CHAPTER-IV
SYNTHESIS AND CHARACTERIZATION OF NEW 2-BENZYL-OXY-5-ALKYNE SUBSTITUTED PYRIMIDINE DERIVATIVES AND THEIR ANTICANCER ACTIVITY
4.1. Introduction

Cancer is a major health problem worldwide. Improvements in treatment and prevention have led to a decrease in cancer deaths, but the number of new diagnoses continues to rise. Chemotherapy is one of the most commonly used treatment options, especially for unrespectable patients. However, the use of conventional cytotoxic drugs, including doxorubicin, cisplatin and fluorouracil, has not shown any improvement in survival, and severe adverse effects have been frequently observed in treated patients. Thus, it is urgent to develop novel chemotherapeutic agents for the treatment of cancer.

Many heterocyclic compounds have been synthesized because of their wide range of biological activity.\textsuperscript{1} Pyrimidines are the most important compounds in six membered heterocyclics containing two nitrogen atoms. The pyrimidine ring system has wide occurrence in nature as substituted and ring fused compounds and derivatives, including the nucleotides, thiamine (vitamin B1) and alloxan (C\textsubscript{4}H\textsubscript{2}N\textsubscript{2}O\textsubscript{4}). Pyrimidine derivatives serve both as biomimetic and reactive pharmacophores due to their diverse medicinal properties, such as antitumor,\textsuperscript{2} anticancer (lungs, breasts, and CNS cancers),\textsuperscript{3} immunodelator,\textsuperscript{4} antifolate,\textsuperscript{5} antiviral,\textsuperscript{6} tyrosine kinase inhibitors,\textsuperscript{7} COX-2 inhibitors,\textsuperscript{8} antihypertensive,\textsuperscript{9} and also active against Y181C HIV-1 mutant strain.\textsuperscript{10} Various drugs containing pyrimidine nucleus were synthesized and used as anticancer agents like 5-Fluorouracil (5-FU) (1), Tegafur (2) and Thioguanine (3)\textsuperscript{11} (Fig. 1).

\textbf{Fig. 1.} Structures of 5-Fluorouracil (5-FU), Tegafur and Thioguanine
4.2. Sonogashira coupling

The Sonogashira coupling of aryl halides and terminal acetylenes remains the most important method for the formation of C(sp\(^2\))–C(sp) bonds.\(^{12}\) Traditionally palladium complexes, very often in combination with copper (I) salts, are the preferred catalysts for such reactions, despite the fact that in recent years numerous other metals were also claimed to be effective.\(^{12c,13}\) Closely related approaches leading to the same products involve the reactions of alkynyl halides and arenes (“inverse Sonogashira reaction”)\(^{14}\) or of acetylenes and heterocycles (“direct alkynylation”)\(^{15}\) or the reactions of aryl boronic acids with acetylenes.\(^{16}\)

The mechanism of the Sonogashira reaction is not understood in detail, also since there can be additional complications due to CuI and the metal coordination of acetylenes.\(^{17}\) Nevertheless, primarily empirical studies led to a large number of powerful catalyst recipes, which allow the efficient conversion of aryl iodides and bromides using small catalyst loading\(^{18}\) or aryl chlorides.\(^{19}\) With an ever larger number of catalysts and reaction conditions published in the literature, it is not easy for the non specialist to choose the best reaction conditions for certain substrates. In this respect, answers are needed concerning the factors determining the reactivity of individual substrates in Sonogashira reactions. Several studies focusing on the influence of steric and electronic variables on the individual steps in the catalytic cycles, such as the oxidative addition,\(^{20}\) transmetalation and reductive elimination, were done, and a few general rules concerning cross-coupling reactions were derived\(^{21}\): (i) the oxidative addition in Ar-X is promoted by electron-withdrawing groups at the aryl halide; (ii) steric bulk of phosphines or NHC(N-Heterocyclic carbine) ligands coordinated to Pd promote the formation of a formally monoligated complex PdL\(_1\), which turns out to be highly active for oxidative addition; (iii) there is a pronounced steric effect in the transmetalation, while the ligand bite angle and the electronic effect are less important; and (iv) reductive elimination tends to be favored by less electrondonating ligands and steric bulk.\(^{22}\)

4.2.1. Mechanism of the Sonogashira reaction

This coupling of terminal alkynes with aryl halides is performed with a palladium catalyst, a copper (I) cocatalyst, and an amine base. Typically, the reaction
requires anhydrous and anaerobic conditions, but newer procedures have been
developed where these restrictions are not important. The Sonogashira reaction
mechanism is not clearly understood but the textbook mechanism revolves around a
palladium cycle and a copper cycle that is less well known.23

The palladium cycle mechanism

- An inactive palladium Pd(II) catalyst is activated by a reduction to the
  Pd⁰ compound.
- The active palladium catalyst is the 14 electron compound Pd⁰L₂, complex A,
  which reacts with the aryl or vinyl halide in an oxidative addition to produce a
  Pd(II) intermediate, complex B. This step is believed to be the rate-limiting
  step of the reaction.
- Complex B reacts in a transmetalation with the copper acetylide, complex F,
  which is produced in the copper cycle, to give complex C, expelling the copper
  halide, complex G.
- Both organic ligands are trans oriented and convert to cis in a trans-cis
  isomerization to produce complex D.
- In the final step, complex D undergoes reductive elimination to produce the
  alkyne, with regeneration of the palladium catalyst.
- The oxidation of triphenylphosphine to triphenylphosphine oxide can also lead to
  the formation of Pd⁰ in situ when catalysts such as bis(triphenylphosphine)
  palladium(II) chloride are used.

The copper cycle mechanism

- It is suggested that the presence of base results in the formation of a pi-alkyne
  complex, complex E, which makes the terminal proton on the alkyne more acidic,
  leading to the formation of the copper acetylide, compound F.
- Compound F continues to react with the palladium intermediate B, with
  regeneration of the copper halide, complex G.
Mechanistic studies suggest that these catalytic cycles represent the preferred reaction pathway. Some of the biological active molecules were synthesized through Sonogashira cross coupling reaction and some are shown below.
4.3. Literature Review

Ian J. S. Fairlamb and co-workers\textsuperscript{24} have synthesized a novel of 6-methyl-4-(2-phenylethynyl)-2H-pyran-2-one derivatives by Sonogashira couplings of substituted halo compounds with terminal alkynes, and Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} in the presence of a CuI co-catalyst (Fig. 2).

![Fig. 3](image)

Fig. 3

Muralidharan, A and co-workers\textsuperscript{25} have synthesized a series of 2-alkynyl imidazo[4,5-b]pyridines derivatives through Sonogashira coupling reaction of 3-cyclopentyl-2-halo imidazo[4,5-b]pyridines (I, Br, Cl) in presence of PdCl\textsubscript{2}(PCy\textsubscript{3})\textsubscript{2} catalyst and tetrabutylammonium acetate system (Fig. 3).

![Fig. 4](image)

Fig. 4

Josef Michl and co-workers\textsuperscript{26} have synthesized hexadehydrotribenzo-[a,e,i][12]annulene by insertion of acetylene into an open chain diiodo precursor under Sonogashira coupling conditions (Fig. 4).
Piotr Pawluc and co-workers\textsuperscript{27} have synthesized a novel of carbazole-containing (E)-but-1-en-3-ynes derivatives by palladium-catalyzed Sonogashira cross coupling reaction (Fig. 5).

Scott G. Stewart and co-workers\textsuperscript{28} have synthesized a library of new thalidomide C4/5 analogues containing alkyne tether were synthesized using Sonogashira cross coupling reactions from their aryl halogenated precursors. All thalidomide analogues were tested for their ability to inhibit the expression of the proinflammatory cytokine Tumor Necrosis Factor (TNF). More explicitly the use of a novel reporter system utilizing the promoter region of the TNF gene in a human T-cell line provided a rapid and effective measure of NFkB transcriptional activity (Fig. 6).
Wei Lu and co-workers\textsuperscript{29} have synthesized a series of 7-substituted camptothecins analogues by copper-free Sonogashira cross coupling reaction (Fig. 7).

Julio Alvarez-Builla and co-workers\textsuperscript{30} have synthesized a series of pyridinium N-(pyridin-2-yl)aminides, pyridinium N-(pyrimidin-2-yl) and N-(pyrazin-2-yl) aminides by Sonogashira copper-free coupling reaction (Fig. 8).

Surajit Sinha and co-workers\textsuperscript{31} have synthesized a series of 5-alkynylated uracil morpholino monomers by Sonogashira coupling (Fig. 9).
Xuegong She co-workers\textsuperscript{32} have described a simple and efficient synthesis of tribenzohexadehydro[12]-annulene and related derivatives in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate through Sonogashira coupling reaction (Fig. 10).

Javed Iqbal and co-workers\textsuperscript{33} synthesized new cyclic peptide derivatives by copper-free intramolecular Sonogashira coupling reaction (Fig. 11).

Sven Doye and co-workers\textsuperscript{34} have reported a series of unsymmetrically substituted diarylalkynes through Pd/Cu-catalyzed Sonogashira coupling (Fig. 12).
Christian Melander and co-workers\textsuperscript{35} have synthesized new 2-aminoimidazole derivatives for antibiofilm screening utilizing the Sonogashira reaction. The reaction proceeds in excellent yield regardless of the alkyne and aryl halide scaffold used. The biological screening of the analogues as modulators of biofilm growth and maintenance is currently underway (Fig. 13).

Michael Schmittel and co-workers\textsuperscript{36} have synthesized a series of 3,8-unsymmetric phenanthrolines derivatives through regioselective Sonogashira coupling reaction (Fig. 14).

Christina Moberg and co-workers\textsuperscript{37} have synthesized new polymer-supported pyridine-bis(oxazoline) derivatives through Sonogashira coupling (Fig. 15).
Yusuf Yagci and co-workers\textsuperscript{38} have synthesized polybenzoxazine derivatives through Sonogashira coupling reaction with iodo functional bisbenzoxazine and diacetylenes palladium tetrakis(triphenylphosphine). Curing behaviors of both the monomer and polymers were studied by differential scanning calorimetry (DSC). Thermal properties of the cured polymers were also investigated by thermogravimetric analysis (TGA) (Fig. 16).

Erik Van der Eycken and co-workers\textsuperscript{39} have synthesized new substituted 5-chloro-3-alkynylpyrazinones from the corresponding 5-chloro-3-(phenylsulfanyl) pyrazin-2(1\textit{H})-ones through Sonogashira cross coupling (Fig. 17).
Troels Skrydstrup and co-workers\textsuperscript{40} have reported a new palladium catalyzed carbonylative Sonogashira coupling of aryl bromides (Fig. 18).

Courtney C. Aldrich and co-workers\textsuperscript{41} have developed an efficient Pd-catalyzed system for direct alkynylation of tautomerizable heterocycles \textit{via} C-OH bond activation using PyBrOP. The protocols showed great versatility and efficiency, enabling cross couplings between a variety of tautomerizable heterocycles and terminal alkynes with diverse electronic and steric features. The mechanism of the direct Cu-free cross-coupling is proposed to proceed through a stepwise process of C-OH activation using PyBrOP followed by Cu-free Sonogashira type catalytic cycle (Fig. 19).
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Masahiro Miura and co-workers have described effective nickel- and copper-based catalyst systems for the direct alkylnylation of azoles and polyfluoroarenes with terminal alkynes using molecular oxygen as the sole oxidant. These strategies are regarded as direct Sonogashira coupling (Fig. 20).

Arnaud Tatibouët and co-workers have synthesized new substituted 2-phenylethynylxazoles through Sonogashira cross-coupling. A cooperative effect of two different copper (I) species- CuI and CuTC (Cu(I)-thiophene-2-carboxylate) accounts for this new copper-catalyzed desulfurative carbon-carbon cross-coupling reaction (Fig. 21).
Richard P. Hsung and co-workers\textsuperscript{44} have described Sonogashira coupling of ynamides with aryl and vinyl iodides. The coupling protocol circumvents the problem of competing homocoupling of ynamides and provides a practical entry to novel urethane- and sulfonamide-terminated conjugated acetylenic systems (Fig. 22).

Mark A. Matulenko and co-workers\textsuperscript{45} have identified novel non-nucleoside inhibitors of AK with an acetylene functional group. The \textit{in vitro} potency of these acetylene analogs compared favorably to ABT-702. The efficacy in animal models of pain, however, was diminished compared to ABT-702. This lack of \textit{in vivo} efficacy is thought to result from lower plasma levels after systemic dosing of these aryl acetylene analogs relative to the pyridopyrimidines like ABT-702 (Fig. 23).
Mathew Thomas and co-workers\textsuperscript{46} have synthesized a novel series of five and six membered monocycles as alternate hinge-binding templates to replace the 6, 5-fused imidazopyridazine core of ponatinib. Like ponatinib, these monocycles are tethered to pendant toluanilides \textit{via} an ethynyl linker. Several compounds in this series displayed excellent \textit{in vitro} potency against both native BCR–ABL and the T315I mutant. Notably, a subset of inhibitors exhibited desirable PK and was orally active in a mouse model of T315I-driven CML (Fig. 24).
Craig W. Lindsley and co-workers\textsuperscript{47} has described the synthesis and SAR of a series of analogues of the mGlu5 partial antagonist 5-(phenylethynyl) pyrimidine. A regioisomeric pyrimidine congener \textsuperscript{39} resulted in full NAMs (negative allosteric modulators) activity \textit{in vitro} and \textit{in vivo}. The incorporation of an amino methyl group into the 2-position of the pyrimidine core resulted in PAMs (positive allosteric modulators) activity, and this new molecular “switch” was able to override previously identified NAMs molecular “switches”. In this series, \textsuperscript{40} represents the most potent mGlu5 PAMs reported to date and the first example of \textit{in vivo} efficacy of a pure mGlu5 PAMs in reversing amphetamine-induced hyperlocomotion. The resulting mGlu5 NAMs \textsuperscript{39} and PAM \textsuperscript{40} showed \textit{in vivo} efficacy in rodent models of anxiety and schizophrenia, respectively, which mirrored the observed \textit{in vitro} mode of pharmacology (Fig. 25).

![Fig. 26](image)

Ken-Tsung Wong and co-workers\textsuperscript{48} have synthesized a new series of aza-substituted analogues, based on the 1,4-bis(phenylethynyl)benzene moiety by the selective Pd-catalyzed Sonogashira coupling reaction from 5-bromo-2-iodopyrimidine (Fig. 26).

![Fig.27](image)

Ken-Tsung Wong and co-workers\textsuperscript{49} have synthesized a series of dipolar pyrimidine moieties in the $\Pi$-conjugated backbone by a Pd-catalyzed Sonogashira coupling reaction (Fig. 27).
Raymond Ziessel and co-workers\textsuperscript{50} have synthesized a new bipyrimidine, phenanthroline, and terpyridine modules by Sonogashira cross coupling reaction with multitopic ligands (Fig. 29).

Jean-Francois Morin and co-workers\textsuperscript{51} have synthesized cruciform alkynylated anthanthrene compounds using Sonogashira coupling (Fig. 30).
Andra’s Kotschy and co-workers\textsuperscript{52} have synthesized a series of substituted chlorotetrazines were reacted with different terminal alkynes under Sonogashira coupling conditions to furnish alkynyl-tetrazines in good to moderate yields. The electron-donating properties of the substituent on the tetrazine core were found to have a significant influence on the success of the reaction. These results constitute the first cross-coupling reactions on tetrazines (Fig. 31).

Jeffrey B. Arterburn and co-workers\textsuperscript{53} have synthesized a novel of biotin-derived alkynes’ by using palladium-catalyzed Sonogashira and methodology (Fig. 32).
Fumitoshi Shibahara and co-workers\textsuperscript{54} have synthesized 1-alkynyl- and 1-alkenyl-3-arylimidazo [1, 5-a] pyridines derivatives by Sonogashira coupling of 3-aryl-1-iodimidazo [1, 5-a]-pyridines and various terminal alkynes with Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (10 mol \%) and Cul (10 mol \%) in triethylamine at 80 °C for 12 h (Fig. 33).

In view of above information of pyrimidines and Sonagashira coupling reaction, it is decided to synthesize 2-benzyloxy-5-alkyne substituted pyrimidine derivatives through Songanashira cross coupling reaction.
4.4. Experimental Section

4.4.1. Materials and Methods

All reactions were carried out in oven-dried glassware (120°C) under an atmosphere of nitrogen unless as indicated otherwise. Ethyl acetate and hexanes from Mallinckrodt Chemical Co. were dried and distilled from CaH₂. Tetrahydrofuran from Chemlabs Chemicals, were dried by distillation from sodium and benzophenone under an atmosphere of nitrogen and dimethylformamide were purchased from Merck. Diethyl amine was purchased from Finar labs and PdCl₂ (PPh₃)₂ were purchased from comb blocks. CuI were purchased from Merck, 2-chloro-5-bromo pyrimidine were purchased from Sigma-Aldrich. 3-Butyn-1-ol was purchased from Sigma-Aldrich, 4-pentyn-1-ol was purchased from Sigma-Aldrich and 9-decyn-1-ol was purchased from TCI chemicals. Benzyl alcohol and substituted benzyl alcohols were purchased from Sigma-Aldrich and Alfa Aesar.

Thin layer chromatography (TLC) was performed on percolated plates (silica gel 60 F₂₅₄), which were purchased from Merck Inc. Purification by gravity column chromatography was carried out by use of Silicycle ultra-pure silica gel (particle size 40–63 µm, 100–200 mesh). Purity of products was checked by High-resolution mass spectra (HRMS) obtained by means of Q-TOF micro mass spectrometer and HPLC (Waters 2695). Proton NMR spectra were obtained on a MR (400 MHz) and Vnmrs (300 MHz) spectrometer by use of dimethylsulfoxide-d₆ (DMSO) as solvent and TMS as internal standard. Proton NMR chemical shifts were referenced to residual protonated solvents (δ 2.5 ppm for dimethylsulfoxide) and carbon-13 NMR spectra were obtained on a MR (100 MHz) and Vnmrs (75MHz) spectrometer by use of dimethylsulfoxide as the solvent and TMS as internal standard. Carbon-13 chemical shifts are referenced to the center of the DMSO septet (δ 39.5 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs broad singlet; bd, broad doublet; J, coupling constant (hertz). Melting points were obtained with a Buchi MP-B540 melting point apparatus.
4.4.2 General procedure for synthesis of 2-benzyloxy-5-alkyne substituted pyrimidine derivatives (58a-p).

To an oven dried 25 mL round bottom flask were added 5-bromo-2-substituted benzyloxy) pyrimidine (56a-d) (1.0 eq), aryl alkynes or aliphatic alkynes (57a-e) (1.2 eq), CuI (0.1 eq) and DIEA (2.5 eq) followed by THF (10 vol) and were degassed by bubbling with nitrogen gas for 30 min. PdCl$_2$ (PPh$_3$)$_2$ (0.1 eq) was added to the above reaction mixture and then heated to 60 °C for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 35-40 % ethyl acetate/hexane) to obtained 58a-p with good yields.

**Synthesis of 4-(2-(4-fluorobenzyloxy) pyrimidin-5-yl) but-3-yn-1-ol (58a).** To a oven dried 25 mL round bottom flask were added 5-bromo-2-(4-fluorobenzyloxy) pyrimidine (56a) (0.5 g, 1.76 mmol), 3-butyn-1-ol (57a) (0.148 g, 2.11 mmol), CuI (0.033 g, 0.176 mmol) and DIEA (0.321 g, 4.4 mmol) followed by THF (5 mL) and were degassed by bubbling with nitrogen gas for 30 min. PdCl$_2$ (PPh$_3$)$_2$ (0.123 g, 0.176 mmol) was added to the above reaction mixture and then heated to 60 °C for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 35-40 % ethyl acetate/hexane) to obtained 58a (427 mg, 89 %) as a yellow solid.

![Chemical Structure](image)

Analytical data: Mp: 108-111 °C, TLC Rf. 0.28 (30% ethyl acetate in hexane as a eluent); $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 8.68 (s, 2H, pyrimidine-H), 7.62 - 7.41 (m, 2H, ArH), 7.32 - 7.12 (m, 2H, ArH), 5.38 (s, 2H, ArCH$_2$), 4.92 (t, 1H, $J = 5.6$ Hz,OH), 3.69 - 3.50 (m, 2H, CH$_2$), 2.59 (t, 2H, $J = 6.7$ Hz,CH$_2$); $^{13}$C NMR (DMSO-d$_6$ + CDCl$_3$, 75 MHz): δ 162.66, 161.55, 159.94, 159.40, 130.93, 128.94, 128.83, 114.10, 113.81, 112.41, 91.94, 73.15, 67.17, 58.87, 22.49; IR (KBr) 2230 (C≡C) cm$^{-1}$;
MS (ES+) exact mass calculated for [M+H]$^+$ (C$_{13}$H$_{13}$FN$_2$O$_2$) requires \( m/z \) 273.1 found \( m/z \) 273.0.

**Synthesis of 5-(2-(4-fluorobenzyloxy) pyrimidin-5-yl) pent-4-yn-1-ol (58b).** To a oven dried 25 mL round bottom flask were added 5-bromo-2-(4-fluorobenzyloxy) pyrimidine (56a) (0.5 g, 1.76 mmol), pent-4-yn-1-ol (57b) (0.177 g, 2.11 mmol), CuI (0.033 g, 0.176 mmol) and DIEA (0.321 g, 4.4 mmol) followed by THF (5 mL) and were degassed by bubbling with nitrogen gas for 30 min. PdCl$_2$ (PPh$_3$)$_2$ (0.123 g, 0.176 mmol) was added to the above reaction mixture and then heated to 60 °C for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 35-40 % ethyl acetate/hexane) to obtained 58b (460 mg, 91%) as a yellow solid.

\[
\begin{align*}
\text{HO} & \quad \text{N} & \quad \text{O} & \quad \text{F} \\
\text{\equiv} & \quad \text{N} & \quad \text{O} & \quad \text{F}
\end{align*}
\]

Analytical data: Mp. 94-97 °C, TLC Rf. 0.28 (30% ethyl acetate in hexane as a eluent); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 8.67 (s, 2H, pyrimidine-H), 7.59 – 7.44 (m, 2H, ArH), 7.31 – 7.11 (m, 2H,ArH), 5.38 (s, 2H,ArCH$_2$), 4.54 (t, 1H, $J = 5.1$ Hz,OH), 3.51 (q, 2H, $J = 5.9$ Hz,CH$_2$), 2.50 (dq, 2H, $J = 3.5$, 1.7 Hz, CH$_2$), 1.69 (p, 2H, $J = 6.7$ Hz, CH$_2$); $^{13}$C NMR (DMSO-d$_6$ + CDCl$_3$, 75 MHz): $\delta$ 162.84, 161.67, 159.97, 159.58, 131.07, 121.06, 128.95, 114.25, 113.97, 112.72, 94.31, 72.47, 67.33, 59.11, 30.36, 14.83; IR (KBr) 2227 (C≡C) cm$^{-1}$; MS (ES+) exact mass calculated for [M+H]$^+$ (C$_{16}$H$_{15}$FN$_2$O$_2$) requires \( m/z \) 287.1 found \( m/z \) 287.0.

**Synthesis of 10-(2-(4-fluorobenzyloxy) pyrimidin-5-yl) dec-9-yn-1-ol (58c).** To a oven dried 25 mL round bottom flask were added 5-bromo-2-(4-fluorobenzyloxy) pyrimidine (56a) (0.5 g, 1.76 mmol), dec-9-yn-1-ol (57c) (0.325 g, 2.11 mmol), CuI (0.033 g, 0.176 mmol) and DIEA (0.321 g, 4.4 mmol) followed by THF (5 mL) and were degassed by bubbling with nitrogen gas for 30 min. PdCl$_2$ (PPh$_3$)$_2$ (0.123 g, 0.176 mmol) was added to the above reaction mixture and then heated to 60 °C for 60
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minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 35-40 % ethyl acetate/hexane) to obtained 58c (591 mg, 94%) as a brown solid.

![Structural formula of 58c](image)

Analytical data: Mp: 65-68 °C, TLC Rf. 0.27 (30% ethyl acetate in hexane as a eluent); $^1$H NMR (DMSO-d6, 400 MHz): $\delta$ 8.66 (s, 2H, pyrimidine-H), 7.59 – 7.44 (m, 2H, ArH), 7.24 (m, 2H, ArH), 5.38 (s, 2H, ArCH$_2$), 4.31 (t, 1H, $J$ = 5.2 Hz,OH), 3.37 (td, 2H, $J$ = 6.5, 5.0 Hz,CH$_2$), 2.45 (t, 2H, $J$ = 7.0 Hz, CH$_2$), 1.60–1.49 (m, 2H, CH$_2$), 1.41 (dq, 4H, $J$ = 12.6, 5.9 Hz, 2CH$_2$), 1.34–1.20 (m, 6H, 3CH$_2$); $^{13}$C NMR (75 MHz, DMSO + CDCl$_3$): $\delta$ 163.01, 161.81, 160.11, 159.75, 131.21, 129.19, 129.08, 114.40, 114.11, 112.94, 94.74, 72.62, 67.48, 60.90, 31.81, 28.26, 28.00, 27.73, 27.37, 24.81,18.36; IR (KBr) 2218 (C≡C) cm$^{-1}$, MS (ES+) exact mass calculated for [M+H]$^+$ (C$_{21}$H$_{25}$FN$_2$O$_2$) requires m/z 357.1 found m/z 357.0.

Synthesis of 2-(4-fluorobenzyloxy)-5-(2-(2-chlorophenyl)ethynyl)pyrimidine (58d).

To a oven dried 25 mL round bottom flask were added 5-bromo-2-(4-fluorobenzyloxy) pyrimidine (56a) (0.5 g, 1.76 mmol), 1-chloro-2-ethynylbenzene (57d) (0.288 g, 2.11 mmol), CuI (0.033 g , 0.176 mmol) and DIEA (0.321g, 4.4 mmol) followed by THF (5 mL) and were degassed by bubbling with nitrogen gas for 30 min. PdCl$_2$ (PPh$_3$)$_2$ (0.123 g, 0.176 mmol) was added to the above reaction mixture and then heated to 60 °C for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 3-5 % ethyl acetate/hexane) to obtained 58d (538 mg, 90 %) as a pale yellow solid.
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Analytical data: Mp: 146-149 °C, TLC Rf. 0.15 (5% ethyl acetate in hexane as a eluent); $^1$H NMR (DMSO-d6, 400 MHz): $\delta$ 8.86 (s, 2H, pyrimidine-H), 7.62 – 7.50 (m, 3H, ArH), 7.49 – 7.42 (m, 3H, ArH), 7.28 – 7.19 (m, 2H, ArH), 5.42 (s, 2H, ArCH$_2$); $^{13}$C NMR (DMSO-d6 + CDCl$_3$, 75 MHz): $\delta$ 163.04, 162.38, 160.28, 159.85, 134.51, 134.12, 132.22, 130.95, 129.28, 129.16, 128.35, 126.67, 125.79, 121.10, 114.42, 114.14, 111.77, 89.88, 86.46, 67.73; IR (KBr) 2218 (C≡C) cm$^{-1}$; MS (ES+) exact mass calculated for [M+H]$^+$ (C$_{19}$H$_{12}$ClFN$_2$O) requires m/z 339.06 found m/z 338.9.

Synthesis of 2-(4-fluorobenzyloxy)-5-(2-phenylethynyl) pyrimidine (58e). To a oven dried 25 mL round bottom flask were added 5-bromo-2-(4-fluorobenzyloxy) pyrimidine (56a) (0.5 g, 1.76 mmol), ethynylbenzene (57e) (0.215 g, 2.11 mmol), CuI (0.033 g, 0.176 mmol) and DIEA (0.321g, 4.4 mmol) followed by THF (5 mL) and were degassed by bubbling with nitrogen gas for 30 min. PdCl$_2$ (PPh$_3$)$_2$ (0.123 g, 0.176 mmol) was added to the above reaction mixture and then heated to 60 °C for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 2-5 % ethyl acetate/hexane) to obtained 58e (484 mg, 90.2 %) as a brown solid.

Analytical data: Mp: 145-148 °C, TLC Rf. 0.17 (5% ethyl acetate in hexane as a eluent); $^1$H NMR (DMSO-d6, 400 MHz): $\delta$ 8.87 (s, 2H, pyrimidine-H), 7.70 (dd, 1H, J = 7.5, 1.9 Hz, ArH), 7.62 (dd, 1H, $J = 7.8$, 1.5 Hz, ArH), 7.58 – 7.51 (m, 2H, ArH), 7.45 (dtd, 3H, $J = 19.9$, 7.5, 1.6 Hz, ArH), 7.28 – 7.18 (m, 2H, ArH), 5.44 (s, 2H,ArCH$_2$); $^{13}$C NMR (DMSO-d6 + CDCl$_3$, 75 MHz): $\delta$ 162.919, 162.103, 160.085,
Synthesis of 2-(benzyloxy)-5-(2-phenylethynyl) pyrimidine (58f). To a oven dried 25 mL round bottom flask were added 2-(benzyloxy)-5-bromopyrimidine (56c) (0.5 g, 1.88 mmol), ethynylbenzene (57e) (0.231 g, 2.26 mmol), CuI (0.035 g, 0.188 mmol) and DIEA (0.343 g, 4.7 mmol) followed by THF (5 mL) and were degassed by bubbling with nitrogen gas for 30 min. PdCl₂ (PPh₃)₂ (0.131 g, 0.188 mmol) was added to the above reaction mixture and then heated to 60 °C for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over (Na₂SO₄), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 5-10 % ethyl acetate/hexane to obtained 58f (497 mg, 92.2 %) as a brown solid.

Analytical data: Mp: 111-114 °C, TLC Rf. 0.44 (10% ethyl acetate in hexane as a eluent); Mp: 111-114 °C, ¹H NMR (DMSO-d₆, 400 MHz): δ 8.86 (s, 2H, pyrimidine-H), 7.61–7.55 (m, 2H, ArH), 7.50 – 7.32 (m, 8H, ArH), 5.45 (s, 2H, ArCH₂); ¹³C NMR (DMSO-d₆ + CDCl₃, 75 MHz): δ 162.31, 160.19, 158.57, 135.05, 130.48, 127.94, 127.52, 127.45, 127.14, 127.06, 121.13, 112.06, 93.10, 81.46, 68.39;IR (KBr) 2218 (C≡C) cm⁻¹; MS (ES+) exact mass calculated for [M+H]⁺ (C₁₉H₁₃FN₂O) requires m/z 305.1 found m/z 305.0.

Synthesis of 2-(benzyloxy)-5-(2-(2-chlorophenyl) ethynyl) pyrimidine (58g). To a oven dried 25 mL round bottom flask were added 2-(benzyloxy)-5-bromopyrimidine (56c) (0.5 g, 1.88 mmol), 1-chloro-2-ethynylbenzene (57d) (0.308 g, 2.26 mmol), CuI (0.035 g, 0.188 mmol) and DIEA (0.343 g, 4.7 mmol) followed by THF (5 mL) and were degassed by bubbling with nitrogen gas for 30 min. PdCl₂ (PPh₃)₂ (0.131 g, 0.188 mmol) was added to the above reaction mixture and then heated to 60 °C for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over (Na₂SO₄), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 5-10 % ethyl acetate/hexane to obtained 58f (497 mg, 92.2 %) as a brown solid.

Analytical data: Mp: 111-114 °C, TLC Rf. 0.44 (10% ethyl acetate in hexane as a eluent); Mp: 111-114 °C, ¹H NMR (DMSO-d₆, 400 MHz): δ 8.86 (s, 2H, pyrimidine-H), 7.61–7.55 (m, 2H, ArH), 7.50 – 7.32 (m, 8H, ArH), 5.45 (s, 2H, ArCH₂); ¹³C NMR (DMSO-d₆ + CDCl₃, 75 MHz): δ 162.31, 160.19, 158.57, 135.05, 130.48, 127.94, 127.52, 127.45, 127.14, 127.06, 121.13, 112.06, 93.10, 81.46, 68.39;IR (KBr) 2218 (C≡C) cm⁻¹; MS (ES+) exact mass calculated for [M+H]⁺ (C₁₉H₁₃FN₂O) requires m/z 287.1 found m/z 287.0.
minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over (Na₂SO₄), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 5-10 % ethyl acetate/hexane) to obtained 58g (551 mg, 91.2 %) as a brown solid.

Analytical data: Mp: 101-104 °C, TLC Rf. 0.4 (10% ethyl acetate in hexane as a eluent); ¹H NMR (DMSO-d₆, 400 MHz): δ 8.87 (s, 2H, pyrimidine-H), 7.70 (dd, 1H, J = 7.6, 1.9 Hz, ArH), 7.62 (dd, 1H, J = 7.8, 1.4 Hz, ArH), 7.52 – 7.32 (m, 7H, ArH), 5.46 (s, 2H, ArCH₂); ¹³C NMR (DMSO-d₆ + CDCl₃, 75 MHz): δ 162.98, 160.73, 135.44, 135.09, 129.41, 128.79, 127.87, 127.57, 127.47, 126.12, 121.63, 112.18, 90.31, 86.89, 68.93; IR (KBr) 2220 cm⁻¹(stretching), MS (ES+) exact mass calculated for [M+H]+ (C₁₉H₁₃ClN₂O) requires m/z 321.07 found m/z 320.9.

**Synthesis of 2-(4-methoxybenzoyloxy)-5-(2-phenylethynyl) pyrimidine (58h).** To a oven dried 25 mL round bottom flask were added 5-bromo-2-(4-methoxybenzoyloxy)pyrimidine (56b) (0.5 g, 1.69 mmol), ethynylbenzene (57e) (0.207 g, 2.03 mmol), CuI (0.032 g , 0.169 mmol) and DIEA (0.309 g, 4.22 mmol) followed by THF (5 mL) and were degassed by bubbling with nitrogen gas for 30 min. PdCl₂ (PPh₃)₂ (0.118 g, 0.169 mmol) was added to the above reaction mixture and then heated to 60 °C for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over (Na₂SO₄), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 5-8 % ethyl acetate/hexane) to obtained 58h (471 mg, 88 %) as a white crystalline powder.
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Analytical data: Mp: 139-141 °C, TLC Rf. 0.2 (5% ethyl acetate in hexane as a eluent); $^1$H NMR (DMSO-d6, 400 MHz): $\delta$ 8.84 (s, 2H, pyrimidine-H), 7.61 – 7.53 (m, 2H, ArH), 7.49–7.37 (m, 5H, ArH), 7.00–6.91 (m, 2H, ArH), 5.36 (s, 2H,ArCH2), 3.76 (s, 3H); $^{13}$C NMR (DMSO-d6 + CDCl3, 75 MHz): $\delta$ 162.34, 160.10, 158.50, 130.45, 128.96, 127.88, 127.49, 127.05, 121.18, 112.79, 111.86, 93.04, 81.51, 68.21, 54.19; IR (KBr) 2216 (C≡C) cm$^{-1}$(stretching), MS (ES+) exact mass calculated for [M+H]$^+$ (C20H16N2O2) requires m/z 317.12 found m/z 317.0.

**Synthesis of 2-(4-methoxybenzylxyloxy)-5-(2-(2-chlorophenyl) ethynyl) pyrimidine (58i).** To a oven dried 25 mL round bottom flask were added 5-bromo-2-(4-methoxybenzylxyloxy)pyrimidine (56b) (0.5 g, 1.69 mmol), 1-chloro-2-ethynylbenzene (56d) (0.277 g, 2.03 mmol), CuI (0.032 g, 0.169 mmol) and DIEA (0.309 g, 4.22 mmol) followed by THF (5 mL) and were de-gassed by bubbling with nitrogen gas for 30 min. PdCl$_2$ (PPh$_3$)$_2$ (0.118 g, 0.169 mmol) was added to the above reaction mixture and then heated to 60 °C for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 5-8 % ethyl acetate/hexane) to obtained 58i (531 mg, 89.4 %) as an off white crystalline powder.

Analytical data: Mp: 107-110 °C, TLC Rf. 0.2 (5% ethyl acetate in hexane as a eluent); $^1$H NMR (DMSO-d6, 400 MHz): $\delta$ 8.86 (s, 2H, pyrimidine-H), 7.70 (dd, 1H, J = 7.4, 1.9 Hz, ArH), 7.62 (dd, 1H, J = 8.0, 1.5 H, ArH z), 7.53–7.34 (m, 4H, ArH), 7.00–6.89 (m, 2H, ArH), 5.37 (s, 2H, ArCH2), 3.76 (s, 3H, OMe); $^{13}$C NMR ( DMSO-d6 + CDCl3, 75 MHz): $\delta$ 162.34, 160.10, 158.50, 134.23, 133.45, 132.53, 128.96, 127.88, 127.49, 127.05, 121.18, 112.79, 111.86, 93.04, 81.51, 68.21, 54.19; IR (KBr) 2222 (C≡C) cm$^{-1}$(stretching), MS (ES+) exact mass calculated for [M+H]$^+$ (C$_{20}$H$_{15}$ClN$_2$O$_2$) requires m/z 351.08 found m/z 350.9.
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**Synthesis of 5-(2-(4-methoxybenzyloxy) pyrimidin-5-yl) pent-4-yn-1-ol (58j).** To a oven dried 25 mL round bottom flask were added 5-bromo-2-(4-methoxybenzyloxy)pyrimidine (56b) (0.5 g, 1.69 mmol), pent-4-yn-1-ol (57b) (0.17 g, 2.03 mmol), CuI (0.032 g, 0.169 mmol) and DIEA (0.309 g, 4.22 mmol) followed by THF (5 mL) and were degassed by bubbling with nitrogen gas for 30 min. PdCl2 (PPh3)2 (0.118 g, 0.169 mmol) was added to the above reaction mixture and then heated to 60 °C for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over (Na2SO4), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 25-30 % ethyl acetate/hexane) to obtained 58j (444 mg, 88 %) as an yellow solid.

![Chemical Structure](image)

Analytical data: Mp: 91-94 °C, TLC Rf. 0.14 (30% ethyl acetate in hexane as a eluent); 1H NMR (DMSO-d6, 300 MHz): δ 8.66 (s, 2H, pyrimidine-H), 7.39 (d, 2H, J = 8.4 Hz, ArH), 6.94 (d, 2H, J = 8.4 Hz, ArH), 5.31 (s, 2H, ArCH2), 4.54 (t, 1H, J = 5.1 Hz, OH), 3.75 (s, 3H, OMe), 3.51 (q, 2H, J = 5.9 Hz,CH2), 2.55 – 2.44 (m, 2H, CH2), 1.69 (p, 2H, J = 6.7 Hz, CH2), 13C NMR (DMSO-d6 + CDCl3, 75 MHz): δ 162.25, 160.33, 158.74, 129.14, 127.47, 113.03, 94.46, 72.96, 68.33, 59.72, 54.48, 30.73, 15.24; IR (KBr) 2225 (C≡C) cm⁻¹; MS (ES+) exact mass calculated for [M+H]+ (C17H18N2O3) requires m/z 299.13 found m/z 299.0.

**Synthesis of 10-(2-(4-methoxybenzyloxy) pyrimidin-5-yl) dec-9-yn-1-ol (58k).** To a oven dried 25 mL round bottom flask were added 5-bromo-2-(4-methoxybenzyloxy) pyrimidine (56b) (0.5 g, 1.69 mmol), dec-9-yn-1-ol (57c) (0.313 g, 2.03 mmol), CuI (0.032 g, 0.169 mmol) and DIEA (0.309 g, 4.22 mmol) followed by THF (5 mL) and were degassed by bubbling with nitrogen gas for 30 min. PdCl2 (PPh3)2 (0.118 g, 0.169 mmol) was added to the above reaction mixture and then heated to 60 °C for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over
(Na$_2$SO$_4$), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 25-30 % ethyl acetate/hexane) to obtained 58k (567 mg, 91 %) as an yellow solid.

Analytical data: Mp: 71-74 ºC, TLC Rf. 0.25 (30% ethyl acetate in hexane as a eluent); Mp: 71-74 ºC, $^1$H NMR (DMSO-d$_6$, 400 MHz): $\delta$ 8.65 (s, 2H, pyrimidine-H), 7.42 – 7.36 (m, 2H, ArH), 6.97 – 6.91 (m, 2H, ArH), 5.31 (s, 2H, ArCH$_2$), 4.32 (t, 1H, $J = 5.1$ Hz, OH), 3.75 (s, 3H, OMe), 3.37 (td, 2H, $J = 6.5$, 5.1 Hz, CH$_2$), 2.45 (t, 2H, $J = 7.0$ Hz, CH$_2$), 1.54 (p, 2H, $J = 7.0$ Hz, CH$_2$), 1.40 (s, 4H, 2CH$_2$), 1.28 (s, 6H, 3CH$_2$); $^{13}$C NMR (DMSO-d$_6$ + CDCl$_3$, 75 MHz): $\delta$ 162.191, 160.252, 158.693, 129.090, 127.450, 112.995, 94.763, 72.878, 68.249, 61.201, 54.428, 32.000, 28.458, 28.201, 27.941, 27.581, 24.994, 18.558; IR (KBr) 2055 (C≡C) cm$^{-1}$; MS (ES+) exact mass calculated for [M+H]$^+$ (C$_{22}$H$_{28}$N$_2$O$_3$) requires m/z 369.21 found m/z 369.0.

**Synthesis of 4-(2-(benzyloxy) pyrimidin-5-yl) but-3-yn-1-ol (58l).** To a oven dried 25 mL round bottom flask were added 2-(benzyloxy)-5-bromopyrimidine (56c) (0.5 g, 1.88 mmol), but-3-yn-1-ol (57a) (0.158 g, 2.26 mmol), CuI (0.035 g, 0.188 mmol) and DIEA (0.343 g, 4.7 mmol) followed by THF (5 mL) and were degassed by bubbling with nitrogen gas for 30 min. PdCl$_2$ (PPh$_3$)$_2$ (0.131 g, 0.188 mmol) was added to the above reaction mixture and then heated to 60 ºC for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 25-30 % ethyl acetate/hexane) to obtained 58l (441 mg, 92 %) as a brown solid.
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Analytical data: Mp: 75-78 °C, TLC Rf. 0.16 (30% ethyl acetate in hexane as a eluent); $^1$H NMR (400 MHz, DMSO): δ 8.68 (s, 2H, pyrimidine-H), 7.48 – 7.43 (m, 2H, ArH), 7.42 – 7.31 (m, 3H, ArH), 5.40 (s, 2H, ArCH$_2$), 4.92 (t, 1H, J = 5.6 Hz, OH), 3.59 (q, 2H, J = 6.4 Hz, CH$_2$), 2.59 (t, 2H, J = 6.7 Hz, CH$_2$); $^{13}$C NMR (DMSO-d6 + CDCl$_3$, 75 MHz): δ 161.7; 159.97; 155.48, 135.07, 127.28, 126.86, 112.63, 92.20, 68.52, 59.81, 54.64, 23.20; IR (KBr) 2237 (C≡C) cm$^{-1}$ (stretching), MS (ES+) exact mass calculated for [M+H]$^+$ (C$_{15}$H$_{14}$N$_2$O$_2$) requires $m/z$ 255.11 found $m/z$ 255.0.

**Synthesis of 5-(2-(benzyloxy) pyrimidin-5-yl) pent-4-yn-1-ol (58m).** To a oven dried 25 mL round bottom flask were added 2-(benzyloxy)-5-bromopyrimidine (56c) (0.5 g, 1.88 mmol), pent-4-yn-1-ol (57b) (0.19 g, 2.26 mmol), CuI (0.035 g, 0.188 mmol) and DIEA (0.343 g, 4.7 mmol) followed by THF (5 mL) and were degassed by bubbling with nitrogen gas for 30 min. PdCl$_2$ (PPh$_3$)$_2$ (0.131 g, 0.188 mmol) was added to the above reaction mixture and then heated to 60 °C for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 25-30 % ethyl acetate/hexane) to obtained 58l (468 mg, 92.5 %) as a pall yellow solid.

![structure](image)

Analytical data: Mp: 82-85 °C, TLC Rf. 0.16 (30% ethyl acetate in hexane as a eluent); $^1$H NMR (DMSO-d6, 400 MHz): δ 8.67 (s, 2H, pyrimidine-H), 7.45 (d, 2H, J = 7.1 Hz, ArH), 7.42 – 7.31 (m, 3H, ArH), 5.40 (s, 2H, ArCH$_2$), 4.54 (t, 1H, J = 5.1 Hz, OH), 3.51 (q, 2H, J = 5.8 Hz, CH$_2$), 2.48 (t, 2H, J = 6.9 Hz, CH$_2$), 1.69 (p, 2H, J = 6.7 Hz, CH$_2$); $^{13}$C NMR (DMSO-d6 + CDCl$_3$, 75 MHz): δ 161.7; 159.97; 155.48, 135.07, 127.28, 126.86, 112.63, 94.25, 72.51,68.04, 59.12, 30.36, 14.83; IR (KBr) 2226 (C≡C) cm$^{-1}$; MS (ES+) exact mass calculated for [M+H]$^+$ (C$_{15}$H$_{14}$N$_2$O$_2$) requires $m/z$ 269.12 found $m/z$ 269.0.
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**Synthesis of 5-(2-(3-fluorobenzyloxy) pyrimidin-5-yl) pent-4-yn-1-ol (58n).** To a oven dried 25 mL round bottom flask were added 5-bromo-2-(3-fluorobenzyloxy) pyrimidine (56d) (0.5 g, 1.76 mmol), pent-4-yn-1-ol (57b) (0.177g, 2.211 mmol), CuI (0.033 g, 0.176 mmol) and DIEA (0.321g, 4.4 mmol) followed by THF (5 mL) and were degassed by bubbling with nitrogen gas for 30 min. PdCl₂ (PPh₃)₂ (0.123 g, 0.176 mmol) was added to the above reaction mixture and then heated to 60 °C for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over (Na₂SO₄), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography (100-200 mesh) silica gel, eluted with 25-30 % ethyl acetate/hexane) to obtained 58n (475 mg, 95.1 %) as a brown solid.

![Structure of 58n](image)

Analytical data: Mp: 87-90 °C, TLC *Rf.* 0.17 (30% ethyl acetate in hexane as a eluent); ¹H NMR (DMSO-d₆, 400 MHz): δ 8.68 (s, 2H, pyrimidine-H), 7.44 (td, 1H, *J* = 8.0, 6.0 Hz, ArH), 7.33 – 7.24 (m, 2H, ArH), 7.22 – 7.12 (m, 1H, ArH), 5.42 (s, 2H, ArCH₂), 4.54 (t, 1H, *J* = 5.2 Hz, OH), 3.51 (td, 2H, *J* = 6.2, 5.0 Hz, CH₂), 2.53 – 2.47 (t, 2H, *J* = 6.9 Hz, CH₂), 1.74–1.65 (p, 2H, *J* = 6.7 Hz, CH₂); ¹³C NMR (DMSO-d₆ + CDCl₃, 75 MHz): δ 163.71, 162.14, 160.59, 160.46, 138.27, 129.49, 122.73, 114.35, 114.08, 113.41, 94.83, 72.98, 67.72, 59.94, 30.83, 15.40; IR (KBr) 2227 (C≡C) cm⁻¹; MS (ES+) exact mass calculated for [M+H]⁺ (C₁₆H₁₅FN₂O₂) requires *m/z* 287.11 found *m/z* 287.12.

**Synthesis of 4-(2-(3-fluorobenzyloxy) pyrimidin-5-yl) but-3-yn-1-ol (58o).** To a oven dried 25 mL round bottom flask were added 5-bromo-2-(3-fluorobenzyloxy) pyrimidine (56d) (0.5 g, 1.76 mmol), but-3-yn-1-ol (57b) (0.148 g, 2.11 mmol), CuI (0.033 g, 0.176 mmol) and DIEA (0.321 g, 4.4 mmol) followed by THF (5 mL) and were degassed by bubbling with nitrogen gas for 30 min. PdCl₂ (PPh₃)₂ (0.123 g, 0.176 mmol) was added to the above reaction mixture and then heated to 60 °C for 60
minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over \((Na_2SO_4)\), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography \((100-200 \text{ mesh})\) silica gel, eluted with 25-30 % ethyl acetate/hexane) to obtained 58o \((440 \text{ mg}, 91.7 \%)\) as a brown solid.

![Chemical structure](image)

Analytical data: Mp: 98-101 °C, TLC \(R_f\) 0.16 (30% ethyl acetate in hexane as a eluent); Mp: 98-101 °C, \(^1\)H NMR (DMSO-d6, 300 MHz): \(\delta\) 8.68 (s, 2H, pyrimidine-H), 7.44 (td, 1H, \(J = 8.1, 6.1 \text{ Hz}, \text{ ArH}\)), 7.34 – 7.24 (m, 2H, ArH), 7.23 – 7.12 (m, 1H, ArH), 5.42 (s, 1H, ArCH\(_2\)), 4.92 (s, 1H,OH), 3.59 (t, \(J = 6.7 \text{ Hz}, \text{ CH}_2\)), 2.59 (t, \(2H, J = 6.7 \text{ Hz}, \text{ CH}_2\)); \(^{13}\)C NMR (DMSO-d6 + CDCl\(_3\), 75 MHz): \(\delta\) 163.137, 161.657, 160.178, 159.881, 137.851, 129.075, 122.317, 113.837, 113.626, 113.337, 112.746, 92.161, 73.318, 67.180, 59.115, 22.689; IR (KBr) (C≡C) cm\(^{-1}\); MS (ES+) exact mass calculated for [M+H]\(^+\) (C\(_{15}\)H\(_{13}\)FN\(_2\)O\(_2\)) requires \(m/z\) 273.1 found \(m/z\) 273.0.

**Synthesis of 10-(2-(3-fluorobenzyloxy) pyrimidin-5-yl) dec-9-yn-1-ol (58p).** To a oven dried 25 mL round bottom flask were added 5-bromo-2-(3-fluorobenzyloxy) pyrimidine (56d) \((0.5 \text{ g}, 1.76 \text{ mmol})\), dec-9-yn-1-ol (57c) \((0.325 \text{ g}, 2.11 \text{ mmol})\), CuI \((0.033 \text{ g}, 0.176 \text{ mmol})\) and DIEA \((0.321\text{ g}, 4.4 \text{ mmol})\) followed by THF \((5 \text{ mL})\) and were degassed by bubbling with nitrogen gas for 30 min. PdCl\(_2\) (PPh\(_3\))\(_2\) \((0.123 \text{ g}, 0.176 \text{ mmol})\) was added to the above reaction mixture and then heated to 60 °C for 60 minutes. The mixture was cooled to room temperature and diluted with water, extracted with ethyl acetate. The organic layer was washed with brine, dried over \((Na_2SO_4)\), filtered and concentrated under reduced pressure to afford crude product, which was purified by column chromatography \((100-200 \text{ mesh})\) silica gel, eluted with 25-30 % ethyl acetate/hexane) to obtained 58p \((591 \text{ mg}, 94 \%)\) as an off white solid.
Analytical data: Mp: 59-62 °C, TLC Rf. 0.3 (30% ethyl acetate in hexane as a eluent);

$^1$H NMR (DMSO-d₆, 300 MHz): $\delta$ 8.67 (s, 2H, pyrimidine-H), 7.44 (td, 1H, $J = 8.0, 6.0$ Hz, ArH), 7.34 – 7.23 (m, 2H, ArH), 7.17 (td, 1H, $J = 9.2, 8.6, 2.7$ Hz, ArH), 5.42 (s, 2H, ArCH₂), 4.31 (t, 1H, $J = 5.1$ Hz, OH), 3.37 (td, 2H, $J = 6.4, 5.0$ Hz,CH₂), 2.45 (t, 2H, $J = 7.0$ Hz, CH₂), 1.53 (q, 2H, $J = 7.1$ Hz, CH₂), 1.41 (t, 4H, $J = 6.5$ Hz, 2CH₂), 1.28 (d, 6H, $J = 2.6$ Hz, 3CH₂), IR (KBr) 2220 (C≡C) cm$^{-1}$(stretching), MS (ES+) exact mass calculated for [M+H]$^+$ (C₂₁H₂₅F₂N₂O₂) requires $m/z$ 357.19 found $m/z$ 357.0.

4.5. Results and Discussion

4.5.1. Synthesis

The work was commenced with commercially available 2-chloro-5-bromo pyrimidine (54) as an ideal starting material. The reason for selecting the bromopyrimidine is 1. the chloro group of the compound 54 can be easily displaced with appropriately substituted benzyl alcohols (55a-d) in presence of a base. This is due to the electronegative nitrogen atoms induced polarization in the sigma bond framework of the pyrimidine ring. The resultant increase in electron deficiency at the 2, 4, and 6 positions makes these carbon atoms more susceptible to the nucleophilic attack. This nucleophilic attack is especially feasible when the substituent is a displaceable halide. 2. The resultant bromopyrimidines (56a-d) could serve as ideal candidates for palladium-catalyzed Sonogashira cross-coupling.

As shown in Scheme 1, treatment of 2-chloro-5-bromopyrimidine (54) with 4-flouro benzyl alcohol (55a) in the presence of cesium carbonate in CH₃CN and DMF at room temperature for 12 h afforded the desired 5-Bromo-2-(4-fluorobenzyl)oxy) pyrimidine (56a) in quantitative yield as a white solid. Similarly, compound 54 was reacted with differently substituted benzyl alcohols (55b-d; e.g., OMe, F, etc.) to give the
corresponding 2-benzyloxy-5-bromo pyrimidines (i.e., 56b-d) in good yields (Table 1).

![Chemical Reaction](image)

**Scheme 1**

**Table 1**: Different substituents instead of “R” on compounds (56a-d).

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>56a</td>
<td><img src="image" alt="F" /></td>
<td>94%</td>
</tr>
<tr>
<td>56b</td>
<td><img src="image" alt="OCH3" /></td>
<td>71%</td>
</tr>
<tr>
<td>56c</td>
<td><img src="image" alt="OCH3" /></td>
<td>97%</td>
</tr>
<tr>
<td>56d</td>
<td><img src="image" alt="F" /></td>
<td>97%</td>
</tr>
</tbody>
</table>

- Note: All the yields are isolated after crystallization
- Yields refer to purity by $^1$H NMR, $^{13}$C NMR and MS

From Table 1 it is clearly indicate that the substituted bezyl alcohols containing electron withdrawing fluoro group (56a & 56d) obtained in higher yields when compared to the electron releasing methoxy group (OMe) containing the benzyl alcohol (56b). Electron withdrawing fluro group present at meta position on the benzyl alcohol afforded more yield (56d, 97%) compared to the para- position (56a, 94%).
The resultant new compounds (i.e., 56a-d) were well characterized by \(^1\)H NMR, \(^{13}\)C NMR, and mass spectral analyses (See experimental section in chapter-III).

With these intermediates (i.e., 56a-d) in hand, our next aim is to explore these bromopyrimidines for the syntheses of 2-bezyloxy-5-alkyne substituted pyrimidines (58a-p) by the use of Sonogashira cross-coupling. Consequently, it is planned to develop a general synthetic route for the syntheses of diversely substituted 2-bezyloxy-5-alkyne substituted pyrimidines (58a-p) using palladium-catalyzed Sonogashira cross-coupling as a key step as in Scheme 2.

Later the optimization of suitable coupling condition was studied for the formation of carbon-carbon bond between 5-Bromo-2-(4-fluorobenzyloxy) pyrimidine (56a) with but-3-yn-1-ol (57a) by evaluation of various Pd catalysts, solvents, and bases (See Table 2). The first attempt was coupling of 5-bromo-2-(4-fluorobenzyloxy) pyrimidine (56a) with but-3-yn-1-ol (57a) with a Pd(PPh\(_3\))\(_4\) catalyst, a copper (I) cocatalyst, and an isopropylamine base in tetrahydrofuran as solvent at 75 °C for 12 h afforded the resultant coupling product 58a with only 48 % yield as shown in Table 2.

Table 2. Exploration of Various Pd Catalysts, Solvents, and Bases for the Sonagashira coupling

<table>
<thead>
<tr>
<th>Pd Catalyst</th>
<th>Ligand</th>
<th>Bases</th>
<th>Solvent</th>
<th>Co Catalyst</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh(_3))(_4)</td>
<td>-</td>
<td>'Pr(_2)NH</td>
<td>THF</td>
<td>Cul</td>
<td>75</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>Pd(MeCN)(_2)Cl(_2)</td>
<td>X-phos</td>
<td>Et(_3)N</td>
<td>PEG-600/H(_2)O</td>
<td>-</td>
<td>RT</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>Pd/PVP</td>
<td>-</td>
<td>K(_2)CO(_3)</td>
<td>EtOH</td>
<td>-</td>
<td>80</td>
<td>6.0</td>
<td>13</td>
</tr>
<tr>
<td>Pd(acac)(_2)</td>
<td>dppf</td>
<td>K(_3)PO(_4)</td>
<td>DMSO</td>
<td>Cul</td>
<td>125</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Pd(PPh(_3))(_4)</td>
<td>-</td>
<td>'Pr(_2)NH</td>
<td>DMF</td>
<td>Cul</td>
<td>75</td>
<td>12</td>
<td>42</td>
</tr>
<tr>
<td>PdCl(_2)(PPh(_3))(_2)</td>
<td>-</td>
<td>Et(_3)N</td>
<td>THF</td>
<td>Cul</td>
<td>75</td>
<td>3.5</td>
<td>56</td>
</tr>
<tr>
<td>PdCl(_2)(PPh(_3))(_2)</td>
<td>-</td>
<td>DIPEA</td>
<td>Dioxane</td>
<td>Cul</td>
<td>80</td>
<td>5.0</td>
<td>44</td>
</tr>
<tr>
<td>PdCl(_2)(PPh(_3))(_2)</td>
<td>-</td>
<td>DIEA</td>
<td>THF</td>
<td>Cul</td>
<td>60</td>
<td>0.5</td>
<td>84-94</td>
</tr>
</tbody>
</table>
Another better attempt was coupling of 5-bromo-2-(4-fluorobenzyl)pyrimidine (56a) with but-3-yn-1-ol (57a) with a PdCl₂(PPh₃)₂ catalyst, a copper (I) cocatalyst, and an triethylamine base in tetrahydrofuran as solvent at 75 °C for 3.5 h afforded the resultant coupling product 58a with 56 % yield. So, in order to further improve the yields several attempts were made to optimize the conditions as shown in Table 2.

Finally, coupling of compound 56a with but-3-yn-1-ol (57a), PdCl₂ (PPh₃) catalyst, copper (I) cocatalyst, and an diethylamine base in tetrahydrofuran solvent was achieved at about 60 °C for 30 minutes and afforded the resultant coupling product 58a with 89 % yield. Performance of this reaction at >60 °C caused decomposition of the target molecules. In order to test the applicability of the reaction similar conditions have been applied for the synthesis of diverse 2-bezyloxy-5-alkyne substituted pyrimidines (i.e., 58b-p) with various alkynes as shown in Scheme 2 and Table-3.

![Scheme 2](image)

**Table 3.** Compounds of 2-bezyloxy-5-alkyne substituted pyrimidine (58a-p) derivatives.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R¹</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>58a</td>
<td>4-fluoro</td>
<td>HO-</td>
<td>89</td>
</tr>
<tr>
<td>58b</td>
<td>4-fluoro</td>
<td>HO-</td>
<td>91</td>
</tr>
<tr>
<td>58c</td>
<td>4-fluoro</td>
<td>HO-</td>
<td>94</td>
</tr>
</tbody>
</table>
Among the synthesized compounds $p$-fluoro (58a-e)/ $m$-fluoro (58n-p)-benzyloxy substitution at C-2 of pyrimidine ring, the compounds obtained from longer alkynol chain (58c and 58p) were found to be showed higher yields (94%) when compared to shorter alkynol chain compounds (58a, b, 58l-o). The resultant new compounds of $p$-methoxybenzyloxy (58h-k) were showed little lower yields (88-
91%) when compared with \(p\)-fluoro benzyloxy (\(58a-e\)) benzoylxy (\(58f-g, 58l-m\))/ \(m\)-fluoro benzyloxy (\(58n-p\)) compounds yields (89-94%). The resultant 2-bezyloxy-5-alkyne substituted pyrimidines (i.e., \(58a-p\)) were well characterized by \(^1\)H NMR, \(^{13}\)C NMR, and mass spectral analyses.

On the other hand, the substituted 2-(benzyloxy) group in 2-bezyloxy-5-alkyne substituted pyrimidines (i.e., \(58a-p\)) could be cleaved under standard hydrogenalysis conditions to yield 2-hydroxy-5-alkyne pyrimidines (may be either as keto form). These hydroxy intermediates are useful scaffolds for the syntheses diverse functionalized pyrimidines.

4.5.2. In Vitro cytotoxic activity and SAR study

The synthesized compounds (\(58a-p\)) were evaluated for their anticancer activity on A549 (Human lung adenocarcinoma cell line) cell using MTT cell proliferation assay. The compounds were screened for anticancer activity at 100 \(\mu\)g/mL and compounds which showed more than 50 % cell growth inhibition were selected for dose response study using different concentrations (0-100 \(\mu\)g/mL).

The newly synthesized pyrimidines (\(58a-58p\)) were studied for cytotoxic activity against A549 (Human lung adenocarcinoma cell line) human cancer cell line and IC\(_{50}\) values were calculated and presented in Table-4.

**Table 4.** IC\(_{50}\) of compounds (\(58a, b, c, 58g, 58i, 58j, k, 58m, n, p\)) (0-100 \(\mu\)g/mL).

<table>
<thead>
<tr>
<th>Compound</th>
<th>A-549 (IC(_{50}) ((\mu)g/mL))</th>
</tr>
</thead>
<tbody>
<tr>
<td>58a</td>
<td>55.68</td>
</tr>
<tr>
<td>58b</td>
<td>32.38</td>
</tr>
<tr>
<td>58c</td>
<td>31.81</td>
</tr>
<tr>
<td>58g</td>
<td>53.91</td>
</tr>
<tr>
<td>58i</td>
<td>45.02</td>
</tr>
<tr>
<td>58j</td>
<td>32.06</td>
</tr>
<tr>
<td>58k</td>
<td>27.41</td>
</tr>
<tr>
<td>58m</td>
<td>80.18</td>
</tr>
<tr>
<td>58n</td>
<td>45.78</td>
</tr>
<tr>
<td>58p</td>
<td>22.76</td>
</tr>
<tr>
<td>Etoposide</td>
<td>4.7</td>
</tr>
</tbody>
</table>
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The results clearly showed that most of the compounds were showing significant in vitro cytotoxic activity against A549 cell line. The compounds 58p (IC$_{50}$ = 22.76 µg /mL) and 58k (IC$_{50}$ = 27.41 µg /mL) were showed more potent anticancer activity among the compounds 58a-58p, and then followed by 58c (IC$_{50}$ = 31.81 µg /mL), 58j (IC$_{50}$ = 32.06 µg /mL), 58b (IC$_{50}$ = 32.38 µg /mL), 58i (IC$_{50}$ = 45.02 µg /mL), 58n (IC$_{50}$ = 45.78 µg /mL), 58g (IC$_{50}$ = 53.91 µg /mL), 58a (IC$_{50}$ = 55.68 µg /mL) and 58m (IC$_{50}$ = 80.18 µg /mL). These results are indicative for the established synthetic methodology, useful for the syntheses of diversely substituted 2-benzyloxy-5-alkyne pyrimidines in high yields and under mild reaction conditions for development of new anticancer lead compounds.

A comparison of the IC$_{50}$ values for the 2-benzyloxy-5-alkyne pyrimidines presented in Table 4. The compounds of p-methoxybenzyloxy (58j-k) and p-fluoro/m-fluoro benzyl (58b, 58c and 58p) coupled with longer alkylnol chain were found to be showed effective cytotoxicity. The three derivatives with the longest alkylnol chain (58c, 58k and 58p, with n=7) showed the better IC$_{50}$ values (range 22.76 to 31.81 µg /mL). When the alkylnol chain on the 5-position of pyrimidine ring is substituted with an aryl-yne substituent, the activity decreased, indicating the importance of the long alkylnol chain at the said position of the pyrimidine ring. Pyrimidine derivates are well known to possess good cytotoxic properties. A variety of novel thieno[3,2-d]pyrimidines have been evaluated for their in vitro cytotoxic activity against human breast cancer cell line (MCF-7). Novel thiazolyl-pyrimidines have been reported for their cytotoxic activity in vitro against human cancer cell lines including Ishikawa, A549, BEL-7404, SPC-A-01 and SGC-7901. It is anticipated that these brief structure-activity relationships will help to design future derivatives with promising anticancer activity for better therapeutics.

4.6. Biological activity

4.6.1. Method for evaluation of cytotoxicity

The compounds (58a-p) were tested on A549 (Human lung adenocarcinoma cell line) cells using MTT cell proliferation assay. A549 cell line was obtained from National Centre for Cell Science (NCCS), Pune (India) and cultivated in Dulbecco's modified Eagle's red medium (DMEM) (Sigma Life Science, USA) containing 10% fetal bovine serum (FBS). The cells (2000 cells per well) were seeded in a 96 – well
microplate containing 100 µL of DMEM + 10% FBS medium per well and incubated at 37 °C with 5% CO₂. The cells were treated different concentration of compounds up to 72 hours for every 24 hours interval. Controls were maintained with 0.5% DMSO. After 72 hours treatment, 5µL of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5,- diphenyltetrazolium bromide) reagent (R&D Systems, USA) along with 45 µL of phenol red free DMEM (Sigma Life Science, USA) without FBS was added to each well and plates were incubated at 37°C with 5% CO₂ for 4 hours. Thereafter, 50 µL of solublization buffer (R&D Systems, USA) was added to each well to dissolve the colored formazan crystals produced by the reduction of MTT. After 24 hours, the optical density was measured at 550 nm using microplate reader (Bio-Rad, USA).

4.7. Conclusion

In conclusion, an efficient and two steps approach for the syntheses of 2-benzyloxy-5-alkyne substituted pyrimidines (58a-p) by use of Sonagashira reaction as key step has been reported. The optimized catalytic reaction conditions (i.e.; PdCl₂ (PPh₃)₂, CuI, THF, 60 °C, 30 min) resulted sixteen new 2-benzyloxy-5-alkyne substituted pyrimidines (58a-p) in good yields (84-95%). The key precursors (i.e.; 2-benzyloxy-5-bromo pyrimidines (56a-d) for Sonagashira coupling have been prepared by the reaction of 2-chloro-5-bromopyrimidine (54) with substituted benzyl alcohols (55a-d) in presence of Cs₂CO₃ in CH₃CN: DMF (1:1). In addition, the newly synthesized pyrimidines were studied for cytotoxic activity against A549 (Human lung adenocarcinoma cell line) human cancer cell lines, 58l and 58p shows moderate in vitro cytotoxic activity against A549. This established synthetic methodology useful for the syntheses of diversely substituted 2-benzyloxy-5-alkyne pyrimidines in high yields and under mild reaction conditions for development of new anticancer lead compounds.
4.8. Spectra of some representative compounds

Analytical data of Compound 58a

Fig. 34. $^1$H NMR spectra of Compound 58a

Fig. 35. $^{13}$C NMR spectra of Compound 58a
Analytical data of Compound 58b

Fig.36. Mass spectra of Compound 58a

Fig.37. $^1$H NMR spectra of Compound 58b
Fig. 38. $^{13}$C NMR spectra of Compound 58b

Fig. 39. Mass spectra of Compound 58b
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Analytical data of Compound 58c

Fig. 40. $^1$H NMR spectra of Compound 58c

Fig. 41. $^{13}$C NMR spectra of Compound 58c
Analytical data of Compound 58

Fig.42. Mass spectra of Compound 58c

Fig.43. $^1$H NMR spectra of Compound 58d
Fig. 44. $^{13}$C NMR spectra of Compound 58d

Fig. 45. Mass spectra of Compound 58d
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Analytical data of Compound 58e

Fig.46. $^1$H NMR spectra of Compound 58e

Fig.47. $^{13}$C NMR spectra of Compound 58e
Fig. 48. Mass spectra of Compound 58e

Analytical data of Compound 58g

Fig. 49. $^1$H NMR spectra of Compound 58g
Fig. 50. \(^{13}\)C NMR spectra of Compound 58g

Fig. 51. Mass spectra of Compound 58g
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Analytical data of Compound 58h

Fig. 52. $^1$H NMR spectra of Compound 58h

Fig. 53. $^{13}$C NMR spectra of Compound 58h
Fig. 54. Mass spectra of Compound 58h

Analytical data of Compound 58j

Fig. 55. $^1$H NMR spectra of Compound 58j
Fig. 56. $^{13}$C NMR spectra of Compound 58j

Fig. 57. Mass spectra of Compound 58j
4.9. References


