University of Dundee

A Continuous Flow Strategy for the Facile Synthesis and Elaboration of Semi-Saturated Heterobicyclic Fragments

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1. Fragment criteria of the Drug Discovery Unit (DDU)'s fragment library

Fragment criteria ^a		DDU range
LogP		-2 to 2
LogD		-2 to 2
Heavy atom count		5 to 18
Hydrogen bond acceptor		≤ 6
Hydrogen bond donor		≤ 3
Total polar surface area		≤ 90
Rotable bonds		≤ 3
Solubility	Sample concentration > 1 mM based on comparison to residual DMSO-d ₆ peak.	
Stability	< 1% increase in impurities after 48 hours	
Aggregation	No evidence in the waterLOGSY of aggregation of the compound in buffer.	
Purity		≥ 95%
[a] Physicochemical and quality control parameters employed by the DDU.		

2. NMR spectra

methyl 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-b]pyridine-6-carboxylate (**18**)

N-(4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b]pyridin-5-yl)acetamide (**19**)

1,2,3,4-tetrahydroquinolin-5-ol (**20**)¹

1,2,3,4-tetrahydroisoquinolin-6-amine (**21**)²

4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (**22**)³

5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (**23**)⁴

5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-5-carboxylic acid (**24**)⁵

ethyl 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-3-carboxylate (**25**)⁶

methyl 5,6,7,8-tetrahydroindolizine-7-carboxylate (**26**)

N-(1,2,3,4-tetrahydroquinoxalin-6-yl)acetamide (**27**)

ethyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-2-carboxylate (**28**)⁷

1,2,3,4-tetrahydropyrido[3,4-b]pyrazine (**29**)⁸

methyl 4,5,6,7-tetrahydro-1H-indazole-5-carboxylate (**30**)⁹

methyl 4,5,6,7-tetrahydro-1H-benzo[d]imidazole-5-carboxylate (**31**)¹⁰

methyl indoline-7-carboxylate (**32**)¹¹

5,6,7,8-tetrahydroimidazo[1,2-b]pyridazine (**33**)¹²

1-(5-hydroxy-3,4-dihydroquinolin-1(2H)-yl)ethan-1-one (**35**)

1-(7,8-dihydroimidazo[1,2-b]pyridazin-5(6H)-yl)ethan-1-one (**36**)

1-(methylsulfonyl)-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine (**37**)

6-(methylsulfonyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (**38**)

tert-butyl 6-amino-3,4-dihydroisoquinoline-2(1H)-carboxylate (**39**)¹³

tert-butyl 1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridine-6-carboxylate (**40**)¹⁴

methyl 4-methyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-b]pyridine-6-carboxylate (**41**)

ethyl 7-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-2-carboxylate (**42**)¹⁵

N-methyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-b]pyridine-6-carboxamide (**43**)

N-methyl-4,5,6,7-tetrahydro-1H-indazole-5-carboxamide (**44**)

Reference:

1. R. L. Atkins, D. E. Bliss, *J. Org. Chem.* **1978**, *43*, 1975 – 1980.
2. A. P. Carpino, A. P. Jardine DaSilva, A. B. Lefker; Ragan, A. John, *PCT Int. Appl.*, WO 9635713, **1996**.
3. Z. Guo, P. Orth, Z. Zhu, R. D. Mazzola, Y. Tin, H. A. Vaccaro, B. McKittrick, J. A. Kozlowski, J. B. Lavey, G. Zhou, S. Paliwal, P. C. Ting, K. E. Rosner, G. W. Shipps, M. A. Siddiqui, D. B. Belanger, C. Dai, D. Li, V. M. Girjavallabhan, W. Yu, L. Zhao, *PCT Int. Appl.*, WO 2005121130, **2005**.
4. Mishchuk, N. Shtil, M. Poberezhnyk, K. Nazarenko, T. Savchenko, A. Tolmachev, M. A. Mikhail, *Tetrahedron Lett.* **2016**, *57*, 1056-1059.
5. C. Schlepphorst, M. P. Wiesenfeldt, F. Glorius, *Chem. Eur. J.* **2018**, *24*, 356-359.
6. S. M. Allin, W. R. S. Barton, W. R. Bowman, T. McInally, *Tetrahedron Lett.* **2002**, *43*, 4191-4193.
7. X. Cao, Z. Sun, Y. Cao, R. Wang, T. Cai, W. Chu, W. Hu, Y. Yang, *J. Med. Chem.* **2014**, *57*, 3687-3706.
8. S. Singh, G. Das, O. V. Singh, H. Han, *Org. Lett.* **2007**, *9*, 401-404.
9. D. McMinn, H. Johnson, S. Bowers, D. C. Moebius, *PCT Int. Appl.*, WO 2014152134, **2014**.
10. K. E. Andersen, F. Z. Doerwald, U. G. Sidelmann, K. Rudolf, D. Stenkamp, R. Hurnaus, S. G. Mueller, B. Krist, B. Eriksen, B. Pesche, *PCT Int. Appl.*, WO 2001068652, **2001**.
11. M. Somei, T. Kawasaki, T. Ohta, *Heterocycles*, **1988**, *27*, 2363-2365.
12. P. K. Kadaba, B. Stanovnik, M. Tisler, *Tetrahedron Lett.* **1974**, *42*, 3715-3718.
13. G. Chang, P. H. Dorff, J. G. Quallich, *PCT Int. Appl.*, WO 9640640, **1996**.
14. C. Pawar, D. Pansare, D. Shinde, *Eur. J. Chem.* **2017**, *8*, 400-409.
15. A. M. Venkatesan, A. Agarwal, T. Abe, H. Ushiroguchi, I. Yamamura, M. Ado, T. Tsuyoshi, O. Dos Santos, Y. Gu, F. Sum, Z. Li, G. Francisco, Y. Lin, P. Petersen, Y. Yang, T. Kumagai, W. J. Weiss, D. M. Shlaes, J. R. Knox, T. S. Mansour, *J. Med. Chem.* **2006**, *49*, 4623-4637.