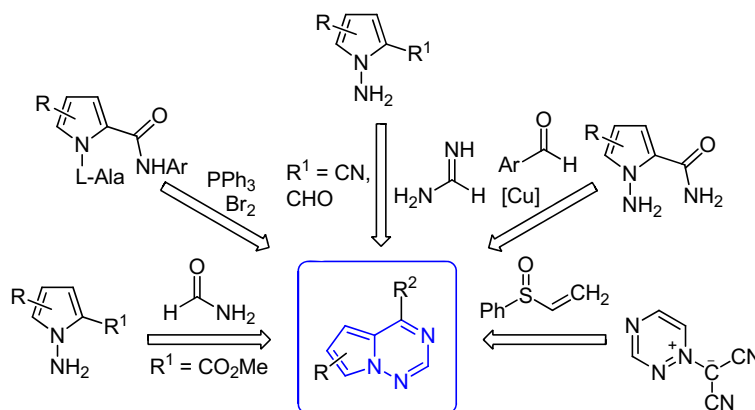# Synthetic strategies for pyrrolo[2,1-*f*][1,2,4]triazine: the parent moiety of antiviral drug remdesivir

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R = I, Cl, Ar, CO_2Me, CO_2Et; R^2 = H, Cl, OH, NH_2
Antiviral activity including SARS-CoV, MERS-CoV,
SARS-CoV-2 (COVID-19), Ebola
Antitumor activity
Antitumorigenic activity

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 hetero-cycle, 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/MERS-CoV) and has shown encouraging 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, anti-tumorigenic 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]
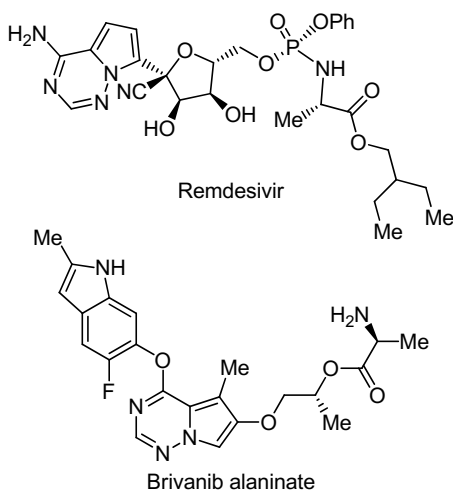
Figure 1. Drugs containing pyrrolo[2,1-*f*][1,2,4]triazine moiety.

anaplastic lymphoma kinase (ALK) inhibitor,[6] IGF-1R and IR kinase inhibitor,[7] pan-Aurora kinase inhibitor,[8] EGFR and HER2 protein tyrosine dual inhibitor,[9] and hedgehog (Hh) signaling pathway inhibitor.[10] Some analogs of pyrrolo[2,1-*f*][1,2,4]triazine have been used in the treatment of Ebola and other emerging viruses.[11] Recent reports have revealed anti-norovirus activity of 4-aminopyrrolo-[2,1-*f*][1,2,4]triazine *C*-nucleosides, which have the ability to inhibit both murine and human norovirus RNA-dependent RNA polymerase (RdRp).[12] Owing to the importance of this heterocycle, this review attempts to summarize different synthetic strategies adopted for pyrrolo[2,1-*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-*f*][1,2,4]triazines was described starting from the *N*-unsubstituted pyrrole derivative **1**.[13] Treating pyrrole **1** with either *O*-(2,4-dinitro-phenyl)hydroxylamine (DnpONH$_2$) or NH$_2$Cl in the presence of NaH, followed by cyclization with formamide at 165°C, yielded pyrrolotriazine **2** (Scheme 1).
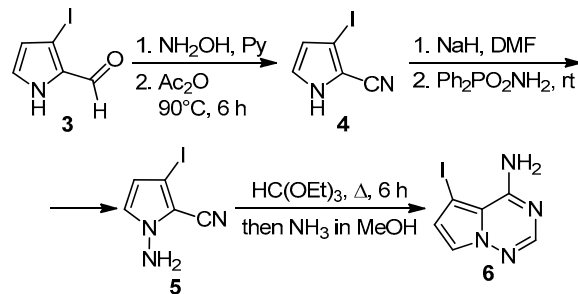
Scheme 1
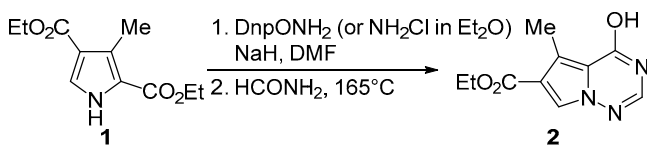
Synthesis of pyrrolotriazine **6** from 3-iodo-1*H*-pyrrole-2-carbaldehyde (**3**) has also been reported.[14] The latter was transformed into pyrrole-2-carbonitrile **4** through a two-step one-pot process *via* the corresponding oxime. Electrophilic *N*-amination of compound **4**, followed by cyclization of the resulting *N*-aminopyrrole **5** with triethyl orthoformate, yielded pyrrolotriazine **6** (Scheme 2).

Aminopyrrole **8** was obtained by *N*-amination of diethyl 3-isopropyl-1*H*-pyrrole-2,4-dicarboxylate (**7**) using either *O*-(diphenylphosphinyl)hydroxylamine or *O*-(mesitylene-sulfonyl)hydroxylamine. Cyclization of compound **8** at

Scheme 2

165°C in DMF yielded bicyclic compound **9**. The latter was deoxidized by heating with POCl$_3$ to give ethyl 4-chloro-5-(propan-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (**10**) in high yield (Scheme 3).[15]
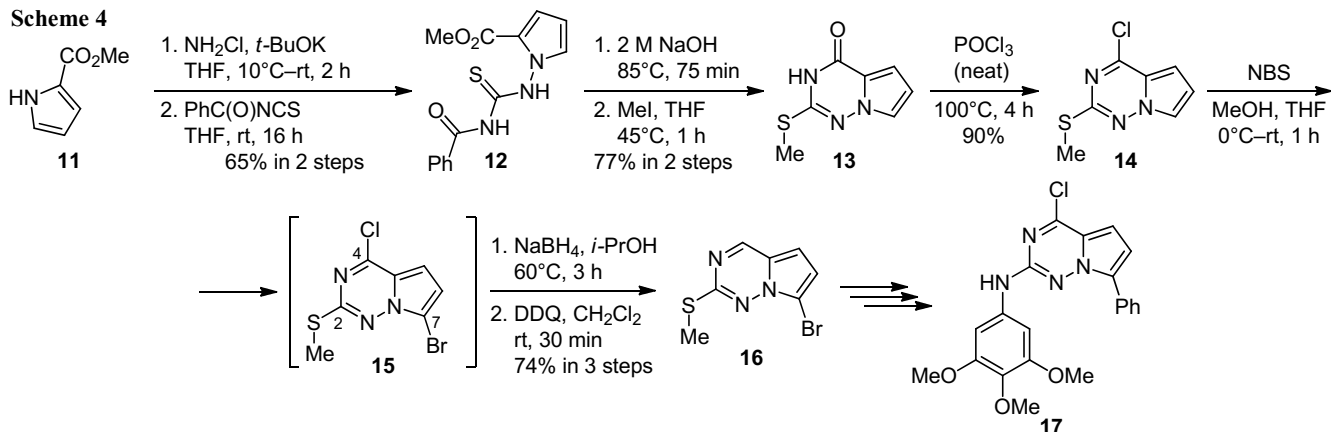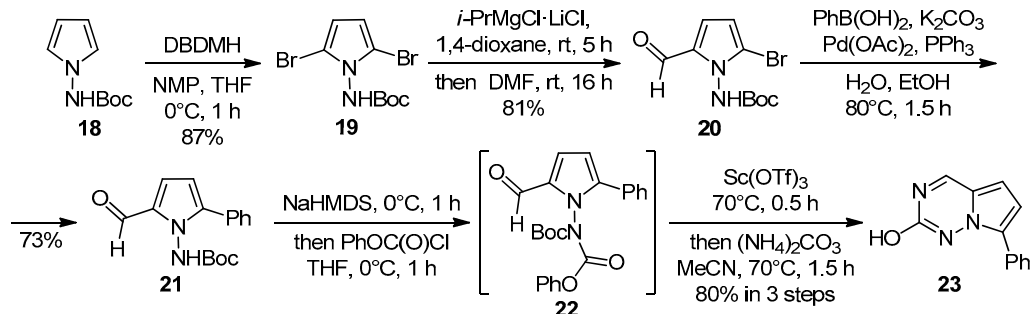
Scheme 3
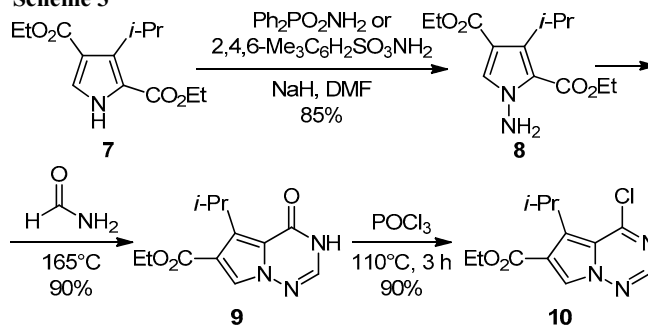
2-Arylaminopyrrolo[2,1-*f*][1,2,4]triazine **17** was synthesized as a new kinase inhibitor template starting from 7-bromo-2-(methylsulfanyl)pyrrolo[2,1-*f*][1,2,4]triazine (**16**) *via* orthogonal approaches.[16] To obtain compound **16**, *N*-amination of methyl pyrrole-2-carboxylate (**11**) was carried out using a suitable aminating agent (NH$_2$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$_3$ was then used to block the highly reactive C-4 position giving rise to chlorinated product **14**. Bromination of compound **14** with NBS proceeded smoothly at the C-7 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$_4$ 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-*f*][1,2,4]-triazin-2-ol (**23**) from pyrrole derivative **18** was also reported.[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-carb-aldehyde **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

Scheme 5

compound **22**. For the selective cleavage of *N*-Boc protective group, Sc(OTf)$_3$ was used, and subsequent condensation with (NH$_4$)$_2$CO$_3$ 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[2,1-*f*][1,2,4]triazine **29** starting from β-substituted acrylate **24**.[17] 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$_2$Cl 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 6
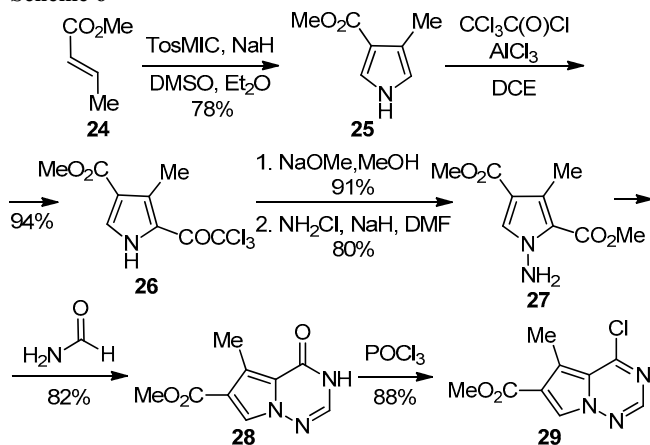
Synthesis *via* bromohydrazone

A practical six-step synthesis of pyrrolotriazine scaffold has been described.[18] The condensation of 2-bromo-1,1-dimethoxyethane (**30**) with NH$_2$NHCbz under acidic conditions gave bromohydrazone **31** (Scheme 7). Different acids, such as HCl, H$_2$SO$_4$, methanesulfonic acid (MSA), TFA, H$_3$PO$_4$, 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$_3$PO$_4$. The next transformation included *C*-alkylation of sodium 1,4-diethoxy-1,4-dioxobut-2-en-
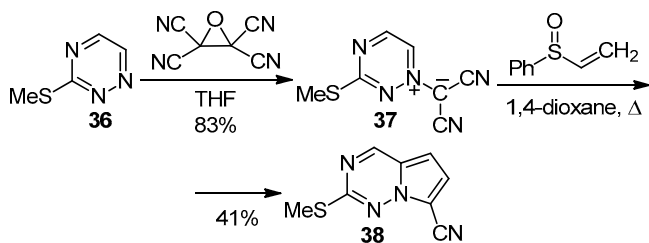
Scheme 7
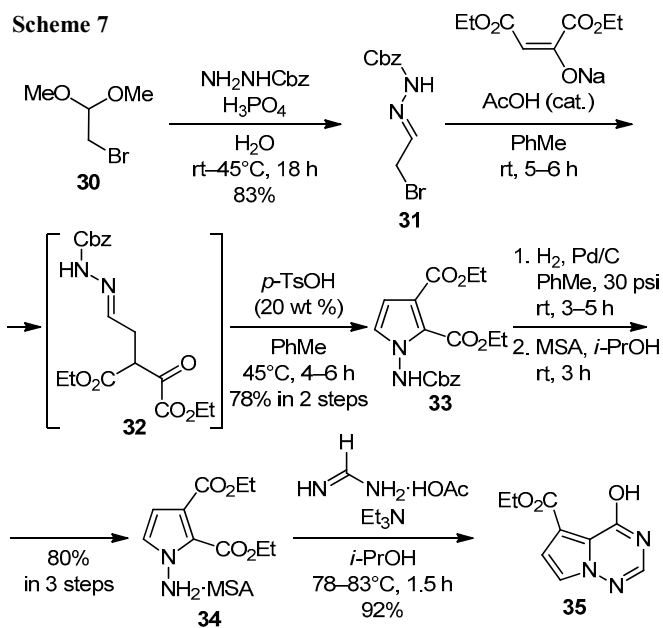
2-olate with bromide **31** to afford keto ester derivative **32**. It was also observed that the use of less polar solvents for this transformation afforded higher yield of the alkylated product. Acid-catalyzed cyclization of compound **32** followed by heating at 45°C afforded protected 1-amino-pyrrole **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 Et$_3$N, 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 dicyano-methylide **37**. Subsequently, [2+2] cycloaddition of phenyl vinyl sulfoxide provided the formation of 2-(methylsulfanyl)-pyrrolo[2,1-*f*][1,2,4]triazine-7-carbonitrile (**38**) (Scheme 8).
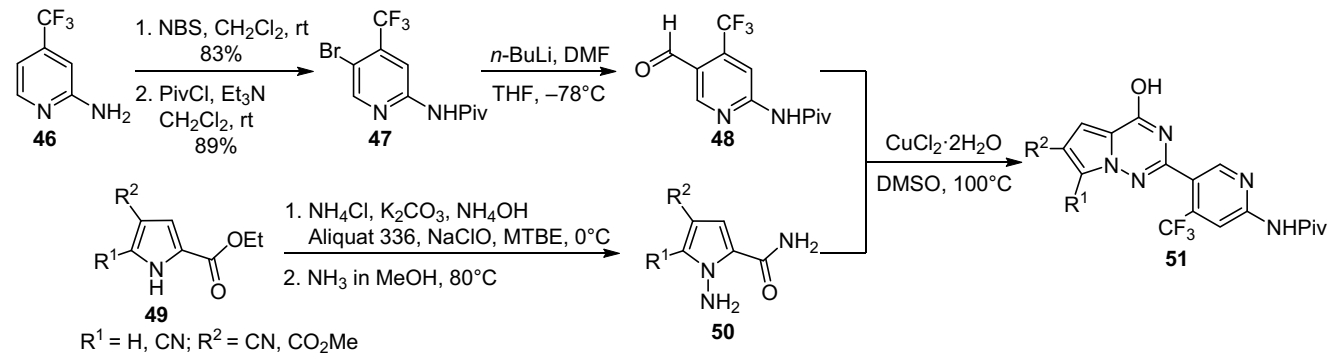
Scheme 8
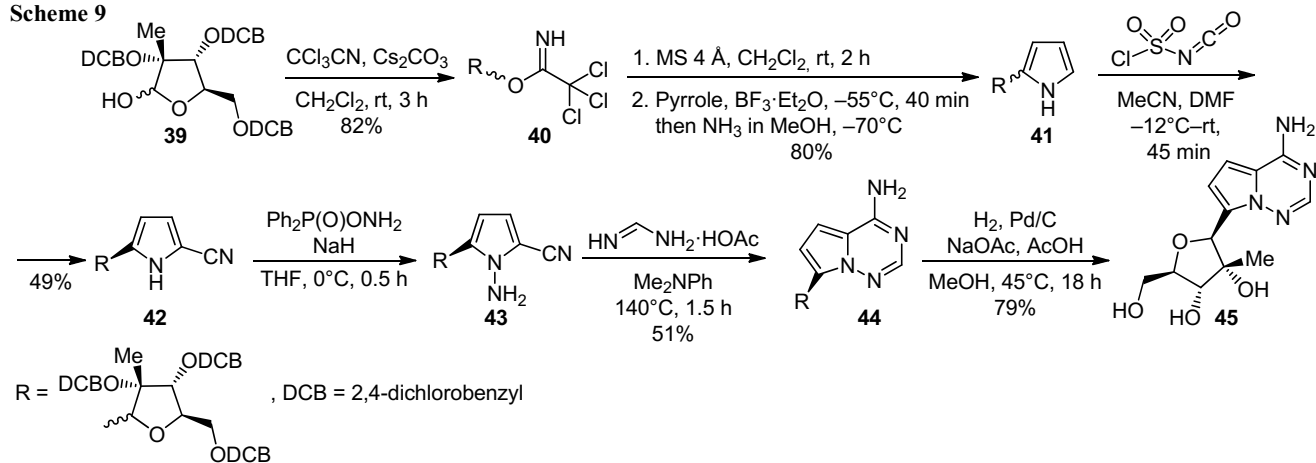
Multistep synthesis

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-amine adenosine analog **45** was synthesized *via* a linear 7-step route (Scheme 9).[20] Initially, the activated trichloroacetamidate **40** was obtained from trichloroacetonitrile and riboside **39**. Subsequent slow addition of pyrrole at low temperature in the presence of BF$_3$·Et$_2$O gave an anomeric 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*-amino-pyrrole **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]triazin-4-amine **44** which under buffer hydrogenolysis conditions formed free pyrrolotriazine-containing adenosine analog **45**.
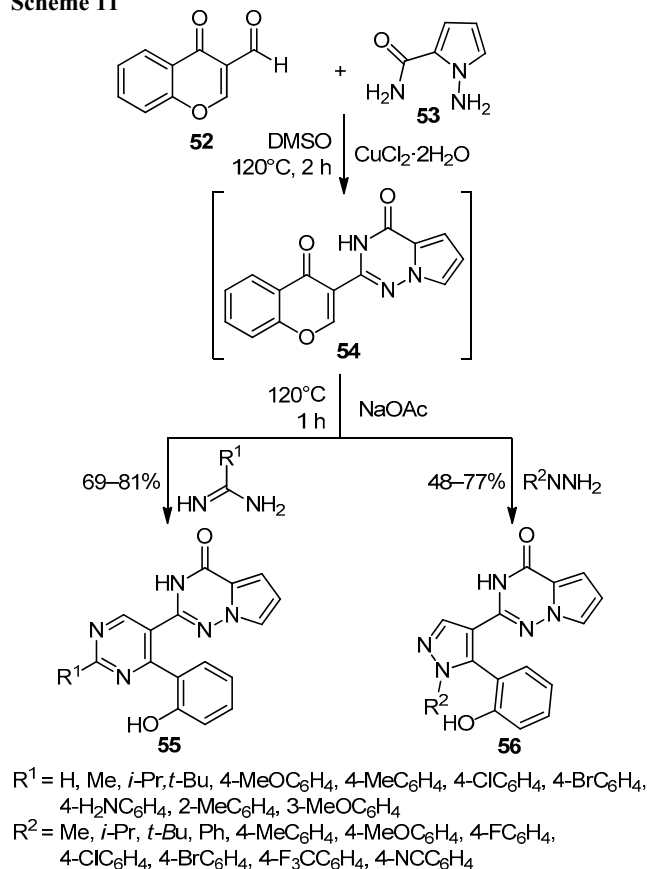
Pyrrolo[2,1-*f*][1,2,4]triazines **51** were synthesized in a multistep procedure using pyridine derivative and *N*-aminated pyrrole. The obtained derivatives showed antiproliferative activity against human cancer cells.[21] 2-Aminopyridine **46** was brominated and then converted into substituted pivaloylamide **47** (Scheme 10). Reaction of amide **47** with

Scheme 9

Scheme 10

n-BuLi and DMF afforded the key intermediate **48**. *N*-Amination of pyrroles **49** was realized in the presence of quaternary ammonium salt and NH$_4$Cl in MTBE giving 1-amino-1*H*-pyrrole-2-carboxamides **50** after treatment with NH$_3$ 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(3*H*)-ones **55** and **56**, in which at least six bonds were formed, have been proposed by Yang group.[22] The Cu(II)-catalyzed reaction of 4-oxo-4*H*-chromene-3-carbaldehyde (**52**) and 1-amino-1*H*-pyrrole-2-carbox-amide (**53**) gave 2-(4-oxo-4*H*-chromen-3-yl)pyrrolo[2,1-*f*]-[1,2,4]triazin-4(3*H*)-one (**54**). The best result was achieved using the CuCl$_2$·2H$_2$O/NaOAc/DMSO catalytic system at 120°C. Intermediate **54** reacted with different amidines and hydrazines in the presence of NaOAc yielding pyrrolo-[2,1-*f*][1,2,4]triazin-4(3*H*)-ones **55** and **56**, respectively (Scheme 11).

Scheme 11

R^1 = H, Me, *i*-Pr, *t*-Bu, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$,
4-H$_2$NC$_6$H$_4$, 2-MeC$_6$H$_4$, 3-MeOC$_6$H$_4$
R^2 = Me, *i*-Pr, *t*-Bu, Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$,
4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-NCC$_6$H$_4$

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).[23] Electron-donating and electron-withdrawing groups of 2-alkynyl-benzaldehydes **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

R = Ph, 4-MeOC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, cyclopropyl
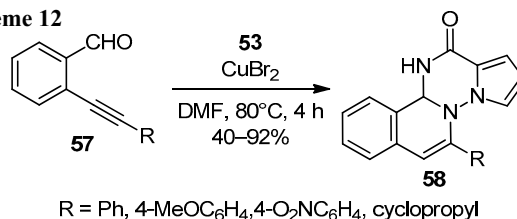
Compounds **60** were obtained *via* Cu(II)-promoted cyclization of *N*-aminopyrroles **53** or **59** with aryl aldehydes upon heating in DMSO in moderate to good yields (Scheme 13).[24] Electron-donating groups of aryl aldehyde accelerated the process as compared to electron-withdrawing substituents.

Scheme 13

R^2 = H, 4-Me, 4-NO$_2$, 3-MeO, 3-Br, 3-NO$_2$, 2-MeO, 2-Br
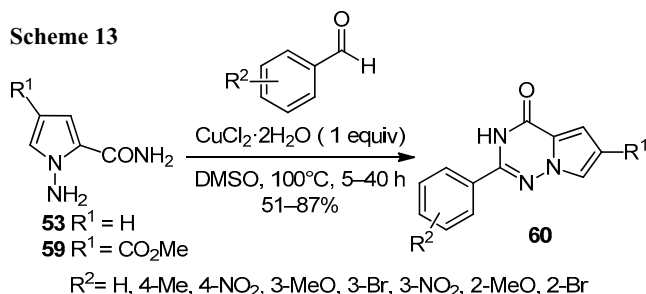
Synthesis *via* rearrangement of pyrrolooxadiazines

A practical synthesis of pyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-ones has been proposed *via* rearrangement of pyrrolo-[1,2-*d*][1,3,4]oxadiazines.[25] The methodology involved synthesis of pyrrole-2-carboxamides **62** from 3-chloro-1*H*-pyrrole-2-carboxylic acid (**61**) (Scheme 14). Treating

Scheme 14

R = Ph, 2-FC$_6$H$_4$, 3-FC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-NCC$_6$H$_4$,
4-MeOC$_6$H$_4$CH$_2$, cyclopropyl
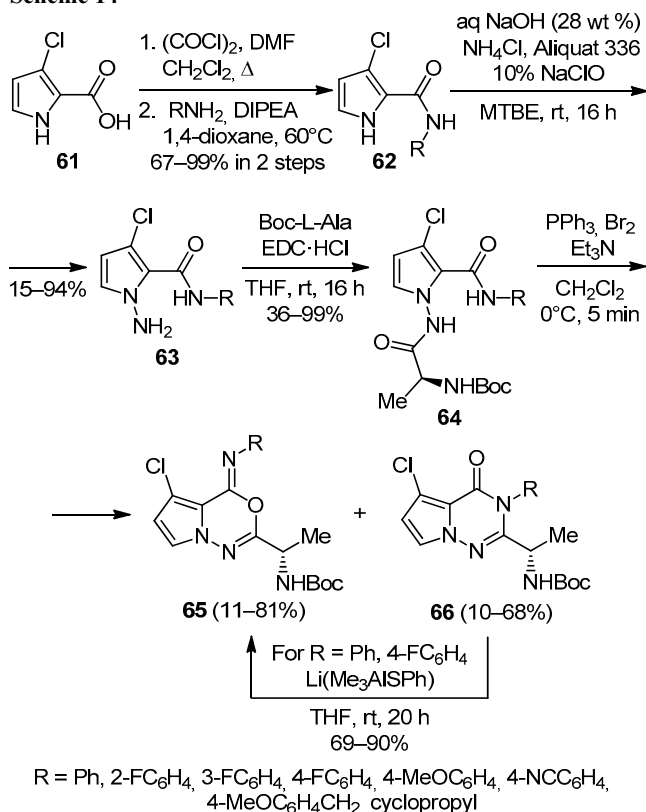
pyrroles **62** with NH$_4$Cl, Aliquat 336, and NaClO afforded 1-aminopyrroles **63**. Interaction of compounds **63** with EDC·HCl and Boc-L-Ala yielded pyrrole derivatives **64**. Regioselective intramolecular cyclization of pyrroles **64** upon treatment with PPh$_3$, Br$_2$, and Et$_3$N in CH$_2$Cl$_2$ 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(phenylsulfido)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-Nanos, 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. Sampognaro, A. J.; Wittman, M. D.; Carboni, J. M.; Chang, C.; Greer, A. F.; Hurlburt, 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.; Mastalerz, H.; Kadow, J. F.; Kim, 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.; Doerffler, 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.; Stray, K. M.; Barauskas, O.; Feng, J. Y.; Xu, 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.; Herdewijn, P. *Eur. J. Med. Chem.* **2020**, 195.
13. Wrobleski, S. T.; Lin, S.; Hynes, J., Jr.,; Wu, H.; Pitt, S.; Shen, D. R.; Zhang, R.; Gillooly, K. M.; Shuster, D. J.; Mclntyre, 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.; Leftheris, 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. S.; Mortillo, S.; Jeyaseelan, R.; Kukral, 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.; Sclafani, 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.; Müslehiddinoğlu, 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.; Gannon, 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.; Simoneau, B.; McKercher, G.; Lagacé, L.; Amad, 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.bmcl.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.