Synthetic strategies for pyrrolo[2,1-f][1,2,4]triazine: the parent moiety of antiviral drug remdesivir

Gaurav S. Rai¹, Jayesh J. Maru¹*

¹ Department of Chemistry, University School of Sciences, Gujarat University, Ahmedabad-380009, Navrangpura, India; e-mail: jaymaru@gujaratuniversity.ac.in

This review summarizes diverse synthetic protocols for the preparation of pyrrolo[2,1-f][1,2,4]triazine derivatives, covering literature sources from the past two decades. For effective representation, the synthetic methods toward the title compound are classified into six distinct categories: 1) synthesis from pyrrole derivatives, 2) synthesis via bromohydrazone, 3) synthesis via formation of triazinium dicyanomethylide, 4) multistep synthesis, 5) transition metal mediated synthesis, and 6) rearrangement of pyrrolooxadiazines. A brief outline of all optimized schemes is provided with relevant examples.

Keywords: pyrrolo[2,1-f][1,2,4]triazine, remdesivir, anti-norovirus activity, antiviral drug, COVID-19, kinase inhibitor.

Pyrrolo[2,1-f][1,2,4]triazine, a unique bicyclic heterocycle, containing N–N bond with a bridgehead nitrogen, possesses numerous activities against diverse therapeutic targets. It was first synthesized in late 1970s, but did not find many applications thereafter. A broad-spectrum antiviral drug remdesivir (Fig. 1) has been recently recognized against wide array of RNA viruses (including SARS-CoV, MERS-CoV, SARS-CoV-2 (COVID-19), Ebola) and has shown promising results in the treatment of recently emerged novel coronavirus (COVID-19).¹ This medication, containing pyrrolo[2,1-f][1,2,4]triazine as an active moiety, has recently been approved (by US FDA in May 2020) for the emergency treatment of people having severe symptoms of COVID-19.

Also, pyrrolo[2,1-f][1,2,4]triazine is an active structural motif of other drugs such as brivanib alaninate (Fig. 1, antitumorigenic drug, approved by US FDA in 2011), BMS-690514, and BMS-599626 (EGFR inhibitor in clinical phase II) and many others.

Meanwhile, different studies in the field of drug research have shown promising potential of pyrrolo[2,1-f][1,2,4]-triazine derivatives and attracted considerable interest among medicinal chemists because of their versatility, with a wide range of biological activities. These include Eg5 inhibitor,² VEGFR-2 inhibitors,³ anticancer agents as dual inhibitors of c-Met/VEGFR-2,⁴ EGFR inhibitor slowing cellular proliferation of the human colon tumor cell line,⁵ etc.
anaplastic lymphoma kinase (ALK) inhibitor.\textsuperscript{6} IGF-1R and IR kinase inhibitor,\textsuperscript{7} pan-Aurora kinase inhibitor,\textsuperscript{8} EGFR and HER2 protein tyrosine dual inhibitor,\textsuperscript{9} and hedgehog (Hh) signaling pathway inhibitor.\textsuperscript{10} Some analogs of pyrrolo[2,1-\textit{f}][1,2,4]triazine have been used in the treatment of Ebola and other emerging viruses.\textsuperscript{11} Recent reports have revealed anti-norovirus activity of 4-aminopyrrollo[2,1-\textit{f}][1,2,4]triazine C-nucleosides, which have the ability to inhibit both murine and human norovirus RNA-dependent RNA polymerase (RdRp).\textsuperscript{12} Owing to the importance of this heterocycle, this review attempts to summarize different synthetic strategies adopted for pyrrolo[2,1-\textit{f}][1,2,4]triazine over the past two decades. The aim is to be more illustrative rather than exhaustive in representing the reported work.

**Synthesis from pyrrole derivatives**

A facile synthesis of pyrrolo[2,1-\textit{f}][1,2,4]triazines was described starting from the \textit{N}-unsubstituted pyrrole derivative 1.\textsuperscript{13}\textsuperscript{1}Treating pyrrole 1 with either \textit{O}-\textit{(2,4-dinitrophenyl)hydroxylamine (DnpONH\textsubscript{2}) or NH\textsubscript{2}Cl in the presence of NaH, followed by cyclization with formamide at 165°C, yielded pyrrolotriazine 2 (Scheme 1).

**Scheme 1**

\[
\text{EtO}_2\text{C} \quad \text{Me} \quad 1. \text{DnpONH}_2 (or \text{NH}_2\text{Cl in EtO}_2) \quad \text{Me} \\
\text{N} \quad \text{OH} \quad \text{EtO}_2\text{C} \\
\text{1} \quad \text{NaH, DMF} \quad \text{HCONH}_2, 165°C \\
\text{EtO}_2\text{C} \quad \text{Me} \quad \text{N} \quad \text{OH} \\
\text{2} \quad \text{EtO}_2\text{C} \\
\]

Synthesis of pyrrolotriazine 6 from 3-iodo-1H-pyrrolo-2-carbaldehyde (3) has also been reported.\textsuperscript{14} The latter was transformed into pyrrole-2-carbonitrile 4 through a two-step one-pot process via the corresponding oxime. Electrophilic \textit{N}-amination of compound 4, followed by cyclization of the resulting \textit{N}-aminopyrrole 5 with triethyl orthoformate, yielded pyrrolotriazine 6 (Scheme 2).

Aminopyrrole 8 was obtained by \textit{N}-amination of diethyl 3-isopropyl-1H-pyrrole-2,4-dicarboxylate (7) using either \textit{O}-(diphenylphosphinyl)hydroxylamine or \textit{O}-(mesitylenesulfonyl)hydroxylamine. Cyclization of compound 8 at 165°C in DMF yielded bicyclic compound 9. The latter was deoxidized by heating with POCl\textsubscript{3} to give ethyl 4-chloro-5-(propan-2-yl)pyrrolo[2,1-\textit{f}][1,2,4]triazine-6-carboxylate (10) in high yield (Scheme 3).\textsuperscript{15}

**Scheme 2**

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{Me} \\
\text{H} & \quad \text{6} \\
& \quad \text{Brivanib alaninate} \\
\text{Me} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{OH} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

2-Arylaminopyrrolo[2,1-\textit{f}][1,2,4]triazine 17 was synthesized as a new kinase inhibitor template starting from 7-bromo-2-(methylsulfanyl)pyrrolo[2,1-\textit{f}][1,2,4]triazine (16) via orthogonal approaches.\textsuperscript{16} To obtain compound 16, \textit{N}-amination of methyl pyrrole-2-carboxylate (11) was carried out using a suitable aminating agent (NH\textsubscript{2}Cl) to introduce the key N–N bond. Subsequent treatment of the obtained crude material with benzoyl isothiocyanate produced pyrrole 12. Hydrolytic cyclization in 2 M NaOH followed by S-methylation gave bicyclic compound 13. POCl\textsubscript{3} was then used to block the highly reactive C-4 atom to give compound 15 with reasonable regioselectivity for the C-7 vs C-5 position (~5:1). Further treatment of the crude compound 15 with NaBH\textsubscript{4} led to the dechlorination and partial reduction of the heterocycle. Finally, oxidation with DDQ restored the aromaticity to give compound 16 in good yield (Scheme 4).

Additionally, synthesis of 7-phenylpyrrolo[2,1-\textit{f}][1,2,4]-triazin-2-ol (23) from pyrrole derivative 18 was also reported.\textsuperscript{15} Initially, dibromopyrrole 19 was obtained from pyrrole 18 using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) along with NMP to increase the yield. Halogen–metal exchange reaction of compound 19 with i-PrMgCl-LiCl followed by the treatment with DMF resulted in the formation of 5-bromopyrrole-2-carbaldehyde 20. The latter was subjected to the Suzuki coupling yielding compound 21 which was alkylated with phenyl chloroformate in the presence of NaHMDS to give
Scheme 4

For the selective cleavage of N-Boc protective group, Sc(OTf)_3 was used, and subsequent condensation with (NH_4)_2CO_3 resulted in the triazine cycle formation to provide the requisite product 23 (Scheme 5).

Wang et al. reported the synthesis of chlorinated derivative of pyrrolo[1,2,4]triazine 29 starting from \( \beta \)-substituted acrylate 24. \(^{14,15}\) Cycloaddition of tosylmethyl isocyanide (TosMIC) with compound 24 in the presence of NaH gave pyrrole derivative 25 which was further acylated with trichloroacetyl chloride at the C-2 position to afford substituted pyrrole 26 in high yield. Reaction of compound 26 with NaOMe and convenient and more economical N-amination with NH_2Cl instead of O-(diphenylphosphinyl)hydroxylamine or O-(mesitylenesulfonyl)hydroxylamine was accomplished. \(^{15}\) Cyclization of N-aminopyrrole 27 with formamide afforded 1,2,4-triazine 28. Chlorination of 1,2,4-triazine 28 with POCl_3 yielded product 29 (Scheme 6).

Scheme 5

Synthesis via bromohydrazone

A practical six-step synthesis of pyrrolothiazine scaffold has been described. \(^{18}\) The condensation of 2-bromo-1,1-dimehtoxymethane (30) with NH_2NHCBz under acidic conditions gave bromohydrazone 31 (Scheme 7). Different acids, such as HCl, H_2SO_4, methanesulfonic acid (MSA), TFA, H_3PO_4, and AcOH were tested as additives to facilitate the condensation reaction. However, the cleanest and fastest reaction was realized in the presence of concentrated H_3PO_4. The next transformation included C-alkylation of sodium 1,4-dithoxy-1,4-dioxobut-2-ene.
2-olate with bromide 31 to afford keto ester derivative 32. It was also observed that the use of less polar solvents for this transformation afforded higher yield of the alkylated product. Acid-catalyzed cyclization of compound 32 followed by heating at 45°C afforded protected 1-aminopyrrole 33. Removal of the Cbz group via hydrogenolysis resulted in 1-aminopyrrole 34. Reaction of 1-aminopyrrole 34 with formamidine acetate, which acted both as a reagent and a solvent in the presence of Et3N, led to the triazine cycle annulation and formation of pyrrolotriazine 35 in high yield (Scheme 7).

**Synthesis via formation of triazinium dicyanomethylide**

A convenient two-step synthesis of pyrrolo[2,1-f][1,2,4]-triazine 38 as a precursor of highly permeant IRAK4 inhibitors was reported.19 Initially, tetracyanoethylene oxide was reacted with triazine 36 to afford triazinium dicyanomethylide 37. Subsequently, [2+2] cycloaddition of phenyl vinyl sulfoxide provided the formation of 2-(methylsulfanyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine adenosine analog 45 was synthesized via a linear 7-step route (Scheme 9).20 Initially, the activated trichloroacetamidate 40 was obtained from trichloroacetominitrile and riboside 39. Subsequent slow addition of pyrrole at low temperature in the presence of BF3·Et2O gave an anomic mixture of pyrrole nucleosides 41. A mixture of anomers was separated and pure β-anomer 42 was obtained using chlorosulfonyl isocyanate in DMF. Electrophilic N-amination of pyrrole derivative 42 with O-(diphenylphosphinyl)hydroxylamine yielded N-aminopyrrole 43. Cyclization of N-aminopyrrole 43 in the presence of formamidine acetate resulted in the formation of substituted pyrrolo[2,1-f][1,2,4]triazine-4-amine which under buffer hydrogenolysis conditions formed free pyrrolotriazine-containing adenosine analog 45.

Pyrrolo[2,1-f][1,2,4]triazines 51 were synthesized in a multistep procedure using pyridine derivative and N-aminated pyrrole. The obtained derivatives showed antiproliferative activity against human cancer cells.21 2-Aminopyridine 46 was brominated and then converted into substituted pivaloylamide 47 (Scheme 10). Reaction of amide 47 with

**Multistep synthesis**

Nucleoside analogs are an important class of antivirals and are used in the treatment of hepatitis C virus as they exhibit cross genotype activity and a high barrier to resistance. Besides, C-nucleosides have shown enhanced metabolism and pharmacokinetic properties compared to the N-nucleosides mainly due to the presence of a strong C-C glycosidic bond and a nonnatural heterocyclic base. Pyrrolo[2,1-f][1,2,4]triazine-4-amino riboside 44 which was obtained from trichloroacetaminitrile and riboside 39. Subsequent slow addition of pyrrole at low temperature in the presence of BF3·Et2O gave an anomic mixture of pyrrole nucleosides 41. A mixture of anomers was separated and pure β-anomer 42 was obtained using chlorosulfonyl isocyanate in DMF. Electrophilic N-amination of pyrrole derivative 42 with O-(diphenylphosphinyl)hydroxylamine yielded N-aminopyrrole 43. Cyclization of N-aminopyrrole 43 in the presence of formamidine acetate resulted in the formation of substituted pyrrolo[2,1-f][1,2,4]triazine-4-amine which under buffer hydrogenolysis conditions formed free pyrrolotriazine-containing adenosine analog 45. 2-Aminopyridine 46 was brominated and then converted into substituted pivaloylamide 47 (Scheme 10). Reaction of amide 47 with

2-olate with bromide 31 to afford keto ester derivative 32. It was also observed that the use of less polar solvents for this transformation afforded higher yield of the alkylated product. Acid-catalyzed cyclization of compound 32 followed by heating at 45°C afforded protected 1-aminopyrrole 33. Removal of the Cbz group via hydrogenolysis resulted in 1-aminopyrrole 34. Reaction of 1-aminopyrrole 34 with formamidine acetate, which acted both as a reagent and a solvent in the presence of Et3N, led to the triazine cycle annulation and formation of pyrrolotriazine 35 in high yield (Scheme 7).

**Synthesis via formation of triazinium dicyanomethylide**

A convenient two-step synthesis of pyrrolo[2,1-f][1,2,4]-triazine 38 as a precursor of highly permeant IRAK4 inhibitors was reported.19 Initially, tetracyanoethylene oxide was reacted with triazine 36 to afford triazinium dicyanomethylide 37. Subsequently, [2+2] cycloaddition of phenyl vinyl sulfoxide provided the formation of 2-(methylsulfanyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine adenosine analog 45 was synthesized via a linear 7-step route (Scheme 9).20 Initially, the activated trichloroacetamidate 40 was obtained from trichloroacetominitrile and riboside 39. Subsequent slow addition of pyrrole at low temperature in the presence of BF3·Et2O gave an anomic mixture of pyrrole nucleosides 41. A mixture of anomers was separated and pure β-anomer 42 was obtained using chlorosulfonyl isocyanate in DMF. Electrophilic N-amination of pyrrole derivative 42 with O-(diphenylphosphinyl)hydroxylamine yielded N-aminopyrrole 43. Cyclization of N-aminopyrrole 43 in the presence of formamidine acetate resulted in the formation of substituted pyrrolo[2,1-f][1,2,4]triazine-4-amine which under buffer hydrogenolysis conditions formed free pyrrolotriazine-containing adenosine analog 45. 2-Aminopyridine 46 was brominated and then converted into substituted pivaloylamide 47 (Scheme 10). Reaction of amide 47 with

2-olate with bromide 31 to afford keto ester derivative 32. It was also observed that the use of less polar solvents for this transformation afforded higher yield of the alkylated product. Acid-catalyzed cyclization of compound 32 followed by heating at 45°C afforded protected 1-aminopyrrole 33. Removal of the Cbz group via hydrogenolysis resulted in 1-aminopyrrole 34. Reaction of 1-aminopyrrole 34 with formamidine acetate, which acted both as a reagent and a solvent in the presence of Et3N, led to the triazine cycle annulation and formation of pyrrolotriazine 35 in high yield (Scheme 7).

**Synthesis via formation of triazinium dicyanomethylide**

A convenient two-step synthesis of pyrrolo[2,1-f][1,2,4]-triazine 38 as a precursor of highly permeant IRAK4 inhibitors was reported.19 Initially, tetracyanoethylene oxide was reacted with triazine 36 to afford triazinium dicyanomethylide 37. Subsequently, [2+2] cycloaddition of phenyl vinyl sulfoxide provided the formation of 2-(methylsulfanyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine adenosine analog 45 was synthesized via a linear 7-step route (Scheme 9).20 Initially, the activated trichloroacetamidate 40 was obtained from trichloroacetominitrile and riboside 39. Subsequent slow addition of pyrrole at low temperature in the presence of BF3·Et2O gave an anomic mixture of pyrrole nucleosides 41. A mixture of anomers was separated and pure β-anomer 42 was obtained using chlorosulfonyl isocyanate in DMF. Electrophilic N-amination of pyrrole derivative 42 with O-(diphenylphosphinyl)hydroxylamine yielded N-aminopyrrole 43. Cyclization of N-aminopyrrole 43 in the presence of formamidine acetate resulted in the formation of substituted pyrrolo[2,1-f][1,2,4]triazine-4-amine which under buffer hydrogenolysis conditions formed free pyrrolotriazine-containing adenosine analog 45. 2-Aminopyridine 46 was brominated and then converted into substituted pivaloylamide 47 (Scheme 10). Reaction of amide 47 with
n-BuLi and DMF afforded the key intermediate 48. N-Amination of pyrroles 49 was realized in the presence of quaternary ammonium salt and NH₄Cl in MTBE giving 1-amino-1H-pyrrole-2-carboxamides 50 after treatment with NH₃ in MeOH. Finally, Cu-catalyzed coupling of pyridine-3-carbaldehyde 48 with N-aminopyrroles 50 afforded pyrrolotriazines 51 (Scheme 10).

**Transition metal mediated synthesis**

A one-pot two-step synthesis of substituted pyrrolo[2,1-f]-[1,2,4]triazin-4(3H)-ones 55 and 56, in which at least six bonds were formed, have been proposed by Yang group. The Cu(II)-catalyzed reaction of 4-oxo-4H-chromene-3-carbaldehyde (52) and 1-amino-1H-pyrrole-2-carboxamide (53) gave 2-(4-oxo-4H-chromen-3-yl)pyrrolo[2,1-f]-[1,2,4]triazin-4(3H)-one (54). The best result was achieved using the CuCl₂·2H₂O/NaOAc/DMSO catalytic system at 120°C. Intermediate 54 reacted with different amides and hydrazines in the presence of NaOAc yielding pyrrolo[2,1-f][1,2,4]triazin-4(3H)-ones 55 and 56, respectively (Scheme 11).

**Scheme 11**

![Diagram of Scheme 11](image)

Compounds 60 were obtained via Cu(II)-promoted cyclization of N-aminopyrroles 53 or 59 with aryl aldehydes upon heating in DMSO in moderate to good yields (Scheme 13). Electron-donating groups of aryl aldehydes accelerated the process as compared to electron-withdrawing substituents.

**Scheme 13**

![Diagram of Scheme 13](image)

A similar approach was reported for the synthesis of isoquinoline-fused pyrrolotriazines 58 via condensation of compound 53 with 2-alkynylbenzaldehydes 57 in the presence of Cu(II) catalyst (Scheme 12). Electron-donating and electron-withdrawing groups of 2-alkynylbenzaldehydes 57 showed low impact on the reaction efficacy affording the target compounds 58 in good to excellent and moderate to excellent yields, respectively.

**Scheme 12**

![Diagram of Scheme 12](image)

**Synthesis via rearrangement of pyrrolooxadiazines**

A practical synthesis of pyrrolo[2,1-f][1,2,4]triazin-4(3H)-ones has been proposed via rearrangement of pyrrolo-[1,2-d][1,3,4]oxadiazines. The methodology involved synthesis of pyrrole-2-carboxamides 62 from 3-chloro-1H-pyrrole-2-carboxylic acid (61) (Scheme 14). Treating...
pyrroles 62 with NH₂Cl, Aliquat 336, and NaClO afforded 1-aminopyrroles 63. Interaction of compounds 63 with EDC-HCl and Boc-L-Ala yielded pyrrole derivatives 64. Regioselective intramolecular cyclization of pyrroles 64 upon treatment with PPh₃, Br₂, and Et₃N in CH₂Cl₂ gave a mixture of the desired compounds 65 and side products 66. The latter were further converted to the desired products 65 using lithium trimethyl(phenylsulfdio)aluminate in THF (Scheme 14).

In conclusion, pyrrolo[2,1-f][1,2,4]triazines are important scaffolds with a broad range of biological activities. This review is an attempt to present the current synthetic strategies adopted for the synthesis of pyrrolo[2,1-f][1,2,4]-triazine derivatives. As evident from the methods available in the literature, there are several efficient routes to synthesize pyrrolo[2,1-f][1,2,4]triazine derivatives. Despite tremendous potential of this moiety, the number of pyrrolo-[2,1-f][1,2,4]triazines is currently very limited. Thus, there is a huge potential for the synthesis of novel products containing pyrrolo[2,1-f][1,2,4]triazine moiety that are more potent in pharmaceutical applications. Moreover, taking into account the recent interest generated by remdesivir, a potential antiviral drug used to treat COVID-19 infection, we believe that there will be renewed efforts to develop more facile synthetic strategies for pyrrolo[2,1-f]-[1,2,4]triazine derivatives.

References
1. Wang, M.; Cao, R.; Zhang, L.; Yang, X.; Liu, J.; Xu, M.; Shi, Z.; Hu, Z.; Zhong, W.; Xiao, G. Cell Res. 2020, 30, 269.
2. Kim, K. S.; Lu, S.; Cornelius, L. A.; Lombardo, L. J.; Borzilleri, R. M.; Schroeder, G. M.; Sheng, C.; Rovnyak, G.; Crews, D.; Schmidt, R. J.; Williams, D. K.; Bhide, R. S.; Traeger, S. C.; McDonnell, P. A.; Mueller, L.; Sheriff, S.; Newitt, J. A.; Pudzianowski, A. T.; Yang, Z.; Wild, R.; Lee, F. Y.; Batorsky, R.; Ryder, J. S.; Ortega-Nanias, M.; Shen, H.; Gottardis, M.; Roussell, D. L. Bioorg. Med. Chem. Lett. 2006, 16, 3937.
3. Borzilleri, R. M.; Cai, Z.-W.; Ellis, C.; Fargnoli, J.; Fura, A.; Gerhardt, T.; Goyal, B.; Hunt, J. T.; Mortillo, S.; Qian, L.; Tokarski, J.; Vyas, V.; Wautlet, B.; Zheng, X.; Bhide, R. S. Bioorg. Med. Chem. Lett. 2005, 15, 1429.
4. Shi, W.; Qiang, H.; Huang, D.; Bi, X.; Huang, W.; Qian, H. Eur. J. Med. Chem. 2018, 158, 814.
5. Hunt, J. T.; Mitt, T.; Borzilleri, R.; Gullo-Brown, J.; Fargnoli, J.; Fink, B.; Han, W.-C.; Mortillo, S.; Vite, G.; Wautlet, B.; Wong, T.; Yu, C.; Zheng, X.; Bhide, R. J. Med. Chem. 2004, 47, 4054.
6. Mesaros, E. F.; Angeles, T. S.; Albom, M. S.; Wagner, J. C.; Aimone, L. D.; Wan, W.; Lu, L.; Huang, Z.; Olsen, M.; Kordwitz, E.; Haltiwanger, R. C.; Landis, A. J.; Cheng, M.; Ruggeri, B. A.; Ator, M. A.; Dorsey, B. D.; Ott, G. R. Bioorg. Med. Chem. Lett. 2015, 25, 1053.
7. Sampognauro, A. J.; Wittman, M. D.; Carboni, J. M.; Chang, C.; Greer, A. F.; Hurlbut, W. W.; Sack, J. S.; Vyas, D. M. Bioorg. Med. Chem. Lett. 2010, 20, 5027.
8. Abraham, S.; Hadd, M. J.; Tran, L.; Vickers, T.; Sindac, J.; Milanov, Z. V.; Holladay, M. W.; Bhagwat, S. S.; Hua, H.; Pulido, J. M. F.; Cramer, M. D.; Gitnick, D.; James, J.; Dao, A.; Belli, B.; Armstrong, R. C.; Trieber, D. K.; Liu, G. Bioorg. Med. Chem. Lett. 2011, 21, 5296.
9. Fink, B. E.; Vite, G. D.; Mastaler, H.; Kadow, J. F.; Kin, S.-H.; Leavitt, K. J.; Du, K.; Crews, D.; Mitt, T.; Wong, T. W.; Hunt, J. T.; Vyas, D. M.; Tokarski, J. S. Bioorg. Med. Chem. Lett. 2005, 15, 4774.
10. Xin, M.; Zhang, L.; Tang, F.; Tu, C.; Wen, J.; Zhao, X.; Liu, Z.; Cheng, L.; Shen, H. Bioorg. Med. Chem. 2014, 22, 1429.
11. Siegel, D.; Hui, H. C.; Doerfler, E.; Clarke, M. O.; Chun, K.; Zhang, L.; Neville, S.; Carra, E.; Lew, W.; Ross, B.; Wang, Q.; Wolfe, L.; Jordan, R.; Soloveva, V.; Knox, J.; Perry, J.; Perron, M.; Strat, K. M.; Barauskas, O.; Feng, J. Y.; Yu, Y.; Lee, G.; Rheingold, A. L.; Ray, A. S.; Bannister, R.; Strickley, R.; Swaminathan, S.; Lee, W. A.; Bavari, S.; Cihlar, T.; Lo, M. K.; Warren, T. K.; Mackman, R. L. J. Med. Chem. 2017, 60, 1648.
12. Li, Q.; Groaz, E.; Rocha-Pereira, J.; Neyts, J.; Herdevijn, P. Eur. J. Med. Chem. 2020, 195.
13. Wroblewski, S. T.; Lin, S.; Hynes, J., Jr.; Wu, H.; Pitt, S.; Shen, D. R.; Zhang, R.; Gillooly, K. M.; Shuster, D. J.; Mchtyre, K. W.; Doweyko, A. M.; Kish, K. F.; Tredup, J. A.; Duke, G. J.; Sack, J. S.; McKinnon, M.; Dodd, J.; Barrish, J. C.; Schieven, G. L.; Lefttheris, K. Bioorg. Med. Chem. Lett. 2008, 18, 2739.
14. Ji, Z.; Dai, Y.; Abad-Zapatero, C.; Albert, D. H.; Bouska, J. J.; Glaser, K. B.; Marcotte, P. A.; Soni, N. B.; Magoc, T. J.; Stewart, K. D.; Wei, R.-Q.; Davidsen, S. K.; Michaelides, M. R. Bioorg. Med. Chem. Lett. 2012, 22, 4528.
15. Borzilleri, R. M.; Zheng, X.; Qian, L.; Ellis, C.; Cai, Z.; Wautlet, B.; Mortillo, S.; Jeayaselvan, R.; Bukral, D. W.; Fura, A.; Kamath, A.; Vyas, V.; Tokarski, J. S.; Barrish, J. C.; Hunt, J. T.; Lombardo, L. J.; Fargnoli, J.; Bhide, R. S. J. Med. Chem. 2005, 48, 3991.
16. Thieu, T.; Selafani, J. A.; Levy, D. V.; McLean, A.; Breslin, H. J.; Ott, G. R.; Bakale, R. P.; Dorsey, B. D. Org. Lett. 2011, 13, 4204.
17. Wang, M.; Gao, M.; Zheng, Q.-H. Bioorg. Med. Chem. Lett. 2014, 24, 3700.
18. Zheng, B.; Conlon, D. A.; Corbett, R. M.; Chau, M.; Hsieh, D.-M.; Yeboah, A.; Hsieh, D.; Müselhiddinogu, J.; Gallagher, W. P.; Simon, J. A.; Burt, J. Org. Proc. Res. Dev. 2012, 16, 1846.
19. Lim, J.; Altman, M. D.; Baker, J.; Brubaker, J. D.; Chen, H.; Chen, Y.; Kleinschek, M. A.; Li; C.; Liu, D.; Maclean, J. K. F.; Mulrooney, E. F.; Presland, J.; Rakhilina, L.; Smith, G. F.; Yang, R. Bioorg. Med. Chem. Lett. 2015, 25, 5384.
20. Draffan, A. G.; Frey, B.; Pool, B.; Bannon, C.; Tyndall, E. M.; Lilly, M.; Francom, P.; Hufton, R.; Halim, R.; Jahangiri, S.; Bond, S.; Nguyen, V. T. T.; Jeynes, T. P.; Wirth, V.; Luttick, A.; Tilmanis, D.; Thomas, J. D.; Pryor, M.; Porter, K.; Morton, C. J.; Lin, B.; Duan, J.; Kukolj, G.; Kuolj, G.; Simonneau, B.; McKercher, G.; Lagacé, L.; Arnad, M.; Bethell, R. C.; Tucker, S. P. ACS Med. Chem. Lett. 2014, 5, 679.
21. Xiang, H.-Y.; Chen, Y.-H.; Wang, Y.; Zhang, X.; Ding, J.; Meng, L.-H.; Yang, C.-H. Bioorg. Med. Chem. Lett. 2020, 30, https://doi.org/10.1016/j.bmclev.2020.127194.
22. Xiang, H.; Chen, Y.; He, Q.; Xie, Y.; Yang, C. RSC Adv. 2013, 3, 5807.
23. Chen, J.; Liu, B.; Chen, Y.; He, Q.; Yang, C. RSC Adv. 2014, 4, 11168.
24. Chen, Y.; Xiang, H.; Tan, C.; Xie, Y.; Yang, C. Tetrahedron 2013, 69, 2714.
25. Son, K.; Park, S. J. Beilstein J. Org. Chem. 2016, 12, 1780.