised by \(^1\text{H}-\text{NMR} \) (Fig.4.2.1.). The peak for the CH₂ protons of propargyl bromide at 4.96 ppm and singlet at 2.27 ppm confirmed the condensation of propargyl bromide.
4. Synthesis of target compounds 7a-h from alkyne 6 with various substituted arylazides by Click-chemistry

Click Reaction: The substituted azides and alkyne 6 with cycloaddition reaction was successfully carried out to form 1,2,3-triazole ring through 1,3-diopolar cycloaddition mechanism, the synthesis of 1,4-disubstituted-1,2,3-triazoles was carried out using the copper (II) catalyzed cycloaddition reaction as follows and the formation of the triazole was observed 7a-h in good yields.

The Click product 7a-h was fully characterized by $^1$H NMR. The formation of 1,2,3-triazole ring was confirmed by the appearance of a clear characteristic peak in the $^1$H-NMR spectrum at 7.91 ppm for the triazoles proton (H8) of compound 7c (Fig.4.3.1.1.).

EXPERIMENTAL

General procedure for the synthesis of ethyl 6-amino-4-(4-substitutedphenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate (4a-k)

A solution of aromatic substituted aldehydes 1 (1mmol), melanonitrile 2 (1mmol), Ethylcyanoacetate 3 (1.2mmol) and ammonia solution taken in R.B flask and stirred for 10 minutes at room temperature. The reaction was monitored by TLC. The solid compound was filtered, washed with cold water and recrystallization from ethanol to obtained pure products.

**Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate 4a**

| IR (KBr) ($v_{\text{max/cm}}^{-1}$): 3402, 2966, 2189, 1693, 1060; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$/ppm: 1.10 (t, 3H, CH$_3$ ester), 2.38 (s, 3H, CH$_3$), 4.05 (q, 2H, CH$_2$ ester), 4.45 (s, 1H, C(4)-H), 4.50 (brs, 2H, NH$_2$), 7.17–7.35 (m, 5H, Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$/ppm: 13.86, 18.37, 38.75, 60.64, 62.58, 108.00, 118.80, 127.17, 127.50, 138.00, 147.30, 148.60, 154.00, 161.00, 167.00, 196.00 |
128.56, 143.72, 156.76, 159.02, 165.83; LC–MS (positive ion mode): m/z 285 (M+H)+ for \( \text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3 \).

**Ethyl 6-amino-5-cyano-4-(4-fluorophenyl)-2-methyl-4H-pyran-3-carboxylate 4b**

\[
\text{IR (KBr) (ν}_{\text{max}}/\text{cm}^{-1}): 3403, 2193, 1691, 1546; \quad ^1\text{H NMR (400 MHz, DMSO-}d_6\text{)} \delta 1.11 (t, 3H, CH}_3\text{-ester), 2.35 (s, 3H, CH}_3\text{), 4.05 (q, 2H, CH}_2\text{-ester), 4.39 (s, 1H, CH}_4\text{), 5.89 (brs, 2H, NH}_2\text{), 6.92 (d, 2H, Ar-H), 7.21 (d, 2H, Ar-H);} \text{13C (100 MHz, DMSO-}d_6\text{)} \delta 13.8, 18.4, 38.2, 59.2, 60.3, 107.5, 115.2, 119.5, 129.0, 140.3, 143.45, 158.3, 161.0, 165.8; \quad \text{LC–MS (positive ion mode): m/z 303 (M+H)+ for} \text{C}_{16}\text{H}_{15}\text{FN}_2\text{O}_3.}
\]

**Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate 4c**

\[
\text{IR (KBr) (ν}_{\text{max}}/\text{cm}^{-1}): 3276, 2979, 1711, 1555, 1489; \quad ^1\text{H NMR (400 MHz, DMSO-}d_6\text{)} \delta/\text{ppm: 1.11 (t, 3H, CH}_3\text{-ester). 2.37 (s, CH}_3\text{), 4.05(q, 2H,CH}_2\text{-ester), 4.42 (s, 1H,CH), 4.55 (s, 2H, NH}_2\text{), 7.14 (d, 2H, Ar-H), 7.28 (d, 2H, Ar-H);} \text{13C NMR (100 MHz, CDCl}_3\text{)} \delta/\text{ppm: 13.89, 18.43, 38.25, 60.75, 61.82, 107.54, 118.65, 128.70, 128.87, 132.90, 142.32, 157.02, 157.45, 165.59; \quad \text{LC–MS (positive ion mode): m/z 319 (M+H)+ for} \text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}_3.}
\]

**Ethyl 6-amino-4-(4-bromophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate 4d**

\[
\text{IR (KBr) (ν}_{\text{max}}/\text{cm}^{-1}): 3401 2930, 1694, 1603, 1427; \quad ^1\text{H NMR (DMSO-}d_6\text{, 400 MHz) }\delta 1.19(t, 3H, CH}_3\text{-ester), 2.30 (s, CH}_3\text{), 4.02 (q, 2H,CH}_2\text{-ester), 4.30 (s, 1H,4H), 6.96 (s, 1H, Ar-H), 7.16 (d, 1H, Ar-H), 7.29 (m, 1H, Ar-H), 7.42 (d, 1H, Ar-H), 8.49 (brs, 2H, -NH}_2\text{ ppm;} \text{13C NMR (DMSO-}d_6\text{, 100 MHz) }\delta 13.9, 18.5, 38.6, 60.8, 61.6, 107.4, 118.7, 122.6, 126.4, 130.1, 130.4, 130.6, 146.1, 157.3, 157.6, 165.5 ppm; \quad \text{LC–MS (positive ion mode): m/z 363 (M+H)+ for} \text{C}_{16}\text{H}_{15}\text{BrN}_2\text{O}_3.}
\]

**Ethyl 6-amino-5-cyano-4-(3,4-dimethoxyphenyl)-2-methyl-4H-pyran-3-carboxylate 4e**

\[
\text{IR (KBr) (ν}_{\text{max}}/\text{cm}^{-1}): 3393, 2933, 1704, 1582, 1433; \quad ^1\text{H NMR (400 MHz, DMSO-}d_6\text{)} \delta/\text{ppm: 1.12 (t, 3H, CH}_3\text{-ester). 2.36 (s, CH}_3\text{), 3.85 (s, 3H,CH}_3\text{), 3.87 (s, 3H, OCH}_3\text{), 4.05 (q, 2H, CH}_2\text{-ester), 4.40 (s, 1H,CH), 4.48 (s, 2H, NH}_2\text{), 6.73 (d, 1H, Ar-H), 6.80 (1H, d, Ar-H), 7.23 (s, 1H, Ar-H);} \text{13C NMR (100 MHz, CDCl}_3\text{)} \delta/\text{ppm: 13.87, 18.38, 33.15, 55.81, 60.44, 61.02, 106.93, 119.30, 123.39, 129.22,}
\]

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141.88, 151.71, 152.74, 156.71, 157.64, 166.01; LC–MS (positive ion mode): m/z 345 (M+H)⁺ for C₁₈H₂₈N₂O₅.

*Ethyl 6-amino-5-cyano-2-methyl-4-(3,4,5-trimethoxyphenyl)-4H-pyran-3-carboxylate 4f*

IR (KBr) (ν max/cm⁻¹): 3387, 2985, 1680, 1502, 1454; ¹H NMR (400 MHz, CDCl₃) δ/ppm: 1.11 (t, 3H, CH₃), 2.35 (s, 3H, CH₃), 3.83 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 3.93 (s, 3H, OCH₃), 4.03 (q, 2H, CH₂), 4.46 (s, 2H, NH₂), 4.69 (s, 1H, CH), 6.59 (d, 1H, Ar-H), 6.77 (d, 1H, Ar-H); ¹³C NMR (100 MHz, CDCl₃) δ/ppm: 13.95, 18.35, 38.28, 55.81, 60.62, 62.39, 110.74, 111.12, 118.95, 119.53, 136.40, 148.01, 148.77, 156.24, 157.26, 165.90; LC–MS (positive ion mode): m/z 375 (M+H)⁺ for C₁₉H₂₂N₂O₆.

*Ethyl 6-amino-5-cyano-4-(4-(furan-2-yl)phenyl)-2-methyl-4H-pyran-3-carboxylate 4g*

IR (KBr) (ν max/cm⁻¹): 3393, 2963, 1693, 1261; ¹H NMR (400 MHz, CDCl₃) δ/ppm: 1.23 (t, 3H, CH₃-ester), 2.37 (s, 3H, CH₃), 4.16 (q, 2H, CH₂-ester), 4.53 (brs, 2H, NH₂), 4.64 (s, 1H, C(4)-H), 6.10 (d, 1H, Ar-H⁵), 6.28 (m, 1H, Ar-H⁴), 7.31 (d, 1H, Ar-H³), 7.59 (d, 1H, Ar-H), 7.87 (d, 1H, Ar-H); ¹³C NMR (100 MHz, CDCl₃) δ/ppm: 14.00, 18.43, 32.37, 59.53, 60.78, 105.71, 105.93, 110.33, 118.62, 122.54, 129.51, 133.20, 138.65, 141.93, 155.13, 157.78, 158.54, 165.63; LC–MS (positive ion mode): m/z 351 (M+H)⁺ for C₂₀H₁₈N₂O₄.

*Ethyl 6-amino-5-cyano-2-methyl-4-(4-(thiophen-2-yl)phenyl)-4H-pyran-3-carboxylate 4h*

IR (KBr) (ν max/cm⁻¹): 3394, 2192, 1669, 1542; ¹H NMR (400 MHz, DMSO-d₆) δ/ppm: 1.14 (t, 3H, CH₂-ester), 2.28 (s, 3H, CH₃), 4.08 (q, 2H, CH₂-ester), 4.61 (s, 1H, H-4), 6.82 (d, 1H, H-5'), 6.91 (m, 1H, H-4'), 7.05 (brs, 2H, NH₂), 7.36 (d, 1H, H-3'), 7.44 (d, 1H, Ar-H), 7.72 (d, 1H, Ar-H); ¹³C (100 MHz, DMSO-d₆) δ/ppm: 13.8, 18.1, 33.8, 56.9, 60.4, 107.6, 119.5, 121.20, 124.0, 124.7, 126.8, 129.30, 132.05, 138.62, 149.3, 156.7, 159.05, 165.2; LC–MS (positive ion mode): m/z 367 (M+H)⁺ for C₂₀H₁₈N₂O₃S.

*Ethyl 6-amino-5-cyano-2-methyl-4-(4-nitrophenyl)-4H-pyran-3-carboxylate 4i*

IR (KBr) (ν max/cm⁻¹): 3402, 2987, 1672, 1531, 1344; ¹H NMR (400 MHz, CDCl₃) δ/ppm: 1.12 (t, 3H, CH₃-ester), 2.41 (s, 3H, CH₃), 4.05 (q, 2H, CH₂-ester), 4.58 (s, 1H, C(4)-H), 4.69 (brs,
NH₂), 7.49 (d, 2H, Ar-H ), 7.58 (d, 2H, Ar-H ); ¹³C NMR (100 MHz, CDCl₃) δ/ppm: 12.90, 17.64, 37.75, 59.95, 63.50, 105.93, 117.33, 121.39, 121.55, 128.51, 133.01, 145.10, 147.47, 156.95, 164.26. LC–MS (positive ion mode): m/z 330 (M+H)⁺ for C₁₆H₁₅N₃O₅.

**Ethyl 6-amino-5-cyano-2-methyl-4-(p-tolyl)-4H-pyran-3-carboxylate 4j**

![Structure 4j](image)

IR (KBr) (ν_max/cm⁻¹): 3401, 2981, 1697, 1604, 1372; ¹H NMR (400 MHz, CDCl₃) δ/ppm: 1.11 (t, 3H, CH₃-ester), 2.33 (s, 3H, CH₃), 2.38 (s, 3H, CH₃), 4.05 (q, 2H, CH₂-ester), 4.41 (s, 1H, C(4)-H), 4.45 (brs, 2H, NH₂), 6.92 (d, 2H, Ar-H), 7.25 (d, 2H, Ar-H); ¹³C NMR (100 MHz, CDCl₃) δ/ppm: 13.86, 18.37, 21.45, 38.68, 60.61, 62.52, 108.08, 118.91, 124.62, 127.96, 128.20, 128.40, 138.07, 156.61, 165.91; LC-MS (positive ion mode): m/z 299 (M+H)+ for C₁₇H₁₈N₂O₃.

**Procedure for the synthesis of ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 5**

A solution of compound 4e (1 mmol) in Ac₂O (1.5 mL) with a catalytic amount of concentrated polyphosphoric acid was heated under reflux for 3 h. The reaction mixture was cooled at room temperature and kept for 1 day. The mixture was poured into water and the formed solid was filtrated, washed with water, and recrystallized using ethanol.

**Ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 5**

![Structure 5](image)

IR (KBr) (ν_max/cm⁻¹): 3394, 2192, 1690, 1542; ¹H NMR (400 MHz, DMSO-d₆) δ/ppm: 1.16 (t, 3H, CH₃-ester), 2.28 (s, 3H, CH₃), 2.63 (s, 3H, CH₃), 4.09 (q, 2H, CH₂-ester), 4.53 (brs, 1H, NH), 4.96 (s, 1H, H-4), 7.20 (d, 2H, Ar-H), 7.26 (d, 2H, Ar-H); ¹³C (100 MHz DMSO-d₆) δ 13.8, 18.1, 33.8, 56.9, 60.4, 107.6, 119.5, 124.0, 124.7, 126.8, 130.8, 139.6, 149.3, 156.7, 159.5, 165.2; LC-MS (positive ion mode): m/z 361(M+H)+ for C₁₈H₁₇ClN₂O₄.

**Procedure for the synthesis of pyrano[2,3-d]pyrimidine-6-carboxylate alkyne 6**

Compound 5 (3 mmol) and potassium carbonate (6 mmol) in 1:2 ratio were taken in 20 ml of DMF in two necked flask. To this mixture propargyl bromide was added dropwise under room temperature for 2 hours and the mixture was concentrated in vacuo.
and added to the ice cold water. The obtained propargylated product was collected by filtration and separated by column chromatography.

**Ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-3-(prop-2-yn-1-yl)-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 6**

IR (KBr) ($\nu_{\text{max}}$/cm$^{-1}$): 3399, 2980, 2189, 1682, 1504; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.14 (t, 3H, CH$_3$-ester), 2.27 (s, 1H, C=CH), 2.28 (s, 3H, CH$_3$), 2.63 (s, 3H, CH$_3$), 4.09 (q, 2H, CH$_2$-ester), 4.92 (s, 1H, H$_4$), 4.96 (4s, 2H, CH$_2$-C=CH), 7.22 (d, 2H, Ar-H), 7.28 (d, 2H, Ar-H); $^{13}$C (50 MHz DMSO-$d_6$) $\delta$ 14.8, 20.1, 36.8, 59.9, 66.4, 110.6, 118.6, 121.0, 123.6, 126.8, 128.9, 132.4, 138.1, 139.2, 146.5, 149.3, 158.5, 159.05, 166.9. LC-MS (positive ion mode): m/z 399 (M+H)$^+$ for C$_{21}$H$_{19}$ClN$_2$O$_4$.

**General procedure for the synthesis of target compounds 7a-h**

The compounds 6 (1 mmol) and various aromatic azide (2 mmol) were suspended in THF (10 ml). Sodium ascorbate (0.3 mmol, in water) was added, followed by copper (II) sulphate pentahydrate (0.03 mmol, in water). The heterogenous mixture was stirred vigorously 5 min and the completion of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with cooled ice water. The crude triazolyl thienopyrimidine product was collected by extraction with ethyl acetate. The product was purified by column chromatography.

**Ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-3-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7a**

IR (KBr) ($\nu_{\text{max}}$/cm$^{-1}$): 2851, 2164, 1690, 1511; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.17 (t, 3H, CH$_3$-ester), 2.49 (s, 3H, CH$_3$), 2.86 (s, 3H, CH$_3$), 3.86 (s, 3H, OCH$_3$), 4.07 (q, 2H, CH$_2$-ester), 4.96 (s, 1H, H-4), 5.13 (d, 1H, CH$_2$), 5.35 (d, 1H, CH$_2$), 7.23 (d, 2H, Ar-H), 7.29 (d, 2H, Ar-H), 7.43-7.64 (3, 5H, Ar-H), 8.03 (s, 1H, triazole-CH); $^{13}$C (100 MHz DMSO- $d_6$) $\delta$ 22.3, 25.9, 31.8, 50.1, 60.9, 67.2, 107.5, 118.4, 120.4, 123.8, 127.6, 129.1, 131.4, 133.2, 137.4, 140.4, 141.4, 148.6, 149.4, 150.2, 154.7, 159.2, 161.4, 164.8, 167.2; LC-MS (positive ion mode): m/z 518 (M+H)$^+$ for C$_{27}$H$_{24}$ClN$_5$O$_4$. 

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Ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-3-((1-(p-tolyl)-1H-1,2,3-triazol-4-yl) methyl)-4,5-dihydro-3H-pyra[2,3-d]pyrimidine-6-carboxylate 7b

IR (KBr) \( (\nu_{\text{max}}/\text{cm}^{-1}) \): 2846, 2262, 1686, 1542; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \( \delta \): 1.22 (t, 3H, CH₃-ester), 2.44 (s, 3H, CH₃), 2.81 (s, 3H, CH₃), 2.86 (s, 3H, CH₃), 4.18 (q, 2H, CH₂-ester), 4.96 (s, 1H, H-4), 5.11 (d, 1H, CH₂), 5.30 (d, 1H, CH₂), 6.92 (d, 2H, Ar-H), 7.21 (d, 2H, Ar-H), 7.48 (d, 2H, Ar-H), 7.76 (d, 2H, Ar-H), 8.21 (s, 1H, triazole-CH); \(^1^3\)C (100 MHz DMSO- \(d_6\)) \( \delta \): 20.1, 24.6, 36.9, 52.4, 59.6, 64.3, 69.4, 109.6, 119.8, 121.6, 126.7, 128.3, 130.9, 136.8, 139.5, 143.6, 145.2, 148.4, 149.6, 151.3, 157.6, 160.4, 163.4, 168.6; LC-MS (positive ion mode): m/z 532 (M+H)+ for C\(_{28}\)H\(_{26}\)ClN\(_5\)O\(_4\).

Ethyl 5-(4-chlorophenyl)-3-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-2,7-dimethyl-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7c

IR (KBr) \( (\nu_{\text{max}}/\text{cm}^{-1}) \): 2976, 2262, 1709, 1667, 1557; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 1.19 (t, 3H, CH₃-ester), 2.48 (s, 3H, CH₃), 2.83 (s, 3H, CH₃), 3.86 (s, 3H, OCH₃), 4.08 (q, 2H, CH₂-ester), 4.96 (s, 1H, H-4), 5.14 (d, 1H, CH₂), 5.35 (d, 1H, CH₂), 6.99 (d, 2H, Ar-H), 7.21 (dd, 4H, Ar-H), 7.51 (d, 2H, Ar-H), 7.91 (s, 1H, triazole-CH); \(^1^3\)C (100 MHz CDCl\(_3\)/DMSO- \(d_6\)) \( \delta \): 13.1, 17.9, 22.3, 35.7, 38.9, 54.7, 59.6, 100.1, 106.9, 113.9, 121.1, 121.3, 127.2, 129.0, 131.3, 141.6, 143.8, 148.5, 157.6, 157.8, 158.2, 158.9, 160.6, 164.9; LC-MS (positive ion mode): m/z 548 (M+H)+ for C\(_{28}\)H\(_{26}\)ClN\(_5\)O\(_5\).

Ethyl 5-(4-chlorophenyl)-3-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2,7-dimethyl-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7d

IR (KBr) \( (\nu_{\text{max}}/\text{cm}^{-1}) \): 2985, 2125, 1668, 1553; \(^1\)H NMR (400 MHz, DMSO- \(d_6\)) \( \delta \): 1.27 (t, 3H, CH₃-ester), 2.43 (s, 3H, CH₃), 2.51 (s, 3H, CH₃), 4.13 (q, 2H, CH₂-ester), 4.96 (s, 1H, H-4), 5.31 (d, 1H, CH₂), 5.35 (d, 1H, CH₂), 7.22 (dd, 4H, Ar-H), 7.49 (d, 2H, Ar-H), 7.57 (d, 2H, Ar-H) 7.99 (s, 1H, triazole-CH); \(^1^3\)C (100 MHz DMSO- \(d_6\)) \( \delta \): 13.9, 18.8, 23.2, 36.6, 39.8, 60.6, 101.3, 107.8, 121.5, 128.2, 129.8, 129.9, 132.5, 134.8, 135.1, 142.2, 147.5, 148.5, 158.6, 158.8, 158.8, 161.7, 165.8; LC-MS (positive ion mode): m/z 552 (M+H)+ for C\(_{27}\)H\(_{23}\)Cl\(_3\)N\(_5\)O\(_4\).
Ethyl 5-(4-chlorophenyl)-2,7-dimethyl-3-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl) methyl)-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7e

IR (KBr) (ν_{max}/cm^{-1}): 2890, 2027, 1690, 1541; ^1H NMR (400 MHz, DMSO-d$_6$) δ 1.20 (t, 3H, CH$_3$-ester), 2.47 (s, 3H, CH$_3$), 2.82 (s, 3H, CH$_3$), 4.19 (q, 2H, CH$_2$-ester), 4.96 (s, 1H, H-4), 5.30 (d, 1H, CH$_2$), 5.39 (d, 1H, CH$_2$), 7.28 (d, 2H, Ar-H), 7.36 (d, 2H, Ar-H), 7.46 (d, 2H, Ar-H), 7.59 (d, 2H, Ar-H), 8.19 (s, 1H, triazole-CH); ^13C (100 MHz DMSO-d$_6$) δ 12.4, 17.1, 21.4, 34.8, 58.7, 99.0, 106.1, 118.9, 120.9, 123.7, 126.4, 128.3, 130.2, 139.3, 140.9, 145.3, 146.4, 149.2, 150.1, 156.8, 157.7, 159.6, 163.8; LC-MS (positive ion mode): m/z 564 (M+H)$^+$ for C$_{27}$H$_{23}$ClN$_6$O$_6$.

Ethyl 5-(4-chlorophenyl)-2,7-dimethyl-3-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl) methyl)-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7f

IR (KBr) (ν_{max}/cm^{-1}): 2759, 2127, 1704, 1549; ^1H NMR (400 MHz, DMSO-d$_6$) δ 1.15 (t, 3H, CH$_3$-ester), 2.48 (s, 3H, CH$_3$), 2.84 (s, 3H, CH$_3$), 4.10 (q, 2H, CH$_2$-ester), 4.96 (s, 1H, H-4), 5.17 (d, 1H, CH$_2$), 5.38 (d, 1H, CH$_2$), 7.22 (dd, 4H, Ar-H), 7.73 (t, 1H, Ar-H), 8.02 (d, 1H, Ar-H), 8.14 (s, 1H, Ar-H), 8.32 (d, 1H, Ar-H), 8.57 (s, 1H, triazole-CH); ^13C (100 MHz DMSO-d$_6$) δ 13.9, 18.7, 23.2, 36.6, 39.7, 60.6, 101.3, 107.8, 108.1, 108.3, 115.6, 115.8, 116.0, 122.2, 128.2, 129.8, 131.2, 132.5, 137.7, 142.2, 142.9, 158.8, 161.7, 163.9, 165.8; LC-MS (positive ion mode): m/z 563 (M+H)$^+$ for C$_{27}$H$_{23}$ClN$_6$O$_6$.

Ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-3-((1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methyl)-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7g

IR (KBr) (ν_{max}/cm^{-1}): 2928, 2313, 1714, 1554; ^1H NMR (400 MHz, DMSO-d$_6$) δ 1.18 (t, 3H, CH$_3$-ester), 2.48 (s, 3H, CH$_3$), 2.84 (s, 3H, CH$_3$), 4.06 (q, 2H, CH$_2$-ester), 4.96 (s, 1H, H-4), 5.11 (d, 1H, CH$_2$), 5.39 (d, 1H, CH$_2$), 7.23 (dd, 4H, Ar-H), 7.39 (d, 1H, Ar-H), 7.65 (t, 1H, Ar-H), 7.84 (d, 1H, Ar-H), 7.99 (s, 1H, Ar-H), 8.11 (s, 1H, triazole-CH); ^13C (100 MHz DMSO-d$_6$) δ 13.2, 15.9, 21.7, 24.6, 28.6, 50.5, 57.1, 107.0, 107.3, 114.9, 114.9, 119.0, 121.2, 121.7, 130.4, 130.5,
137.0, 137.1, 139.7, 142.4, 153.0, 160.3, 161.5, 162.7, 163.6, 168.0; LC–MS (positive ion mode): m/z 586 (M+H)+ for C_{29}H_{25}ClF_{3}N_{5}O_{4}.

Ethyl 5-(4-chlorophenyl)-3-((1-(3-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2,7-dimethyl-4-oxo-4,5-dihydro-3H-pyran-2,3-d]pyrimidine-6-carboxylate 7h

IR (KBr) ($\nu_{\text{max}}$/cm$^{-1}$): 2811, 2067, 1685, 1520; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.18 (t, 3H, CH$_3$-ester), 2.48 (s, 3H, CH$_3$), 2.84 (s, 3H, CH$_3$), 4.08 (q, 2H, CH$_2$-ester), 4.96 (s, 1H, H-4), 5.16 (d, 1H, CH$_2$), 5.34 (d, 1H, CH$_2$), 7.24 (dd, 4H, Ar-H), 7.49 (d, 1H, Ar-H), 7.59 (t, 1H, Ar-H), 7.72 (d, 1H, Ar-H), 7.86 (s, 1H, Ar-H), 8.03 (s, 1H, triazole-CH); $^{13}$C (100 MHz DMSO-$d_6$) $\delta$ 16.9, 24.9, 36.4, 41.9, 52.1, 68.6, 113.8, 119.5, 122.9, 126.4, 130.8, 136.9, 138.9, 139.2, 140.6, 143.5, 148.9, 149.7, 150.5, 151.2, 155.6, 157.2, 159.1, 161.9, 167.6; LC-MS (positive ion mode): m/z 536 (M+H)$^+$ for C$_{27}$H$_{23}$ClF$_{3}$N$_{5}$O$_{4}$.

Biological assay

Antibacterial studies

The newly prepared compounds were screened for their antibacterial activity against Bacillus subtilis, Staphylococcus aureus, Klebsiella pneumonia and Escherichia coli (clinical isolate) bacterial strains by disc diffusion method$^{45,46}$. A standard inoculums (1-2 $\times$ 10$^7$ c.f.u./ml 0.5 McFarland standards) were introduced on to the surface of sterile agar plates and a sterile glass spreader was used for even distribution of the inoculums. The disks measuring 6 mm in diameters were prepared from Whatman no. 1 filter paper and sterilized by dry heat at 140 $^0$C for 1 h. The sterile disks previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. Solvent and growth controls were kept. Amoxicillin (30 $\mu$g) was used as positive control and the disk poured in DMSO was used as negative control and the test compounds were dissolved in DMSO at concentration of 100 and 50 $\mu$g/mL. The plates were inverted and incubated for 24 h at 37 $^0$C. The susceptibility was assessed on the basis of diameter of zone of inhibition against Gram-positive and Gram-negative strains of bacteria. Inhibition of zone of measured and compared with controls. The bacterial zone of inhibition values are given in Table 1.

Antifungal studies

The newly prepared compounds were screened for their antifungal activity against Candida albicans and Aspergillus flavus in DMSO by agar diffusion method$^{47}$. Sabourauds agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and
agar (2 g) in distilled water (100 ml) and adjusting pH 5.7. Normal saline was used to make suspension of corresponding species. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37 °C for 1 h using an agar punch, wells were made and each well was labeled. A control was also prepared in triplicate and maintained at 37 °C for 3-4 days. The fungal activity of each compound was compared with Ketoconazole as a standard drug. Inhibition zone were measured and compared with the controls. The fungal zone of inhibition values are given in Table 2.

Table 1: Antibacterial activity of compounds 7a-h.

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<th>Synthesized compounds</th>
<th>Gram positive</th>
<th>Gram negative</th>
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<tr>
<td></td>
<td>Bacillus subtilis</td>
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<td></td>
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</tr>
<tr>
<td>7h</td>
<td>11.5</td>
<td>10.0</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>15.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Control (DMSO)</td>
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<td>–</td>
</tr>
</tbody>
</table>

Table 2: Antifungal activity of compounds 7a-h.

<table>
<thead>
<tr>
<th>Synthesized compounds</th>
<th>Candida albicans</th>
<th>Aspergillus flavus</th>
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</thead>
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<td></td>
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<tr>
<td>Ketoconazole</td>
<td>20.5</td>
<td>16.0</td>
</tr>
<tr>
<td>Control (DMSO)</td>
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</table>
Result and discussion

The newly synthesized compounds (7a-h) were screened for their in-vitro antibacterial activity against \textit{Bacillus subtilis, Staphylococcus aureus, Klebsiella pneumonia} and \textit{Escherichia coli} using Amoxicillin as standard by disc diffusion method (zone of inhibition)\textsuperscript{50,51}. The test compounds were dissolved in dimethylsulfoxide (DMSO) at concentrations of 50 and 100 µg/mL. The antibacterial screening revealed that all the tested compounds showed good inhibition against various tested microbial strains compared to the standard drug. Along with the synthesized compounds 7d, 7e, 7f, 7g and 7h were found to be more active against tested bacterial strains as compared to the standard. The enhanced antibacterial activity of 7g and 7h were due to presence of fluoro group in the 1,2,3-triazole phenyl moiety at the third position of pyranopyrimidine moiety. And also the compounds 7e and 7f contains nitro group at fourth and third position of 1,2,3-triazole phenyl of pyranopyrimidine ring which accounts for the enhanced antibacterial activity. Compound 7d exhibited good antibacterial activity against all tested bacterial stains due to chloro present on the two phenyl rings of pyranopyrimidine moiety. In general, increase of electron donating strength on phenyl ring on the 1,2,3-triazole with pyranopyrimidine (methyl, methoxy substitution) decreases antibacterial activity. On the other hand, introducing halogen or electron withdrawing phenyl ring on the 1,2,3-triazole with pyranopyrimidine increases the antibacterial activity. The activity exhibited by the synthesized compounds were due to both 1,2,3-triazole and pyranopyrimidine core rings.

The in-vitro antifungal activities of compounds (7a-h) were determined by agar diffusion method\textsuperscript{52}. The results indicate that, among the tested compounds 7f and 7h were active against all tested fungal strains. The enhanced activities of compounds are due to electron withdrawing groups chloro, fluoro and nitro attached to heterocyclic moieties (1,2,3-triazole) of pyranopyrimidine ring. All other compounds such as, 1,2,3-triazole with methyl and phenyl substitution with pyranopyrimidine showed lesser antifungal activity as compared with standard Ketoconazole. The Table 1 and Table 2 depict the antimicrobial screening results of the final compounds.
Fig. 4.1.1. IR spectrum of Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate 4c
Fig. 4.1.1.1. $^1$H NMR spectrum of Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate 4c
Fig. 4.1.1.2. $^{13}$C NMR spectrum of Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate 4c
Fig. 4.1.1.3. Mass spectrum of ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate 4c
Fig. 4.1.2. IR spectrum of ethyl 6-amino-5-cyano-4-(3,4-dimethoxyphenyl)-2-methyl-4H-pyran-3-carboxylate 4e
Fig. 4.1.2.1. $^1$H NMR spectrum of ethyl 6-amino-5-cyano-4-(3,4-dimethoxyphenyl)-2-methyl-4H-pyran-3-carboxylate 4e
Fig. 4.1.2.2. $^{13}$C NMR spectrum of ethyl 6-amino-5-cyano-4-(3,4-dimethoxyphenyl)-2-methyl-4H-pyran-3-carboxylate 4e
Fig.4.1.2.3. Mass spectrum of ethyl 6-amino-5-cyano-4-(3,4-dimethoxyphenyl)-2-methyl-4H-pyran-3-carboxylate 4e
Fig.4.1.3. IR spectrum of ethyl 6-amino-5-cyano-2-methyl-4-(3,4,5-trimethoxyphenyl)-4H-pyran-3-carboxylate 4f
Fig. 4.1.3.1. $^1$H NMR spectrum of ethyl 6-amino-5-cyano-2-methyl-4-(3,4,5-trimethoxyphenyl)-4H-pyran-3-carboxylate 4f
Fig. 4.1.3.2. $^{13}$C NMR spectrum of ethyl 6-amino-5-cyano-2-methyl-4-(3,4,5-trimethoxyphenyl)-4H-pyran-3-carboxylate 4f.
Fig. 4.1.3.3. Mass spectrum of ethyl 6-amino-5-cyano-2-methyl-4-(3,4,5-trimethoxyphenyl)-4H-pyran-3-carboxylate 4f
Fig. 4.2. IR spectrum of ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-3-(prop-2-yn-1-yl)-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 6
Fig. 4.2.1. $^1$H NMR spectrum of ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-3-(prop-2-yn-1-yl)-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 6
Fig. 4.2.2. Mass spectrum of ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-3-(prop-2-yn-1-yl)-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 6
Fig. 4.3.1. IR spectrum of ethyl 5-(4-chlorophenyl)-3-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-2,7-di methyl-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7c
Fig. 4.3.1.1. $^1$H NMR spectrum of ethyl 5-(4-chlorophenyl)-3-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-
2,7-di methyl-4-oxo-4,5-dihydro-3H-pyran[2,3-d]pyrimidine-6-carboxylate 7c
Fig. 4.3.1.2. $^{13}$C NMR spectrum of ethyl 5-(4-chlorophenyl)-3-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-2,7-di methyl-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7c
Fig. 4.3.1.3. Mass spectrum of ethyl 5-(4-chlorophenyl)-3-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-2,7-di methyl-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7c
Fig. 4.3.2. IR spectrum of ethyl 5-(4-chlorophenyl)-3-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2,7-di methyl-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7d
Fig. 4.3.2.1. $^1$H NMR spectrum of ethyl 5-(4-chlorophenyl)-3-\(((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2,7-di methyl-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7d
Fig.4.3.2.2. $^{13}$C NMR spectrum of ethyl 5-(4-chlorophenyl)-3-(((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2,7-di methyl-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7d
Fig.4.3.2.3. Mass spectrum of ethyl 5-(4-chlorophenyl)-3-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2,7-di methyl-4-oxo-4,5-dihydro-3H-pyran[2,3-d]pyrimidine-6-carboxylate 7d
Fig. 4.3.3. IR spectrum of ethyl 5-((4-chlorophenyl)-2,7-dimethyl-3-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7f
Fig. 4.3.3.1. $^1$H NMR spectrum of ethyl 5-(4-chlorophenyl)-2,7-dimethyl-3-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7f
Fig. 4.3.3.2. $^{13}$C NMR spectrum of ethyl 5-(4-chlorophenyl)-2,7-dimethyl-3-(((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7f
Fig. 4.3.3.3. Mass spectrum of ethyl 5-(4-chlorophenyl)-2,7-dimethyl-3-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl) methyl)-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7f
Fig. 4.3.4. IR spectrum of ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-3-((1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methyl)-4,5-dihydro-3H-pyrano[2,3-d] pyrimidine-6-carboxylate 7g
Fig. 4.3.4.1. $^1$H NMR spectrum of ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-3-((1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methyl)-4,5-dihydro-3H-pyrano[2,3-d] pyrimidine-6-carboxylate 7g
Fig. 4.3.4.2. $^1$H NMR spectrum of ethyl5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-3-((1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methyl)-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7g
Fig.4.3.4.3. Mass spectrum of ethyl 5-(4-chlorophenyl)-2,7-dimethyl-4-oxo-3-((1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methyl)-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carboxylate 7g
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184, 3134.